Altered motor dynamics in type 1 diabetes modulate behavioral performance

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Type 1 diabetes (T1D) has been linked to alterations in both brain structure and function. However, the neural basis of the most commonly reported neuropsychological deficit in T1D, psychomotor speed, remains severely understudied. To begin to address this, the current study focuses on the neural dynamics underlying motor control using magnetoencephalographic (MEG) imaging. Briefly, 40 young adults with T1D who were clear of common comorbidities (e.g., vascular disease, retinopathy, etc.) and a demographically-matched group of 40 controls without T1D completed an arrow-based flanker movement task during MEG. The resulting signals were examined in the time-frequency domain and imaged using a beamforming approach, and then voxel time series were extracted from peak responses to evaluate the dynamics. The resulting time series were statistically examined for group and conditional effects using a rigorous permutation testing approach. Our primary hypothesis was that participants with T1D would have altered beta and gamma oscillatory dynamics within the primary motor cortex during movement, and that these alterations would reflect compensatory processing to maintain adequate performance. Our results indicated that the group with T1D had a significantly stronger post-movement beta rebound (PMBR) contralateral to movement compared to controls, and a smaller neural activity between conditions). In addition, a significant group-by-condition interaction was observed in the ipsilateral beta event-related desynchronization (bERD) and the ipsilateral PMBR. We also examined the relationship between oscillatory motor response amplitude and reaction time, finding a differential effect of the driving oscillatory responses on behavioral performance by group. Overall, our findings suggest compensatory activity in the motor cortices is detectable early in the disease in a relatively healthy sample of adults with T1D. Future studies are needed to examine how these subtle effects on neural activity in young, otherwise healthy patients affect outcomes in aging.
attention- and working memory-related tasks, involving widespread cortical regions from parieto-occipital to frontal cortices (Embury et al., 2018a; Embury et al., 2018b). These studies have further shown that participants with T1D tend to recruit task-relevant brain regions more strongly, and utilize contralateral homologue areas to maintain adequate task performance, which may suggest compensatory processing in T1D.

Although psychomotor speed is one of the most consistently reported neuropsychological deficits in T1D (Kodl and Seaquist, 2008; McCrimmon et al., 2012; Ryan et al., 2016), few studies have examined the neural basis of this impairment. One study found that greater activity in the inferior frontal, primary sensorimotor, thalamus and cuneus regions was associated with slower reaction times and chronic glycemic dysregulation (Hwang et al., 2016). A later study connected reduced psychomotor speed to significantly reduced resting state cerebral blood flow in the basal ganglia and superior frontal regions (Ryan et al., 2017). Finally, a recent structural MRI study also linked slower psychomotor speed with reduced gray matter volume in the putamen and thalamus (Nunley et al., 2017). Although these findings reveal some of the underlying brain aberrations in T1D, the neural dynamics of motor control have yet to be examined.

Previous normative studies of the oscillatory dynamics serving motor control have identified at least three critical oscillatory responses. Briefly, there is a significant decrease in beta activity (14–30 Hz) that begins several hundred milliseconds before movement and continues throughout movement execution, which has generally been termed the peri-movement beta event-related desynchronization (bERD). This response has been repeatedly tied to motor planning, with stronger responses in the motor cortex contralateral to the limb being moved (Cheyne et al., 2006; Engel and Fries, 2010; Heinrichs-Graham et al., 2018b; Heinrichs-Graham and Wilson, 2015; Pfurtscheller and Lopes da Silva, 1999; Wilson et al., 2014). Following completion of the movement response, there is an increase in activity in roughly the same beta frequency range, which has been called the post-movement beta rebound (PMBR). This response generally begins about 500 ms after movement termination and lasts for 1–2 s before dissipating to baseline levels. The PMBR response has been found across the sensorimotor network, and has been linked to inhibition and sensory feedback in motor cortices (Gaetz et al., 2010; Heinrichs-Graham et al., 2017a; Jurkiewicz et al., 2006; Wilson et al., 2014). Finally, there is a transient gamma event-related synchronization (ERS; 70–90 Hz) that generally coincides with movement onset and has been linked to the motor execution signal (Cheyne et al., 2008; Gaetz et al., 2011; Heinrichs-Graham et al., 2018a; Muthukumaraswamy, 2010; Nowak et al., 2018; Wilson et al., 2010). These responses have been characterized using a variety of motor control paradigms in healthy adults and youth (Cheyne et al., 2008; Gehringer et al., 2018; Heinrichs-Graham et al., 2016; Heinrichs-Graham et al., 2018a; Heinrichs-Graham et al., 2018b; Heinrichs-Graham and Wilson, 2015; Kaiser et al., 2001). Further, several studies have connected aberrations in these dynamics to various brain disorders that are known to include significant motor-related symptoms (Arpin et al., 2017; Hammond et al., 2007; Heinrichs-Graham et al., 2017b; Heinrichs-Graham et al., 2014; Kühn et al., 2009; Wilson et al., 2013; Wilson et al., 2011).

