The Impact of Type 1 Diabetes on Neural Activity Serving Attention

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Abstract

Type 1 diabetes has been associated with alterations in attentional processing and other cognitive functions, and previous studies have found alterations in both brain structure and function in affected patients. However, these previous neuroimaging studies have generally examined older patients, particularly those with major comorbidities known to affect functioning independent of diabetes. The primary aim of the current study was to examine the neural dynamics of selective attention processing in a young group of patients with type 1 diabetes who were otherwise healthy (i.e., without major comorbidities). Our hypothesis was that these patients would exhibit significant aberrations in attention circuitry relative to closely-matched controls. The final sample included 69 participants age 19–35 years-old, 35 with type 1 diabetes and 34 matched non-diabetic controls, who completed an Eriksen flanker task while undergoing magnetoencephalography (MEG). Significant group differences in flanker interference activity were found across a network of brain regions, including the anterior cingulate, inferior parietal cortices, paracentral lobule, and the left precentral gyrus. In addition, neural activity in the anterior cingulate and the paracentral lobule were correlated with disease duration in patients with type 1 diabetes. These findings suggest that alterations in the neural circuitry underlying selective attention emerge early in the disease process and are specifically-related to type 1 diabetes and not common comorbidities. These findings highlight the need for longitudinal studies in large cohorts to clarify the clinical implications of type 1 diabetes on cognition and the brain.

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Contribution Statement

Keywords

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Type 1 diabetes is a metabolic disorder that is known to be associated with several major complications, including growing recognition of disease-related structural and functional brain alterations. Both grey matter volume and white matter integrity appear to be affected, with a reduction in both metrics in patients with type 1 diabetes (Bednarik et al., 2017; Biessels & Reijmer, 2014; Musen et al., 2006). Neuropsychological studies have identified the cognitive domains most affected, which include psychomotor speed, intelligence, cognitive flexibility, executive function, and attention (McCrimmon, Ryan, & Frier, 2012; Ryan, van Duinkerken, & Rosano, 2016). Importantly, deficits in these domains have been specifically linked to measures of disease status including glycemic control and disease duration (Desrocher & Rovet, 2004; Tonoli et al., 2014). Such cognitive deficits have been shown to induce a circular pattern of dysfunction, whereby chronic dysglycemia leads to specific cognitive deficits, which in-turn lead to impaired ability to monitor and maintain adequate blood sugar levels, and thereby further cognitive decline (Grober, Hall, Hahn, & Lipton, 2011; Hansen et al., 2017).

In cognitive psychology, attention is generally described as the preferential allocation of processing resources to a specific stimulus or set of stimuli. Attention is an essential element in an array of daily activities, including disease care behaviors (i.e. detecting and correcting episodes of dysglycemia), and as mentioned above is known to be affected by key components of the disease (e.g., chronic dysglycemia). Selective attention tasks examine the mechanics of attentional processing in the context of response competition where ignoring distracting information is critical to task performance (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Desimone & Duncan, 1995). In these tasks, functional neuroimaging studies have found recruitment of various components of the fronto-parietal network and the anterior cingulate, with much of the work focusing on the latter region for its role in conflict monitoring processes (Botvinick et al., 2001; Botvinick, Cohen, & Carter, 2004; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Hazeltine, Poldrack, & Gabrieli, 2000). Interestingly, previous functional neuroimaging studies of type 1 diabetes have indicated widespread network activity disruptions across these attention-related brain areas during a variety of cognitive tasks (Bolo et al., 2011; Gallardo-Moreno, Gonzalez-Garrido, Gudayol-Ferre, & Guardia-Olmos, 2015; Hwang et al., 2016; Rooijackers, Wiegers, Tack, van der Graaf, & de Galan, 2016; van Duinkerken et al., 2012). These investigations have often examined participants in hypoglycemic states, usually induced through glycemic clamp approaches, which has allowed them to focus on the acute effects of hypoglycemia on brain function during the resting-state and/or various cognitive tasks (Frier, 2001; Rooijackers et al., 2016; Warren & Frier, 2005). In the present study, we examined a group of young adults with type 1 diabetes during normoglycemic conditions, to more directly examine the longer-term, sustained effects of type 1 diabetes on neurophysiological responses. Further, to minimize the impact of confounding health factors that are often associated with diabetes (e.g., micro- and macro-vascular damage, obesity, organ damage), we focused on healthy young adults with type 1 diabetes who were free of major comorbidities.

