Continuous theta rhythm during spatial working memory task in rodent models of streptozotocin-induced type 2 diabetes

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Introduction

Alzheimer's disease is a neurodegenerative disorder that leads to memory loss thought to be due to neuropathological symptoms such as the buildup of beta amyloid plaques (Ab) and neurofibrillary tangles (NFT). The etiology of Alzheimer's is still unknown; however, potential risk factors such as diabetes may lead to its development. The most common form of diabetes is type 2 diabetes known for persistent insulin resistance leading to a state of hyperglycemia. Insulin resistance has been shown to affect cognitive abilities such as learning, memory and also alters synaptic plasticity. Neural connections between the hippocampus (HC) and anterior cingulate cortex (ACC) are known to be very important for learning and memory and are highly plastic, making them an intriguing target that could be altered by hyperglycemia. We hypothesize that hyperglycemic rodents will exhibit spatial memory deficits that may be associated with cognitively linked interactions between the HC and ACC.

Methods

Subjects: Four male Long-Evans Rats (450 – 600 g) were separated into control and experimental groups.

- **Drug Treatment:** Minimal doses of streptozotocin (STZ), which is toxic to insulin producing beta cells, were given for 9-10 weeks.

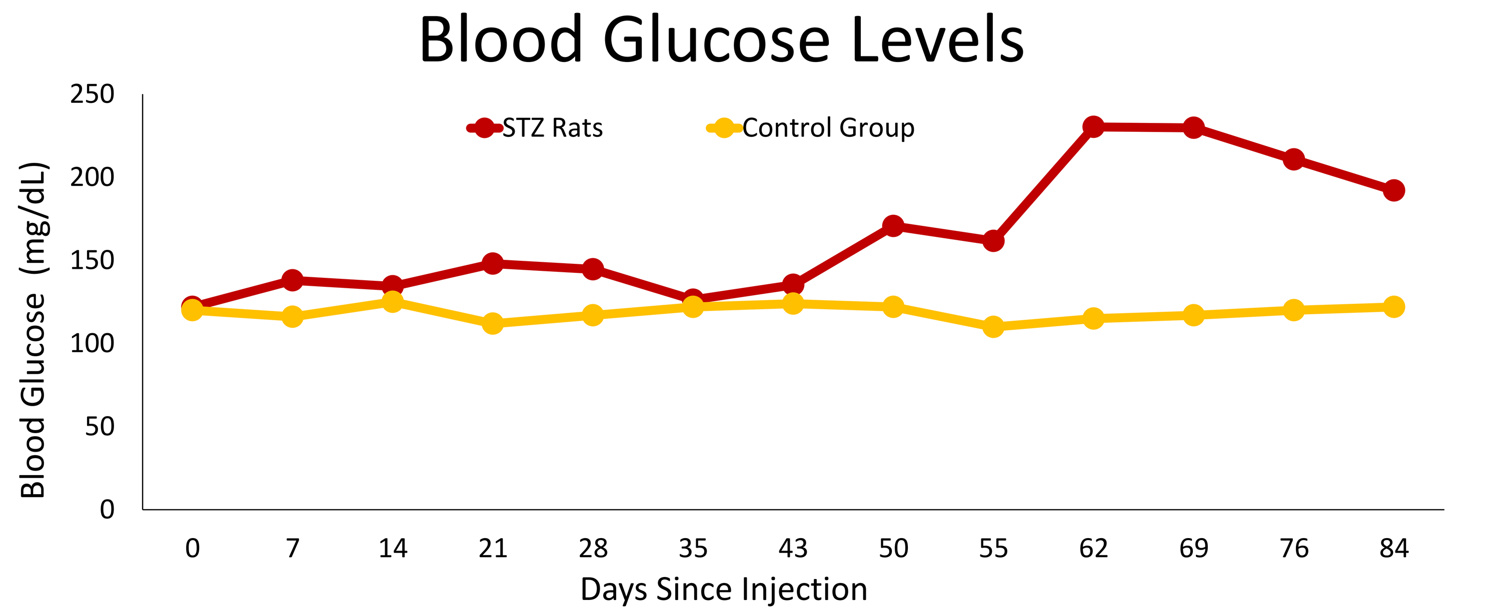
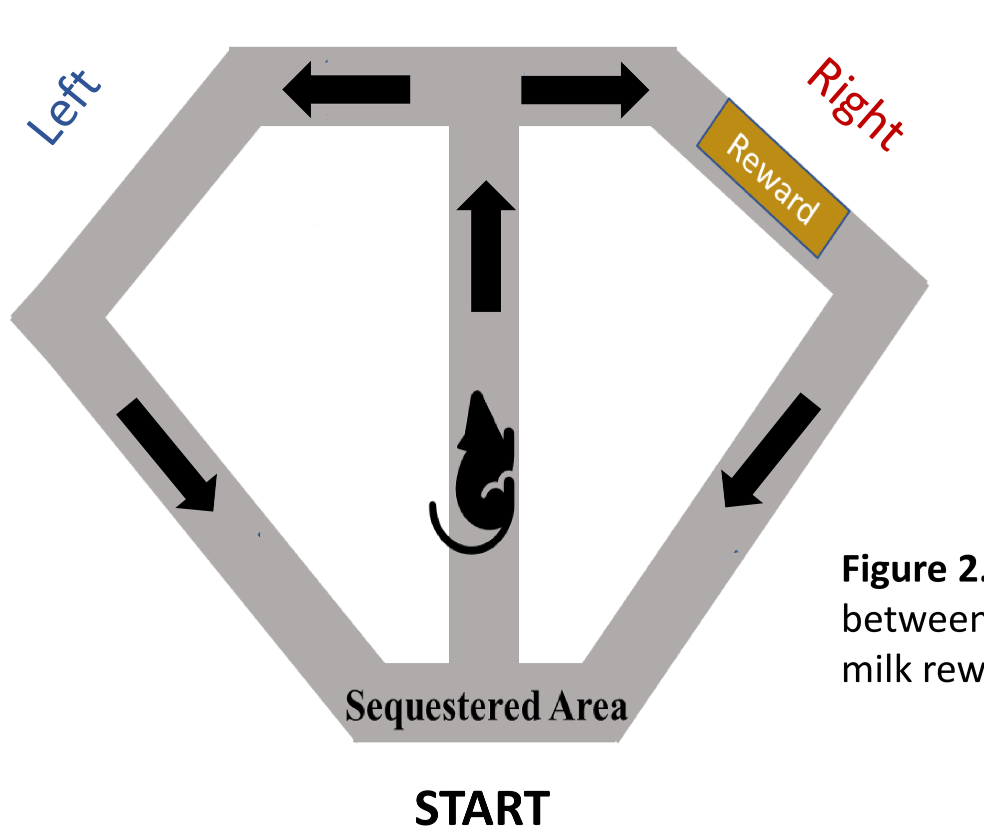