In this study, we used magnetoencephalography (MEG) to quantify the oscillatory dynamics serving motor control in adults with T1D as compared to a group of demographically-matched controls. To circumvent possible confounds associated with vascular disease, retinopathy, and other common comorbidities that are known to affect neurological function independent of diabetes, we focused on adults with T1D who had no major comorbidities or complications. All participants underwent MEG while completing an arrow-based task that required participants to perform a basic motor response according to the direction of a center arrow. The resulting responses were probed for between-group differences and for direct relationships with behavioral performance metrics. We hypothesized that adults with T1D would exhibit aberrant dynamics in the beta and gamma motor responses during movement, and that these dynamics would be predictive of motor performance.

2. Materials and methods

2.1. Participants

A group of 40 participants with T1D 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 (BMI), 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 with loss of consciousness > 5 min, (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 anti-depressants following a 24 h 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 µg/Al/mgCr in the previous 12 months, (2) hypertension (blood pressure > 130/85 mmHg), (3) kidney disease defined by GFR < 60 mL/min/1.73 m², (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 deficieny. In order to study the long-term effects of T1D on the brain in a more controlled manner, relative euglycemia in these participants was a prerequisite for study participation. Participants with T1D measured their blood glucose level using a point-of-care device prior to neuroimaging and cognitive task completion verifying their levels fell within the 70 to 200 mg/dL range. Participants who were mildly hypoglycemic (55 to 70 mg/dL) 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. Participants with blood glucose levels < 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. Written informed consent was obtained from each participant following the guidelines of the UNMCs Institutional Review Board, who approved the study protocol, in accordance with the Declaration of Helsinki.

2.2. Experimental paradigm

During the MEG session, participants were seated in a nonmagnetic chair and completed an arrow-based version of the Eriksen flanker task (Eriksen and Eriksen, 1974), which has been used in several previous normative studies in our lab (Heinrichs-Graham et al., 2018a; McDermott et al., 2018; McDermott et al., 2017). We utilized the flanker task in this study because a recent investigation found that the task elicited robust movement-related gamma activity in healthy adults (Heinrichs-Graham et al., 2018a). Participants initially fixated on a crosshair presented centrally, and after 1450–1550 ms this crosshair replaced by a row of five arrows for 2500 ms. 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 of the flaking arrows were categorized as incongruent. Each trial lasted ~4 s and each participant completed 200 trials; 100 incongruent and 100 congruent, with both arrow directions presented an equal number of times in each condition, in pseudorandomized
2.3. MEG methods and analyses

MEG acquisition and analysis methodology followed standardized pipelines consistent with MEG studies previously published by our group (Heinrichs-Graham et al., 2016, 2018a, 2017a, 2018b; Heinrichs-Graham and Graham, 2015, 2016; McDermott et al., 2017; Proskovec et al., 2018; Wiesman et al., 2017; Wilson et al., 2014). 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 a signal space separation method with a temporal extension (Taaul and Simola, 2006). Each participant’s MEG data were then coregistered with a template structural T1-weighted MRI volume using the scalp surface points. Importantly, this approach has been shown to yield very similar results to using each participant’s individual MRI (Holliday et al., 2003). Artifacts were rejected using an individually-adjusted fixed threshold method. Briefly, the distribution of amplitude and gradient values was computed across all trials in each participant, and trials containing the highest values relative to the full distribution were rejected by selecting a threshold that excluded extreme values. These thresholds were determined individually because MEG signal amplitude is strongly affected by head size, the head’s proximity to the MEG sensors during scanning, and other parameters that vary by participant.