We used high-density magnetoencephalographic (MEG) imaging to identify how type 1 diabetes affects the neurophysiology of selective attention processing and conflict monitoring during the classic Eriksen flanker paradigm (Eriksen & Eriksen, 1974). By utilizing MEG neuroimaging and the classic flanker task paradigm, we were able to assess the neurophysiology of low versus high attention demand through the flanker interference effect in each group, and determine how type 1 diabetes affected the differing degrees of attention processing. The flanker task is also known to tap processes related to conflict monitoring, which are of major interest in type 1 diabetes. Our primary hypothesis was that participants with type 1 diabetes would exhibit aberrant neural responses during the flanker attention task, particularly during the higher-attentional demand trials (i.e., flanker interference effect) relative to closely-matched controls. In addition, we hypothesized that disease duration would be directly related to these aberrant neural responses.

Research Design and Methods

Participants.

A group of 40 patients with type 1 diabetes and no known comorbidities was recruited from the Diabetes Clinic at the University of Nebraska Medical Center (UNMC; age range: 19–35 years, 16 females). A control group ($N = 40$) matched on age, sex, education, body mass index, ethnicity, and handedness to the patient group was also recruited from the greater Omaha area. Exclusionary criteria included: (1) any medical diagnosis affecting CNS function (e.g., psychiatric and/or neurological disease), (2) known brain neoplasm or lesion, (3) history of significant head trauma, (4) current substance use disorder, (5) pregnancy or lactation, (6) hospitalization within the previous three months, (7) any type of cancer, (8) treatment with antipsychotics, antidepressants, and related medications known to affect brain function, with the exception of as-needed antidepressants following a 24 hour washout period, (9) current or prior treatment with statins, and (10) ferromagnetic implants. Patients were additionally excluded for the presence of: (1) micro- or macro-vascular disease defined as a urinary albumin-to-creatinine ratio > 30 ugAL/mgCR in the previous 12 months, (2) hypertension (blood pressure > 130/85 mmHg), (3) kidney disease defined by GFR < 60 mL/min/1.73 m^2, (4) aspartate transaminase-to-alanine transaminase ratio > 2 U/L, (5) a severe hypoglycemic episode within the past three months defined as an event requiring third party assistance, (6) untreated thyroid disease, and/or (7) B12 deficiency. Written informed consent was obtained from each participant following the guidelines of the UNMC's Institutional Review Board, who approved the study protocol, in accordance with the Declaration of Helsinki.

Glucose Measurements and Health Factors.

Prior to MEG, a blood panel, including glycated hemoglobin (HbA$_{1c}$), was completed for participants with type 1 diabetes according to the standards of care described by the American Diabetes Association. Additionally, participants were asked about specific demographic factors, their general medical history, and about the number of hypoglycemic episodes experienced per week. Before undergoing MEG, patients' blood glucose level was measured using a point-of-care device and had to be within the 70 to 200 mg/dl range. If measurements were between 55 to 70 mg/dl, patients were asked to raise their blood sugar to

the normal range, and after one hour in the normal range, these participants started their MEG session. Patients whose blood sugars were less than 55 mg/dl or over 200 mg/dl were rescheduled at least one week later, as such values equate to clinically-significant hypo- and hyperglycemia. For full lab results and general characteristics of the patient group, see Table 1.

Flanker Selective Attention Task.

During the MEG session, participants were seated in a nonmagnetic chair and instructed to fixate on a crosshair presented centrally for 1450–1550 ms. Following fixation, a row of five arrows appeared for 2500 ms and participants were instructed to respond by button press as to the direction the middle arrow. Trials where the middle arrow was pointing in the same direction as the surrounding (i.e., flanking) arrows were categorized as congruent, whereas trials where the middle arrow pointed in the opposite direction relative to the flankers were categorized as incongruent (see Figure 1). Each trial lasted ~4 s and each participant completed 200 trials; 100 per incongruent and congruent conditions, with both arrow directions presented an equal number of times in each condition.

MEG Methods and Analyses.

MEG acquisition and analysis methodology followed standardized pipelines, corresponding to normative studies previously published by our group (McDermott, Wiesman, Proskovec, Heinrichs-Graham, & Wilson, 2017; Proskovec, Heinrichs-Graham, Wiesman, McDermott, & Wilson, 2018; Wiesman, Heinrichs-Graham, Proskovec, McDermott, & Wilson, 2017). Briefly, MEG recordings were conducted within a magnetically-shielded room using a 306-sensor Elekta MEG system (Elekta, Helsinki, Finland). Data were sampled at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz. Each participant's data was corrected for head motion and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Each participant's MEG data were then coregistered with structural T1-weighted MRI data.

