IRB Title: Brain Abnormalities in Type 1 Diabetes: Magnetoencephalographic Evidence
Proposal Title: Attention Processes in Type 1 Diabetes: a MEG Study of Aging with Diabetes
Christine Embury

PROJECT DESCRIPTION
The objective of the proposed study is to investigate the effects of type 1 diabetes on the neural dynamics underlying attention in otherwise healthy older adults.

Attention is a broad cognitive process, underlying many higher order cognitive functions (e.g. working memory, executive functioning, etc.), and is essential for daily living. Many paradigms have been employed to measure attention including the classic Eriksen flanker task (Eriksen & Eriksen, 1974) and the Posner task (Posner, 1980), among others. Recent studies of the underlying neurophysiological responses involved in attention processing implicate widespread regional recruitment, including frontal, parietal and occipital regions (Clark, Squire, Merrikhi, & Noudoost, 2015; McDermott, Wiesman, Proskovec, Heinrichs-Graham, & Wilson, 2017; Petersen & Posner, 2012; Wiesman, Heinrichs-Graham, Proskovec, McDermott, & Wilson, 2017). Interestingly, impairments in attention among other essential cognitive functions have been found in adults with type 1 diabetes (for review, see McCrimmon, Ryan, & Frier, 2012).

Previous neuroimaging studies of adults with type 1 diabetes have found abnormalities in several measures of brain structure and function (Bolo et al., 2011; Gallardo-Moreno, Gonzalez-Garrido, Gudayol-Ferre, & Guardia-Olmos, 2015; Hwang et al., 2016; van Duinkerken et al., 2009; Wessels et al., 2007) likely due to prolonged glycemic dysregulation and comorbid conditions, although many studies in this patient population have used methodologies (i.e. functional magnetic resonance imaging or fMRI) that may be confounded by comorbidities common in this population, including micro- and macro-vascular damage. Briefly, these methods rely on secondary measures of brain function (i.e., blood flow) and are temporally slow, measuring once every few seconds. While these approaches have provided a glimpse into the cognitive deficits associated with type 1 diabetes, a more precise characterization of the underlying mechanisms leading to these decrements has yet to be elucidated. Magnetoencephalography (MEG) is an emerging noninvasive neuroimaging technique that directly measures neural activity through detecting the magnetic fields that naturally emanate from the electrical activity of active brain cells (Figure 1). It’s excellent temporal resolution (in milliseconds) and spatial resolution (in millimeters) measures more closely the dynamics happening within the brain in real time. Considering these characteristics of MEG, this methodology is highly sensitive to the neurophysiological changes incurred by type 1 diabetes disease processes, and these changes can be further related to measures of disease control.

Our preliminary MEG studies of young adults with type 1 diabetes have revealed compensatory mechanisms at play in measures of working memory (Embury et al., under review) and attention (Embury et al., manuscript in progress). In addition, the levels of compensatory activity have been found to relate directly to level of glycemic control (HbA1C) and duration of disease (Embury et al., under review; see Figure 2). Since these patients already must compensate for the impairments incurred by chronic glycemic dysregulation that occurs with type 1 diabetes at such an early life stage, I posit that a steeper aging curve is present in these individuals. Furthermore, with the chronic nature of the disease and the increased burden of comorbidities that is common with increased disease duration, the mechanisms supporting compensation will be overwhelmed and cognitive functioning will be highly affected over the
aging process. By studying the underlying neurophysiology of aging with diabetes, some light may be shed on how diabetes can lead to worse cognitive outcomes in aging, including dementia, and may guide future interventions in this patient population.

**CONCEPTUAL IMPORTANCE**
The characterization of the pathophysiology of type 1 diabetes in the aging brain is important in understanding and illuminating the links between the disease and poor cognitive outcomes seen in the clinic. Neurophysiological responses are hypothesized to resemble an accelerated aging phenotype, particularly in conditions of dysglycemia. This first step in determining the neural dynamics underlying specific cognitive deficits in aging individuals with type 1 diabetes is a stepping stone to developing better approaches to treating the disease process. These findings may influence therapeutic approaches and may potentially lead to better cognitive and health outcomes in patients with type 1 diabetes as they age.