Following artifact rejection, the continuous MEG time series was divided into 3.25 s epochs, with the baseline defined as the −1.65 to −1.00 s window before the motor response (0.0 s). Artifact-free epochs were then transformed into the time-frequency domain using complex demodulation (2.0 Hz and 25 ms), 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 within the −1.65 to 1.00 s time windows. 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 performance period. Each data point in the spectrogram was initially examined using paired-samples t-tests of each active bin compared to the mean baseline (for that frequency bin), and then corrected for multiple comparisons using a false discovery rate method. Data were then transformed into the time-frequency domain to calculate source power for the entire brain volume.

Significant time-frequency windows were imaged at a 4.0 x 4.0 x 4.0 mm resolution using an extension of the dynamic imaging of coherent sources (DICS) beamformer (Gross et al., 2001; Hillebrand et al., 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 preprocessing, sensor and 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 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 average maps (across groups and conditions) for each of the motor-related time-frequency components: bERD, PMBR, and the gamma ERS. From these average maps, the peak of each response was identified and the pseudo-t value for each participant at the specific peak was extracted for further analyses. In addition, the neural time series corresponding to this voxel was computed using a two-orientation orthogonal model for incongruent, congruent, and combined conditions (all incongruent and congruent trials). The vector-sum of the two orientations per voxel was then computed in each participant, and this was used to compute the time series difference between the conditions (i.e., incongruent minus congruent). With these time series, 2 × 2 mixed-model ANOVAs with group (T1D, control) as a between-subjects factor and condition (congruent, incongruent) as within-subjects factor were computed for the imaged time window of each response using a permutation toolbox implemented in MATLAB, with an alpha level of 0.05 and 1000 permutations for each model.

To relate these motor responses directly to behavioral outcomes, we computed regressions of response amplitude per peak (e.g. contralateral bERD peak, ipsilateral bERD peak) on reaction time per group using the peak pseudo-t value from the beamformed images of the combined conditions to determine spectrally-specific predictors of behavior. Note that we focused on the neural responses centered on reaction time (bERD and gamma ERS), as the latter post-movement responses would be less likely to have a role in determining performance. Regressions were computed using SPSS (Version 25).

3. Results

3.1. Demographic, behavioral and disease status results

The group with T1D (N = 39; 15 females; mean age = 25.6 years, SD = 5.0; one excluded for artificial MEG data) and the control group (N = 40; 18 females; mean age = 25.6 years, SD = 3.8) did not differ in age (t(77) = −0.04, p = .972), education level (t(77) = −1.67, p = .099; T1D: mean = 16.4, SD = 1.8, controls: mean = 17.0, SD = 1.3), BMI (t(77) = 0.03, p = .977; T1D: mean = 25.2, SD = 4.0, controls: mean = 25.1, SD = 5.1), ethnicity (X^2 (3, N = 79) = 6.63, p = .085), or handedness (X^2 (1, N = 79) = 0.86, p = .352). Participants with T1D had a mean disease duration of 12.0 years (SD = 7.6 years), and a mean glycated hemoglobin (HbA1c) of 7.97% (SD = 1.46%; 64.0 mmol/mol, SD = 16.0 mmol/mol).

Participants performed the task well, with an accuracy of 97.80% (SD = 4.80%), a mean reaction time of 589.8 ms (SD = 122.06 ms), and an average blinker event-related desynchronization (i.e., difference in reaction time between incongruent and congruent) of 43.81 ms (SD = 30.16 ms). There were no group-wise differences in these behavioral measures, with all ps > 0.380. Considering the ease of the task paradigm, equivalent task performance across groups was expected, particularly since the participants with T1D were otherwise healthy. Such equivalent performance allows for a clearer comparison of the neural data, as it ensured that any group differences in the neural data were not attributable to performance disparities between controls and those with T1D.