Following artifact rejection (e.g. cardiac artifacts), the continuous MEG time series was divided into 2 s segments (i.e., epochs), with the baseline defined as the −0.45 to −0.05 s window before stimulus onset (0.0 s). Artifact-free epochs were transformed into the time-frequency domain using complex demodulation, and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density. These sensor-level data were normalized using the mean baseline power during the −0.45 to −0.05 s time period. The precise time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers during the task period. Each data point in the spectrogram was examined using t-tests, corrected for multiple comparisons using a cluster-based nonparametric permutation testing approach (Ernst, 2004; Maris & Oostenveld, 2007). Based on these analyses, the time-frequency windows that contained significant oscillatory events across all participants and conditions (see Results) were subjected to beamforming.

Significant time-frequency windows were imaged at a $4.0 \times 4.0 \times 4.0$ mm resolution using the dynamic imaging of coherent sources (DICS) beamformer (Gross et al., 2001;

Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005), which employs spatial filters in the time-frequency domain to calculate source power for the entire brain volume. Following convention, we computed noise-normalized source power per voxel in each participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth. Such images are typically referred to as pseudo-t maps, with units (i.e., pseudo-t) that reflect noise-normalized power differences per voxel. All source imaging used the Brain Electrical Source Analysis (BESA) software (Version 6.1; GmbH, Gräfelfing, Germany). Preceding statistical analysis, each participant's functional MEG images were transformed into standardized Montreal Neurological Institute (MNI) space using the transform that was previously applied to the structural images and then spatially resampled (McDermott et al., 2017; Wiesman et al., 2017). After transforming these images into standardized space, we computed maps of the flanker interference effect in each person by subtracting the pseudo-t map of the congruent condition from that of the incongruent condition per time-frequency window. These maps represent the increased neural recruitment induced by the higher demand incongruent condition relative to the congruent condition. These flanker interference maps were then statistically analyzed for group differences using whole brain independent samples t-tests. Group difference maps were thresholded at ($p < 0.005$) and a spatial extent threshold (cluster threshold: $k = 300$) was applied to control for multiple comparisons based on the theory of Gaussian random fields (Worsley et al., 1996). Correlations were then computed using the peak voxel value from each significant cluster and disease duration.

Results

Demographic, Behavioral and Disease Status Results.

Five participants with type 1 diabetes and six controls were excluded at the data analysis phase due to artefactual MEG data. The remaining 35 participants with type 1 diabetes ($M_{age} = 25.3$ years, $SD_{age} = 4.7$; 13 females) and 34 controls ($M_{age} = 25.3$ years, $SD_{age} = 3.6$; 14 females) did not significantly differ in age, sex, or education level. Average education level was 16.3 years ($SD = 1.9$) for patients and 16.9 years ($SD = 1.4$) for controls. The mean disease duration in patients was 12.2 years ($SD = 7.4$), and the mean HbA$_{1C}$ was 64.0 mmol/mol ($SD = 16.2$; 7.99%, $SD = 1.48$).

Both groups performed the flanker task exceptionally well, as was expected, with a mean accuracy rate of 97.65% ($SD = 5.03$), a mean overall reaction time of 587.6 ms ($SD = 119.7$), and an average flanker effect—the difference in reaction times between incongruent and congruent condition—of 42.63 ms ($SD = 29.9$). There were no between-group differences in these behavioral measures (all ps > 0.430). Note that the flanker task is relatively easy and equivalent task performance across groups was by design, as accuracy differences would have confounded our MEG results. Basically, if there had been significant behavioral differences, any significant neural effects could have reflected performance disparities rather than the intended neural impact of the disease.

MEG Sensor Level Results.

In order to identify significant time-frequency windows for anatomical analyses (i.e., beamforming), t-tests of the spectrograms comparing the active period to the baseline were

computed across all participants and conditions, followed by nonparametric testing to correct for multiple comparisons. Time-frequency analyses showed a significant decrease from baseline in the 9–14 Hz (alpha) range from 200–600 ms after stimulus onset, and a significant increase from baseline in the 3–7 Hz (theta) range from 250–650 ms ($p < 0.001$; Figure 2). These windows are in agreement with previous MEG studies using the flanker task in young adults (McDermott et al., 2017). Both the alpha and theta time-frequency windows were imaged using a beamformer to examine these responses in anatomical space.

MEG Brain Level Results.

Maps of flanker interference activity were computed by subtracting maps of the congruent condition from that of the incongruent condition in each person separately for the alpha and theta responses. These flanker interference maps were then examined for group differences using independent samples t-tests. For alpha, group differences in flanker interference activity were found in the right paracentral lobule, left anterior cingulate, and left parietal regions ($p < 0.001$), while differences in theta activity were restricted to the left precentral gyrus ($p < 0.001$; Figure 3). The differences in the right paracentral lobule, left parietal, and left precentral gyrus reflected stronger flanker interference responses in the patients with type 1 diabetes relative to controls, while the opposite pattern (i.e., stronger responses in controls) was observed in the anterior cingulate.