Figure 1. Blood glucose levels across injection timeline: Glucose level of STZ rats reached an average of 230 mg/dL. Control rats maintained a glucose level of 110-124 mg/dL.

Delayed alternation on a T-maze



- **Delayed alternation:** We utilized a spatial working memory task known as delayed alternation (T-maze) to test cognitive impairments.

Figure 2. The rat must alternate between trials to receive chocolate milk reward.

- **Surgery:** Rodents were implanted with a cranial hyperdrive targeting the hippocampus (HC) and anterior cingulate cortex (ACC).
- **LFP Recordings:** We used Open Ephys open source data acquisition software to record neural activity in HC and ACC of rodents during working memory task.

Results

- **Behavior:** We found significant differences between control and experimental rats in working memory accuracy.

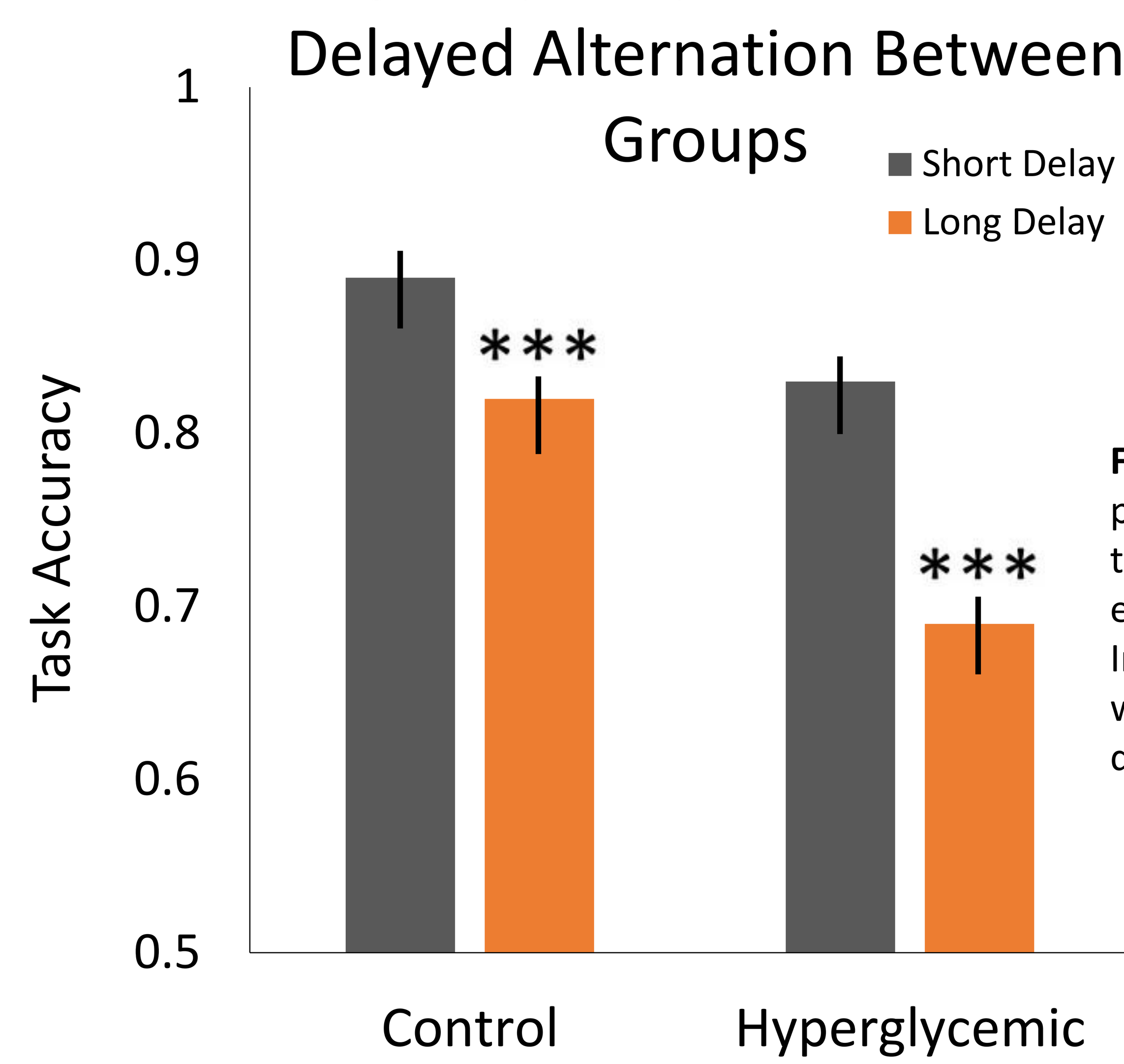


Figure 3. Control rats averaged at 82 percent accuracy for delay greater than 10sec. This fell dramatically in experimental rats to 60 percent. Importantly, no significant difference was found between rats with a short delay period of 1sec.

- **Theta/Delta Ratio:** We measured EEG recordings from the HC and ACC during task performance and found that hyperglycemic rats had nearly continuous theta rhythm during the 30-minute session. Control rats however, displayed normal transitions between theta and lower frequency delta.