**PRODUCT OF THE PROPOSED WORK**
Results from the proposed work will be submitted for publication in a peer-reviewed journal. Previous studies of attentional control from our lab have been published in influential neuroimaging journals including *NeuroImage* (McDermott et al., 2017) and *Human Brain Mapping* (Wiesman et al., 2017). More recently, my work with young adults with type 1 diabetes is under review at the high impact journal *Diabetes*. In addition to manuscripts, results will also be presented at local and international conferences, including the *Organization for Human Brain Mapping Annual Conference* and the *American Diabetes Association’s Annual Scientific Sessions*.

**CONTRIBUTIONS TO GRADUATE STUDIES**
The proposed study is vital to my thesis. My thesis work focuses on the effects of type 1 diabetes on basic and higher order cognitive functioning in the process of aging. My master’s thesis will focus on working memory and attentional components in aging populations with type 1 diabetes. My dissertation work will build from this platform to include those with type 2 diabetes as well. Thus, the proposed project will provide a solid basis for my degrees and long-term research goals.

**METHODOLOGY**
Forty-eight older adults (24 with and 24 without type 1 diabetes; ages 55-75) will be recruited from the Diabetes Clinic at UNMC and from the greater Omaha area, with patient and control groups matched on sex, age, ethnicity, education and body mass index (BMI). Exclusionary criteria will include active substance use or dependence, uncontrolled blood pressure (hypertension), BMI greater than 30, presence of known micro- or macro-vascular disease (urinary albumin to creatinine ratio greater than 30), kidney or liver disease, an episode of severe hypoglycemia requiring 3rd party assistance for resolution within the past 3 months, active hypothyroidism or B12 deficiency, severe psychiatric or neurological disease, history of serious head trauma, pregnancy, and the MEG laboratory’s standard exclusion criteria (magnetic/metallic implants). Full informed consent in compliance with UNMC’s IRB guidelines will be obtained from all participants before beginning study procedures. Continuous glucose monitoring (CGM) will be used to characterize participants’ glycemic control over the two weeks prior to neuroimaging. Participants will be blinded to the output of the CGM (due to the nature of the device) during these two weeks, so as not to influence their behavior. Outputs of this device will be used to correlate glycemic...
control measurements to neurophysiological activity. Prior to any testing, normoglycemia will be established in the patient group.

During the MEG visit, both patient and control groups will undergo neuropsychological testing using the Mini-International Neuropsychiatric Interview (MINI) and the NIH toolbox prior to neuroimaging. During the MEG session, all participants will complete cognitive tasks, including the Eriksen Flanker task. For this task, participants will be shown a centrally presented fixation cross followed by a set of five arrows (Figure 3). Participants will be instructed to respond by button press indicating the direction of the middle (target) arrow while ignoring the flanking arrows. The target arrow direction will be equally presented in the same direction (congruent) and in the opposite direction (incongruent) as the flanking arrows (100 trials per condition, 200 trials total; 14 min total run time). MEG data will be processed and analyzed using standard pipelines (McDermott et al., 2017; Wiesman et al., 2017). Significant relationships between neural activity, behavioral performance, and clinical measures of disease will be investigated using correlations. Neural activity differences between groups and conditions will be examined using the mixed model ANOVA framework within SPM12.

POTENTIAL LIMITATIONS
As we are examining older adults with type 1 diabetes who are otherwise healthy, data must be carefully interpreted in generalizing to the wider population of those with type 1 diabetes. Essentially, many experience common comorbidities with increasing disease duration, and our otherwise healthy adults may not reflect the amount of deficits found in the population as a whole. However, by limiting our current inquiry to older adults with type 1 diabetes without major comorbidities, we may make stronger conclusions about the role that type 1 diabetes directly exerts on the cognitive aging process. Future studies should also delve into the influence of known comorbidities on cognitive outcomes in this age range to fully characterize the general population of older adults with type 1 diabetes.

TIMELINE
March-May Recruitment and Data Collection
May-August Data Analyses
August-December Manuscript and Presentation Preparation

STUDENT AND MENTOR ROLES
I will be developing the research protocol, conducting data collection and analyses for the proposed study. I will also head preparation of manuscripts for publication and abstracts/posters for local and international conferences. My GRACA mentor, Dr. Janelle Beadle, will be actively involved in the critical review of my research protocol and provide guidance during write-up of results. Dr. Beadle has significant experience conducting research in the cognitive neuroscience of aging field, and thus will provide mentorship in the interpretation of my data in the context of these theories.