Finally, we examined how duration of disease correlated with the strength of neural responses in each of the regions identified above in the group-level analyses. These analyses showed that the overall strength of alpha activity in the left anterior cingulate ($r = -0.46$, $p = 0.006$) and right paracentral lobule ($r = -0.42$, $p = 0.013$) correlated with disease duration in the patients with type 1 diabetes (Figure 4). Of note, we repeated these correlations using glucose level at the time of scan as a covariate, and this had almost no effect on the relationship between disease duration and neural activity in either the left anterior cingulate, $r = -0.48$, $p = 0.004$, or the right paracentral lobule, $r = -0.43$, $p = 0.011$. This latter finding suggests that these correlations were not driven by transient glucose levels at time of scan.

Discussion

Utilizing advanced MEG imaging, we found aberrant neural activity during selective attention processing in young adults with type 1 diabetes, under normoglycemic conditions and in the absence of major comorbidities. Specifically, we found greater flanker interference responses in the right paracentral lobule, left parietal, and left precentral gyrus of patients with type 1 diabetes, whereas controls showed a greater interference effect in the left anterior cingulate. Further, the peak amplitude of the responses in the right paracentral lobule and the left anterior cingulate significantly correlated with disease duration in patients with type 1 diabetes. Previous studies of attention processing have implicated both alpha and theta activity in frontal and parietal regional recruitment, with anterior cingulate engagement associated with response competition and conflict monitoring, and parietal activity associated more with response representation for motor planning (Bunge et al., 2002; Clark, Squire, Merrikhi, & Noudoost, 2015; Fassbender, Foxe, & Garavan, 2006; Hazeltine et al., 2000). Further, the paracentral lobule has previously been linked to shifts of attention

(Grosbras, Laird, & Paus, 2005). Below, we discuss the implications of these findings for understanding the impact of type 1 diabetes on neuronal function in attention and response competition circuits. Additionally, due to the associations between disease variables and neural activity, we further discuss the clinical implications of these findings and relevance to glycemic control and general disease management in this population.

One of our most interesting findings was the increased recruitment of the left inferior parietal cortices and the right paracentral lobule in patients with type 1 diabetes. Considering that previous studies have linked the paracentral lobule to shifts in attention, the current study may suggest that its role also extends to suppressing local interference in the context of distractors (i.e., the flanking stimuli) (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Given the correlation of activity in this region with disease duration, we propose that the increased interference response reflects compensatory processing in the patients with type 1 diabetes, which may enable them to maintain high performance levels during the increased interference of the incongruent condition. Interestingly, this pattern was already present in our relatively healthy young adults with type 1 diabetes, which may indicate that eventually these compensatory processes will be exhausted leading to inferior performance on this task and others that tap attention function. Future aging studies, especially longitudinal studies of type 1 diabetes involving both healthy children and adults will be needed to map the trajectory of these neural responses and further disentangle the specific health, lifestyle, and disease management factors that contribute to the decline. In regard to the inferior parietal finding, studies have linked this region with updating and maintaining spatial representations and this would also be expected within the current flanker paradigm. Presumably, the increased alpha activity in this brain area reflects stronger recruitment in patients with type 1 diabetes during stimulus processing, which potentially may help offset the decreased anterior cingulate involvement (see below) in these patients. However, this is speculative and future studies will need to clarify the increased role of this region in patients with type 1 diabetes. Of note, activity in the inferior parietal did not correlate with disease duration, which may suggest that this region's increased involvement is less progressive than that observed in other cortices (e.g., right paracentral). Finally, we also observed increased activity in the left precentral gyrus, which almost certainly reflects differences in motor control. Future studies should focus directly on the motor system in patients with type 1 diabetes and determine whether this system is particularly affected early in the disease process, as this could have major implications for disease management across the lifespan.

Another critical finding of this study was the significantly weaker flanker interference responses in the anterior cingulate of patients with type 1 diabetes. The anterior cingulate is a key brain region in the literature on attention, interference, and associated processes. Specifically, a large number of fMRI studies have shown anterior cingulate activation during the flanker and other related tasks (Botvinick et al., 1999; Botvinick et al., 2001; Botvinick et al., 2004; Bush, Luu, & Posner, 2000; Carter & van Veen, 2007; Casey et al., 2000; Kiehl, Liddle, & Hopfinger, 2000; van Veen & Carter, 2002; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001). In an early fMRI study by Botvinick et al., the anterior cingulate cortex was implicated in conflict monitoring, and examining and correcting errors over multiple trials rather than in a conditional manner (Botvinick et al., 1999). Using fMRI, Van Veen and colleagues have also identified a response competition role for the anterior cingulate in their