3.2. MEG sensor and anatomical level results

The sensor-level time-frequency data were examined using paired t-tests computed across all participants and conditions, followed by nonparametric testing to correct for multiple comparisons. This analysis revealed a significant beta event-related desynchronization from −250 to 100 ms in the 18−26 Hz range, a post-movement beta rebound from 400 to 1000 ms in the 14−24 Hz range, and a gamma response from −100 to 100 ms in the 68−82 Hz range (all ps < 0.001; Fig. 1a). Significant time-frequency windows derived from sensor level analyses were entered into beamformer source reconstruction analyses to project the data into anatomical space. Average beamformer maps of the responses revealed bilateral motor cortex beta activity (bERD and PMBR) and gamma activity in the contralateral motor cortex (Fig. 1b). The time series corresponding to the peak voxel of each response was...
interaction in the contralateral PMBR response. In contrast, a sig-
ificant across both groups. There was no signi-
\[\text{(38)} = 2.54, \text{p} = .016, \text{respectively. Similar to the controls, the gamma} \]
\[\text{ERS response in controls,} \quad \beta = -0.48, t(39) = -3.32, p = .002, \text{such that greater gamma ampli-} \]
\[\text{tude corresponded to a faster reaction time (Fig. 3). The bilateral bERD} \]
\[\text{response (50–100 ms;} \quad p < .001; \text{see Fig. 2), whereby partici-} \]
\[\text{pants with T1D had stronger responses than controls regardless of} \]
\[\text{condition. A significant main effect of condition was also found in the} \]
\[\text{ipsilateral PMBR. No significant clusters survived permutation testing} \]
\[\text{for the interaction or main effects of the gamma ERS response.} \]

### 3.3. Time series results

For each of the time series, \(t\)-tests were run within the imaged time window using a permutation toolbox, with an alpha level of 0.05 and 1000 permutations for each test run. These analyses revealed a group by condition interaction in the ipsilateral bERD response (50–100 ms; \(p < .001\); see Fig. 2), whereby controls had a larger difference between the two conditions relative to participants with T1D. In other words, a larger neural flanker effect was found in this region. No significant clusters survived permutation testing for the condition or group main effects in the ipsilateral bERD response, and neither main effects nor interactions were significant for the contralateral bERD. As per the PMBR, a significant group main effect was found in the contralateral PMBR response (425–625 ms, \(p < .001\); see Fig. 2), whereby participants with T1D had stronger responses than controls regardless of condition. A significant main effect of condition was also found in the contralateral PMBR (400–475 ms, \(p < .001\), not shown), indicating stronger responses in the incongruent relative to the congruent condition across both groups. There was no significant group by condition interaction in the contralateral PMBR response. In contrast, a signif-
ificant group by condition interaction (625–675 ms, \(p < .001\); 850–875, \(p = .044\); see Fig. 2) was observed in the ipsilateral PMBR, whereby the difference between conditions was greater in controls than in participants with T1D, similar to the pattern of activity found in the ipsilateral bERD response. No significant main effects were found in the ipsilateral PMBR. No significant clusters survived permutation testing for the interaction or main effects of the gamma ERS response.

### 3.4. Neural predictors of behavioral outcomes

To examine the predictive value of these neural responses on behavioral outcomes, we computed regression models with each of the bilateral bERD and gamma ERS peak pseudo-\(t\) values from the beamformer images to determine which of these frequency-specific responses predicted reaction time in each group (controls: \(R^2 = 0.313, F(3,36) = 5.48, p = .003\); T1D: \(R^2 = 0.286, F(3,35) = 4.66, p = .008\)). These regressions revealed that gamma was the driving predictor of reaction time above and beyond bilateral bERD responses in controls, \(\beta = -0.48, t(39) = -3.32, p = .002\), such that greater gamma amplitude corresponded to a faster reaction time (Fig. 3). The bilateral bERD responses were not significant predictors of reaction time above and beyond each other or the gamma ERS response in controls: contralateral, \(\beta = 0.22, t(39) = 1.39, p = .173\); ipsilateral, \(\beta = -0.03, t(39) = -0.20, p = .843\). In the participants with T1D, the gamma ERS and the ipsilateral bERD responses were the driving predictors of behavior, \(\beta = -0.42, t(38) = -2.95, p = .006\), and \(\beta = 0.40, t(38) = 2.54, p = .016\), respectively. Similar to the controls, the gamma ERS response amplitude significantly predicted behavioral performance, such that as the amplitude of the response increased, reaction times were faster. Additionally, in this group the ipsilateral bERD was also a significant predictor of behavioral performance, whereby increased recruitment led to faster reaction times, suggesting an increased
bilateral bERD response might be advantageous in the participants with T1D. The contralateral bERD was not a significant predictor above and beyond the ipsilateral bERD and gamma ERS responses in this model, $\beta = -0.22$, $t(38) = -1.36$, $p = .183$.