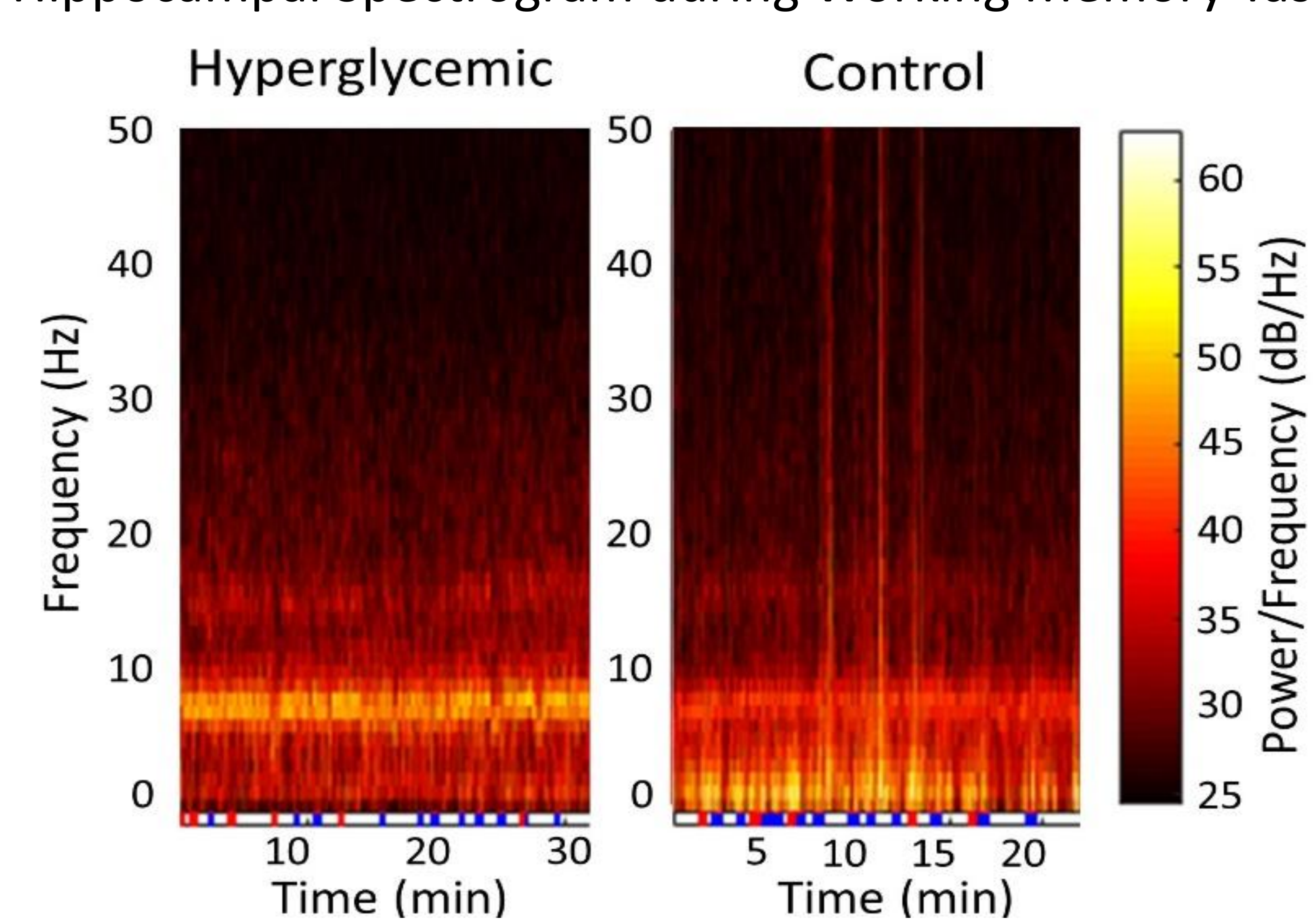


Figure 4. Hyperglycemic rodents displayed high continuous theta (5-12Hz) activity with little low frequency of delta (1-3Hz). The right shows control rat session with transitions of strong theta and strong delta periods. In the left plot a clear light color band near 8Hz theta and little low frequency of delta are present.