PREVIOUS FUSE FUNDING
I have previously received FUSE grant funding ($2000; Fall 2011) to complete my undergraduate thesis on “Dog Therapy as a Stress Buffer in an Induced Stress Event,” under the direction of Dr. Rosemary Strasser, my undergraduate advisor. I was able to present this work at local and regional conferences. I used this funding to complete the research required for completion of my B.S. degree. My current work uses different mechanisms (i.e. neuroimaging) to study human behavior and cognition, this time in the context of aging and disease states. I hope to continue this line of inquiry throughout my research career, particularly as relates to similar disease states.
BUDGET JUSTIFICATION

This project will not be fully funded through this summer grant, as costs associated with MEG scanner time will be covered under the lab’s existing funding. However, this grant will provide funding towards the completion of this work through covering participant stipends and purchasing the continuous glucose monitoring device and most sensors for precise characterization of glycemic control. Funding this project will offer significant support toward my thesis work, which I project to be completed by fall of 2019. This will ensure timely completion of my master’s degree and allow me to progress toward the Ph.D. portion of my program.

<table>
<thead>
<tr>
<th>Expense Category</th>
<th>Description</th>
<th>Amount Requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Stipend</td>
<td>Participants will be reimbursed for time and travel (e.g. gas, parking) for participation in our study. 48 participants x $50 reimbursement</td>
<td>$2400</td>
</tr>
<tr>
<td>Continuous Glucose Monitoring Device</td>
<td>Clinical measurements will be used for correlating with neurophysiological data to discern significant functional activity directly related to glycemic control. Freestyle Libre Pro Device = $65 Freestyle Libre Pro Sensors = $60 x 48 = $2880</td>
<td>$2600</td>
</tr>
</tbody>
</table>
REFERENCES


February 11, 2018

Office of Research and Creative Activity
6001 Dodge Street
Omaha, NE 68182

Dear Members of the Review Panel,

I enthusiastically support Ms. Christine Embury’s GRACA application. I have been impressed with her progress throughout the first year and a half of her graduate career, and see great potential ahead. Christine is a graduate research assistant within the Center for Magnetoencephalography (MEG) under the direction of Dr. Tony Wilson. I have gotten to know Christine through my role as a close collaborator with Dr. Wilson and his Center.

Through the development of Christine’s application, I have become more familiar with her graduate research goals. She plans to build upon her first year research projects, in which she and Dr. Wilson have investigated the effects type 1 diabetes has on neurophysiological responses in young adults while engaged in challenging cognitive tasks. From this line of inquiry, Christine developed her own research questions and I have been impressed with her drive to contribute novel work to the body of cognitive neuroscience literature. Thus, when I was approached to be her GRACA mentor, I was pleased to have the opportunity to contribute to her project in the form of mentoring in the domain of the cognitive neuroscience of aging. I will provide support in interpretation of the results in the context of the cognitive neuroscience of aging field, and help with providing feedback on her manuscript.

Christine designed her project and Dr. Wilson and myself have reviewed the project and its aims. Her timeline is feasible for successful completion of the project. Furthermore, her budget allows for realistic completion of her project and includes participant payments and purchase of glucose monitoring devices. The costs of the MEG imaging will be supplemented by her primary mentor Dr. Wilson. The proposed GRACA project is novel in that it will be the first to use this methodology of neuroimaging (MEG) in a population of older adults with type 1 diabetes, enabling the examination of the effects of the disease process on aging in cognition. She has already demonstrated progress in this research area as her publication on younger adults with type 1 diabetes is already in an advanced stage of peer review for publication.

Christine has already demonstrated her dedication to this important research area, and how this project fits into her long term academic goals. The proposed GRACA is vital to the timely completion of her thesis and progression toward Ph.D. candidacy. I strongly support Christine’s application for this GRACA award.

Sincerely,

Janelle Beadle, PhD
Assistant Professor
Department of Gerontology
University of Nebraska at Omaha
jbeadle@unomaha.edu