studies of flanker interference effects (van Veen & Carter, 2002; van Veen et al., 2001), and a subsequent study associated this role specifically with anterior cingulate cortex rather than distributed across the fronto-parietal network involved in attention (Liston, Matalon, Hare, Davidson, & Casey, 2006). More broadly, studies have implicated the anterior cingulate with autonomic regulation, complex motor control, and emotional processing (Bush et al., 2000). Such widespread functional roles can be attributed to the heterogeneity of this brain area and the known sub-region specificity, with rostral areas associated with error monitoring and autonomic regulation, and dorsal/caudal regions associated with response competition and attention related processes (Carter & van Veen, 2007; Casey et al., 2000; Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Kiehl et al., 2000; Swick & Turken, 2002). Our current findings are within the dorsal anterior cingulate and would overlap with areas previously linked to response competition processes (Critchley et al., 2005; Swick & Turken, 2002).

The well-studied anterior cingulate is also known to be hypo-activated in aging populations and those with disorders like attention deficit/hyperactivity disorder (ADHD), and these studies have directly linked activity in this region to conflict and error monitoring performance (Dickstein, Bannon, Castellanos, & Milham, 2006; Pardo et al., 2007). In our study, deficits in the anterior cingulate appeared to be progressive, as the decrease in anterior cingulate activity significantly correlated with disease duration. Interestingly, previous studies have shown increased anterior cingulate activation during states of hypoglycemia (Page et al., 2009; Teh et al., 2010; Teves, Videen, Cryer, & Powers, 2004), but even in such states this activity was still weaker in type 1 diabetes relative to control subjects, at least under hypoglycemic clamp conditions (Musen et al., 2008). The current finding extends this to the normoglycemia state, indicating chronic hypo-activation in the anterior cingulate in patients with type 1 diabetes, and our correlation analyses suggest that the severity of this deficit intensifies with longer disease durations.

Considering the body of literature examining cognitive impairment in patients with type 1 diabetes, deficits in attentional processes may have a unique impact on daily care behaviors and long term disease management. The impact of chronic hypoglycemia in insulin-treated type 1 diabetes is well-known throughout the literature (Cryer, 2014, 2017; Grober et al., 2011; Hansen et al., 2017; Rooijackers et al., 2016; Seaquist et al., 2013), with these patients experiencing two hypoglycemic episodes on average weekly and an annual incidence of severe hypoglycemia requiring third party intervention of 1.0 to 1.7 episodes per patient (Frier, 2008; McCrimmon & Sherwin, 2010). These recurrent episodes appear to lead to impairment in tracking and rectifying dysglycemia, thereby further impairing neural mechanisms in the process. Previous studies examining cognitive deficits and type 1 diabetes have identified a self-perpetuating loop of disease mismanagement and increased cognitive decline (Grober et al., 2011; Hansen et al., 2017), which may at least partially explain the relationship between attention-related neural dysfunction and disease duration apparent in the current study. With this progressive inability to manage the condition (i.e., maintain normoglycemia) leading to more rapid cognitive dysfunction, it is imperative that patients manage their glycemic levels carefully from the point of diagnosis to prevent detrimental long term outcomes. The long-term consequences of disease mismanagement also suggests that the costs associated with automated methods (e.g., pumps) may be

relatively low for the patient and the health care system given the costs of alternative outcomes.

Before closing, it is important to acknowledge a few limitations with the current study, including the specific focus on the flanker interference paradigm, the young age of the participants, and the absence of major common comorbidities. Although these factors were by design, they may limit the generalizability of these results to the larger population of people living with type 1 diabetes. Future studies should extend these findings to older patients and those with comorbidities. The latter could provide key information about the progressive nature of these neural aberrations and their role in long-term cognitive health. Additionally, the effects of stress and depression in type 1 diabetes were not examined in the current study, although emerging literature suggests these effects should be examined in future studies focusing on differences in cognitive and brain function. In summary, we found abnormal neural activity during a Flanker task in young healthy adults with type 1 diabetes (i.e., without common comorbidities), with particular responses being directly related to disease duration. These findings add to the growing body of literature examining cognitive deficits associated with type 1 diabetes, and in particular provide new data revealing specific neurophysiological differences in multiple brain areas, with some of these deficits progressing with disease duration. Future studies should examine neural and cognitive deficits in relation to complications that commonly arise with type 1 diabetes and in the context of aging. Longitudinal studies will be especially important in discerning the effects of type 1 diabetes on the brain throughout the lifespan.