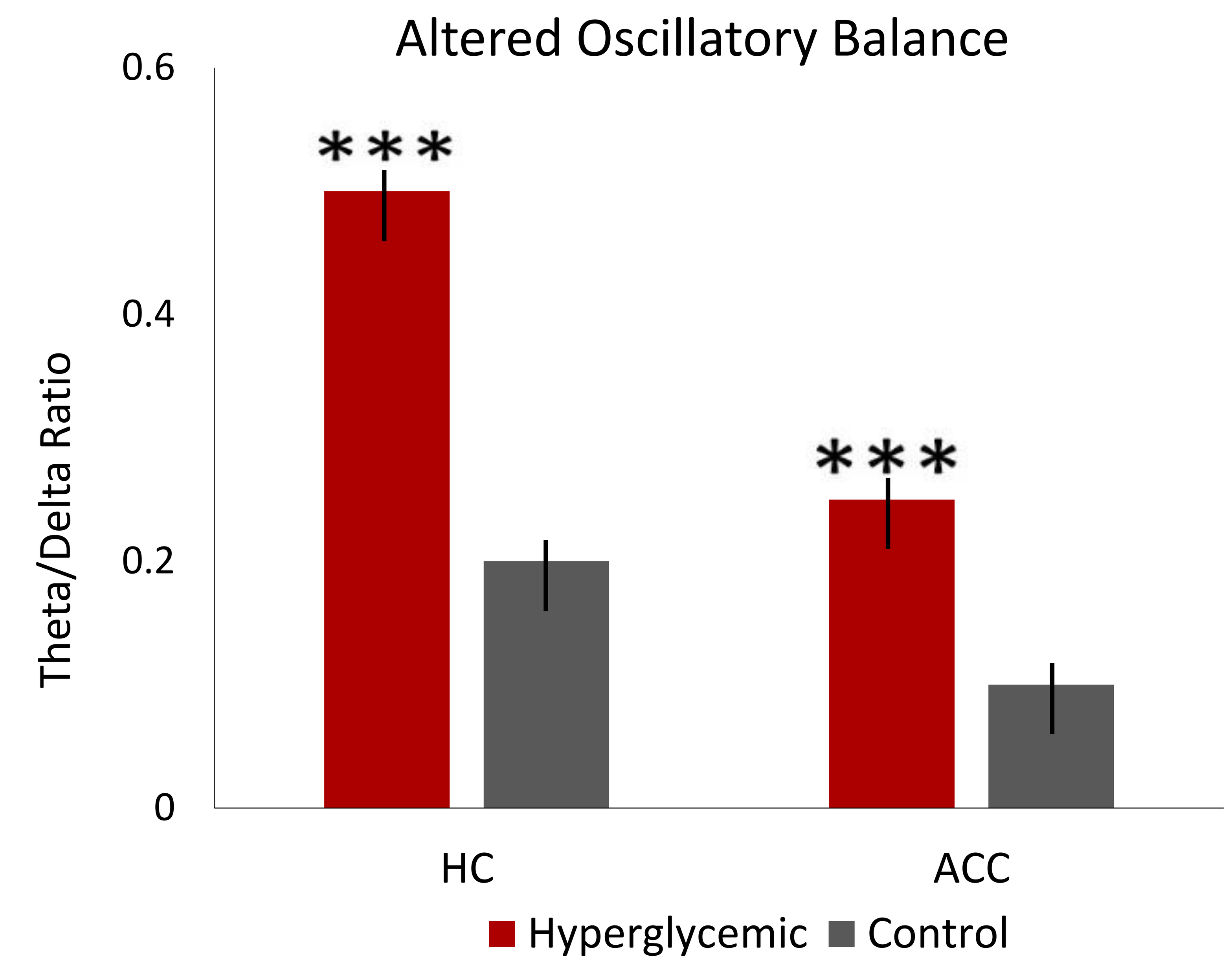


Figure 5. HC and ACC ratios increased in hyperglycemic rats. Controls had a ratio of 0.21 for HC leads, indicating that the HC spent 20% of the time in a strong theta state than in a strong delta state. In STZ rats this went up to 0.51 ratio. Indicating an abnormally high theta ratio of 50% than high delta. Similar increase in ACC, suggesting that effects might be widespread.

Conclusion

- The delay alternation task places strong working memory demands on subjects which may be compromised by a hyperglycemic state.
- These results show that hyperglycemia leads to changes along a circuit critical for learning and memory.
- Neural connectivity may be altered due to a change in frequency activity between the HC and ACC due to diabetes, which is a risk factor in the development of AD impairments.

Acknowledgements

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