4. Discussion

Neuropsychological studies have repeatedly shown reductions in psychomotor speed in patients with T1D, but neural dynamics that may underlie such aberrations are poorly understood. Herein, we found frequency specific group effects in bilateral motor cortices during a simple movement task. Specifically, the bERD and PMBR showed a greater flanker interference effect—or difference in neural activity by condition—in controls over participants with T1D in the ipsilateral, but not the contralateral motor cortex, indicating possible compensatory recruitment of ipsilateral homologue cortices in executing the task goals. Further analysis of the PMBR response also revealed a greater overall recruitment in participants with T1D across both conditions in the contralateral motor cortex. These differences in the beta responses are juxtaposed against no differences in the gamma band, indicating frequency specificity in the effects of T1D on the brain responses serving motor control. The implications of these findings are discussed further below.

One of our most interesting findings was that neural responses directly tied with motor execution were found to influence behavioral performance differentially in the two groups. Essentially, while the gamma ERS was the sole predictor of reaction time in control participants, both the gamma ERS and ipsilateral bERD were predictors of...
found conditional effects in the bERD during performance of the flanker task (Heinrichs-Graham and Wilson, 2015) similar to our findings in the control group. Thus, it is possible that diminished conditional differences in T1D may reflect the involvement of compensatory mechanisms. This process is evident particularly in the PMBR response, where significantly higher amplitude differences across conditions in participants with T1D relative to controls may reflect greater regional recruitment to complete the task. Further supporting this compensation hypothesis was that more bilateral recruitment (i.e. increased ipsilateral bERD activity) predicted better behavioral performance in the T1D group, a finding similar to those reported in the aging literature (Bernard and Seidler, 2012; Cabeza et al., 2002). Taken together, aberrant motor dynamics were apparent in adults with T1D. The alterations in these responses were frequency and oscillatory response specific, and drove behavioral performance differentially in T1D compared to matched healthy controls.

Considering the strong relationship between these brain responses and behavior, alterations in these dynamics have clear implications on disease care and outcomes. A wide variety of daily tasks require efficiency and speed in motor control and execution, including complex tasks like driving. While the current study ensured participants with T1D maintained euglycemia for the study period, previous studies highlight the compounding impact of glycemic dysregulation on cognitive processes, causing more pronounced deficits during these glycemic deviations and likely accumulating further impairment over time in these conditions (Gold et al., 1995; Grober et al., 2011; Hansen et al., 2017; Hwang et al., 2016). Future studies should examine the effects of glycemic dysregulation on motor dynamics in the brain. Understanding the underlying neurophysiological processes affected in the disease may enhance awareness and lead to insights on prevention of these complications across the lifespan.

Before closing, a few minor limitations should be noted in the current study. Different task goals and prescribed movements are known to elicit slightly different dynamics in these responses (Cheyne et al., 2008; Tzagarakis et al., 2010), and the motor dynamics examined in the current study were derived from a single paradigm and future studies should seek to examine these dynamics in a variety of task paradigms to fully characterize responses in T1D across a range of behavioral goals. Additionally, participants with T1D were otherwise healthy, since the presence of major comorbidities or complications was exclusionary. More studies are needed to expand the current findings to adults with T1D who have additional complications. However, finding these differences in an otherwise healthy T1D group strongly indicates that the condition itself, in the absence of other potentially confounding variables, directly impacts motor control components in the brain, thereby affecting behavioral outcomes. In conclusion, we found frequency and response specific alterations in adults with T1D, and these aberrations differentially drove behavioral performance in this group compared to healthy adults. These important findings highlight the need for further studies into the effects of T1D on cognitive and motor outcomes and the underlying dynamic responses in the brain.

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**Declaration of Competing Interest**

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