Acknowledgments

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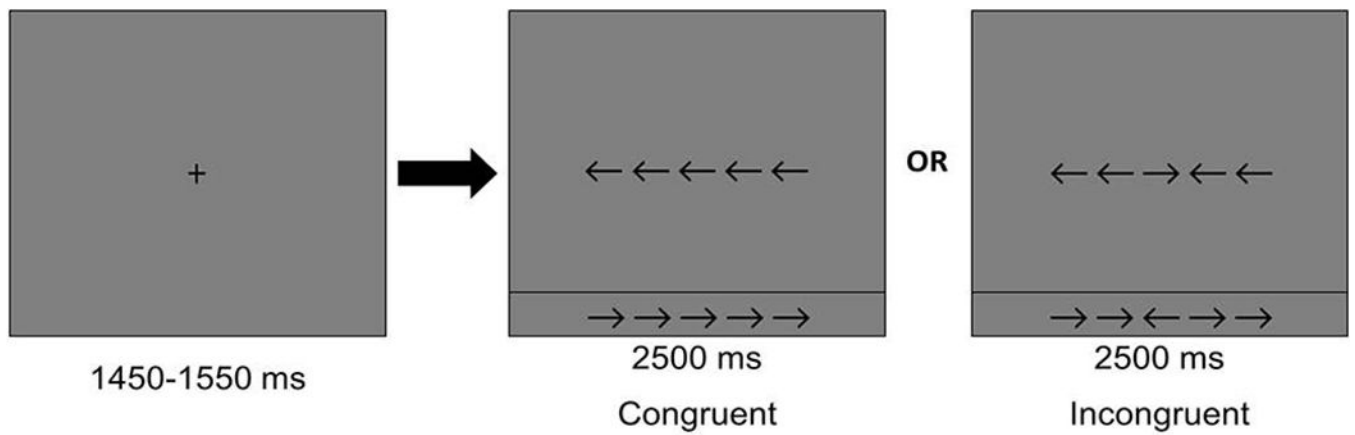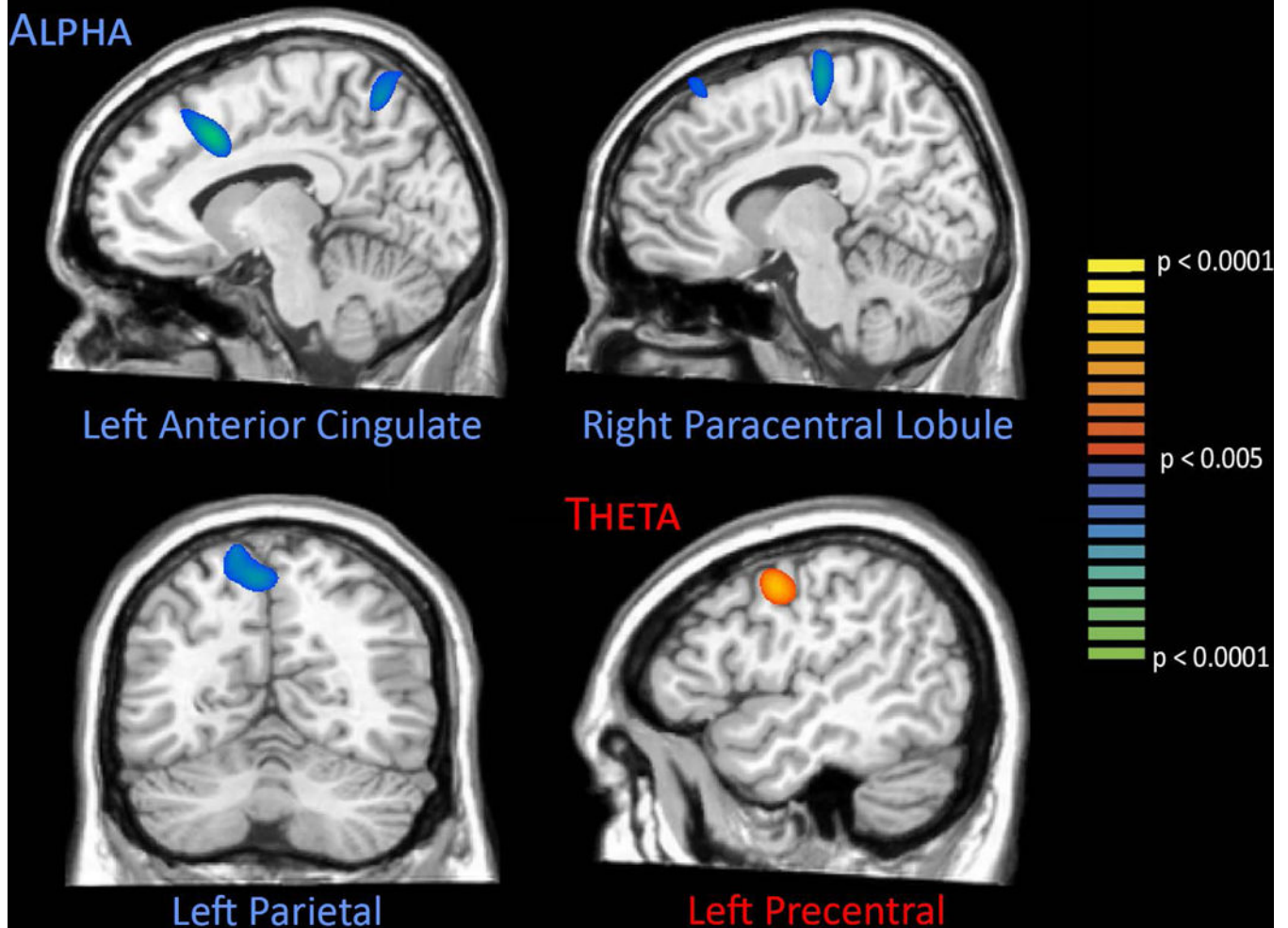
Figure 1.
Eriksen Flanker Attention Paradigm. Participants were shown a row of five arrows (duration: 2500 ms) following fixation and were asked to respond as to the direction of the middle arrow while ignoring the surrounding or flanking arrows. In the congruent condition, all five arrows pointed in the same direction. In the incongruent condition, the middle arrow pointed in the opposite direction of the surrounding arrows. The classic finding is an increase in reaction time in the incongruent relative to the congruent condition.
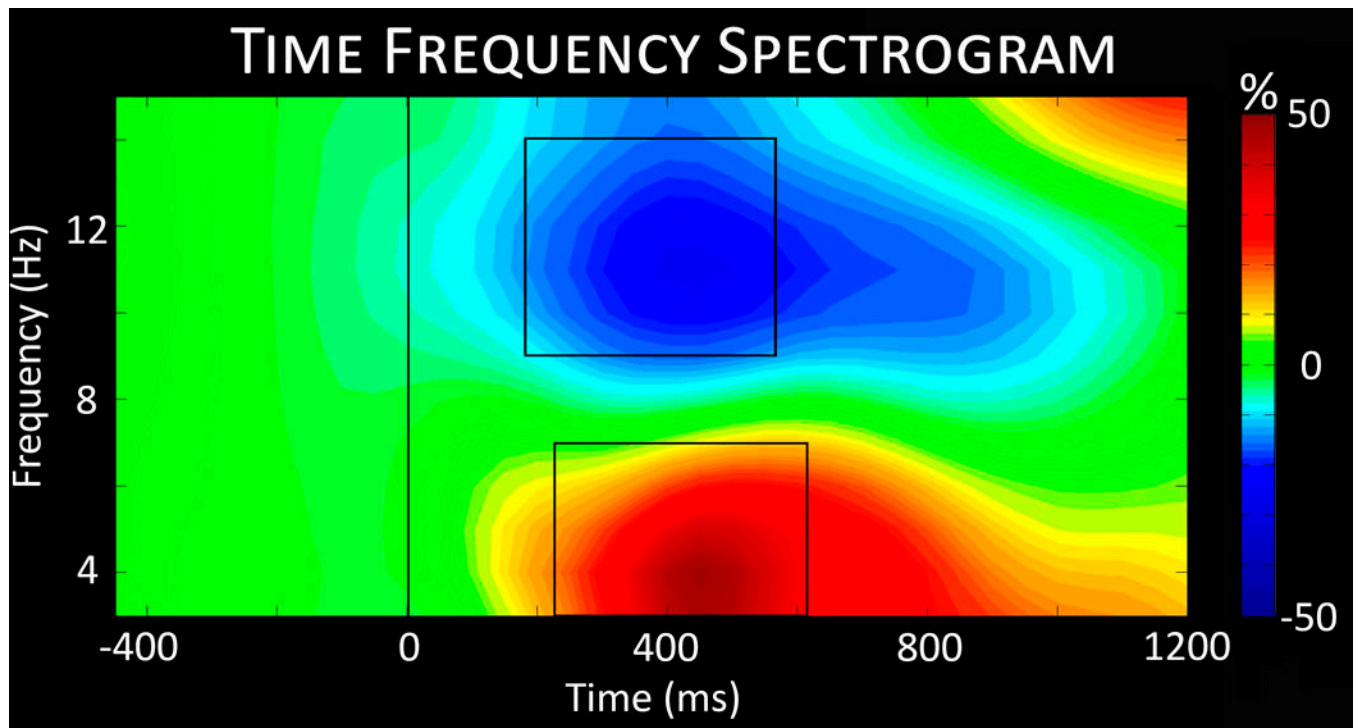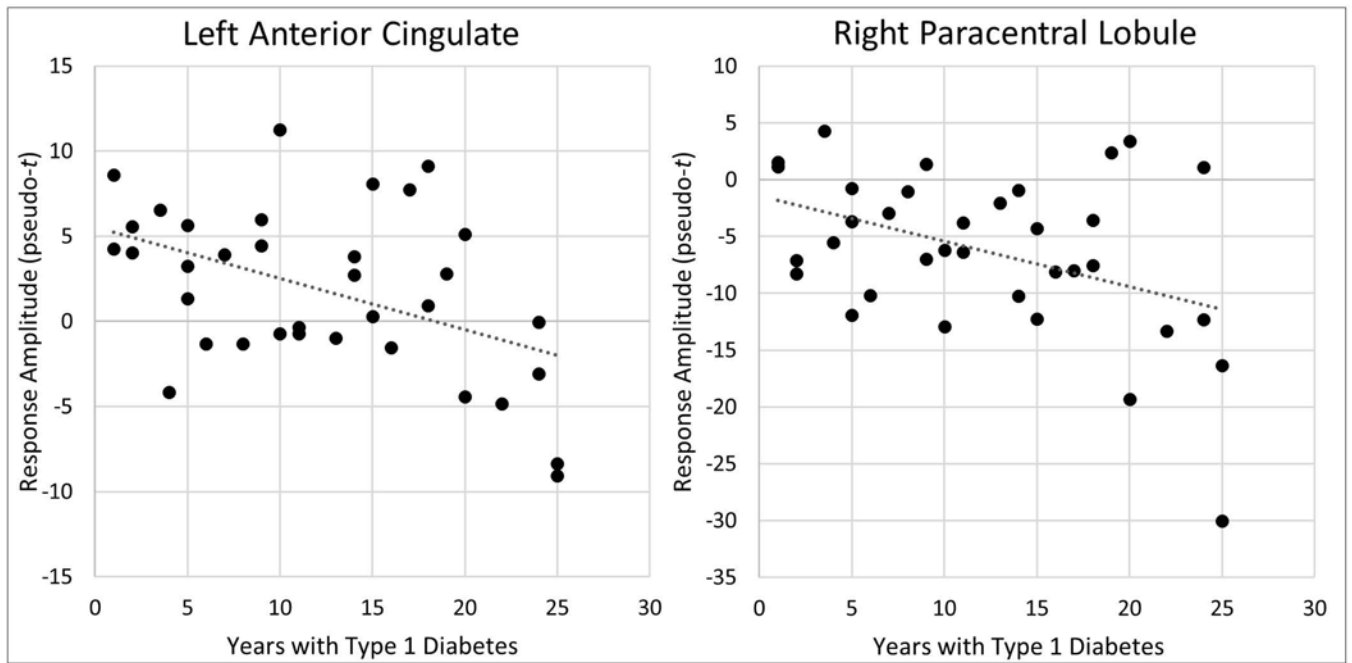
Figure 2.
Time-Frequency Spectrogram. The time-frequency analyses revealed significant oscillatory activity in theta and alpha frequency bands across both conditions (congruent and incongruent) and all participants. The significant windows ($p < 0.001$, corrected) were 9–14 Hz from 200–600 ms (alpha) and 3–7 Hz from 250–650 ms (theta).

Figure 3.
Group Differences in the Flanker Interference Effect. Significant group differences in alpha activity were found in the left anterior cingulate, right paracentral lobule, and left parietal regions, while significant theta differences were found in the left precentral gyrus. Controls exhibited stronger flanker interference responses in the left anterior cingulate, whereas responses were stronger in the patients with type 1 diabetes in all other regions. Data are shown thresholded at $p < 0.005$.

Figure 4.
Correlations with Disease Duration. Years with type 1 diabetes significantly correlated with overall alpha activity levels in the peak flanker interference voxel (peak voxel in Figure 3) of the left anterior cingulate and right paracentral lobule.

Table 1.

Mean Characteristics and Lab Results

Mean Characteristics and Lab Results	
	Type 1 Diabetes
Disease Duration	12.2 ± 7.4 years
Hypoglycemic Episodes per Week	3.02 ± 2.98 episodes
Glucose at Time of MEG Scan	142.66 ± 32.79 mg/dL
A1C	7.99 ± 1.48%
Creatinine	0.85 ± 0.14 mg/dL
GFR	60 mL/min/1.73m^2
AST	16.29 ± 8.76 U/L
ALT	14.91 ± 7.27 U/L
Albumin/Creatinine	8.0 ± 6.60 ugAL/mgCR
TSH	2.34 ± 1.70 mcIU/mL
Vitamin B12	512.97 ± 234.51 pg/mL

Values given in Means ± SD