Investigating Changes in Activity and Circadian Rhythm in a *Drosophila* Model of Frontotemporal Dementia

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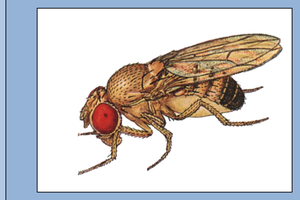
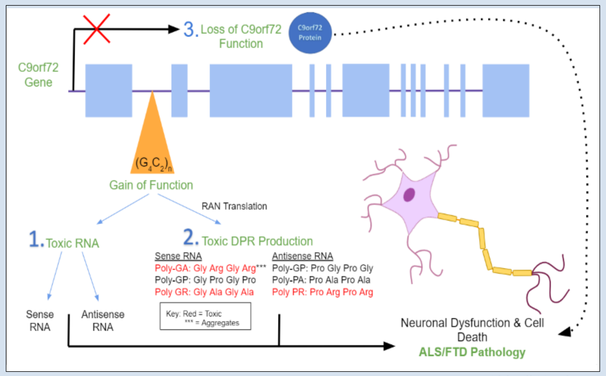


Abstract

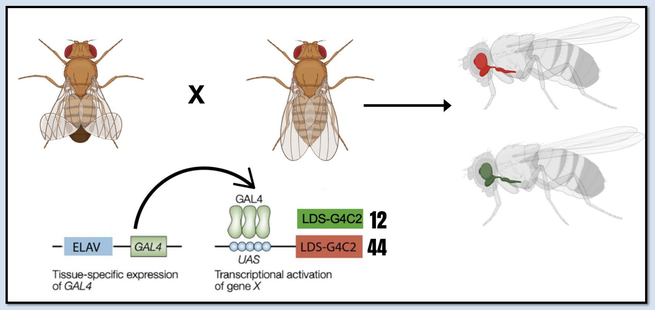
Frontotemporal dementia (FTD) is a neurodegenerative disorder that affects behavior, personality, motor activity, speech, cognition, and sleeping patterns. This disease has many molecular etiologies, but the most common is the C9orf72 hexanucleotide expanded repeat. In FTD patients carrying this mutation, disruptions of circadian rhythm have been observed. We are investigating the cause of these disruptions by studying the expression of clock genes (*per* and *tim*). To this end, we are examining whether the disruptions observed in FTD patients also occur in a *Drosophila* model of the disease. Our research is focused on understanding if the disruptions are caused by irregular expression of the clock genes or by other factors. We conducted quantitative polymerase chain reaction (qPCR) analyses of clock gene expression in *Drosophila* to assess the impact of the disruptions at various time points to identify patterns corresponding to sleep-wake cycle changes. We compared this data with our behavioral analyses of *Drosophila* activity during a normal daylight cycle, as well as when free running (in complete darkness). This research is essential for understanding broader mechanisms of circadian dysregulation in neurodegeneration. It could provide a foundation for exploring clock genes as therapeutic targets to mitigate activity, sleep, and circadian rhythm disturbances in FTD patients.

FTD Background

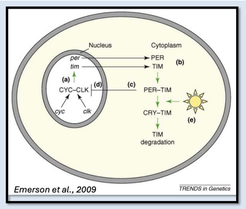


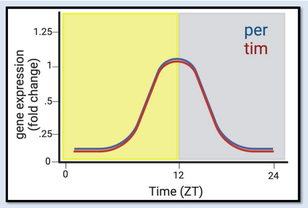
Abigail Harrington

GAL4-UAS Expression System

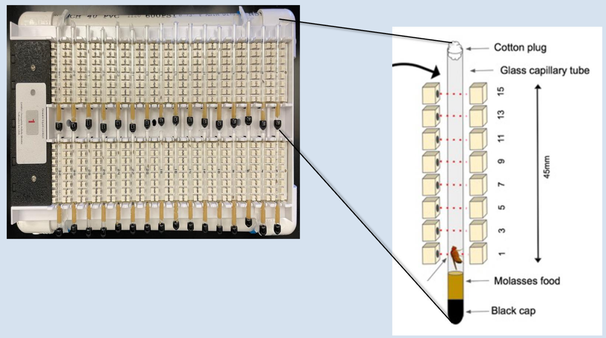


Circadian Rhythm





Experimental Design



1. Collect data with DAM5H
2. Process data with DAM File Scan
3. Analyze sleep and activity with SCAMP in MATLAB
4. Analyze circadian data with FaasX
5. Analyze activity with Clock Lab

FTD flies are active for longer durations

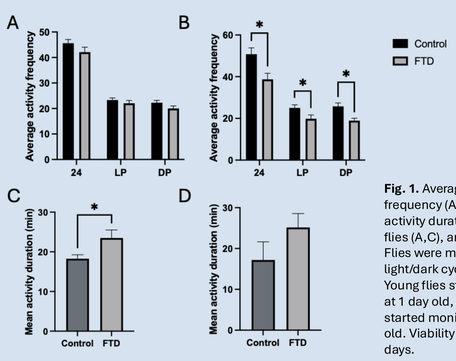


Fig. 1. Average activity frequency (A, B) and mean activity duration (C, D) of young flies (A,C), and old flies (B,D). Flies were monitored in 12-hour light/dark cycle for four days. Young flies started monitoring at 1 day old, and old flies started monitoring at 15 days old. Viability of FTD flies is ~21 days.

FTD flies have reduced sleep frequency

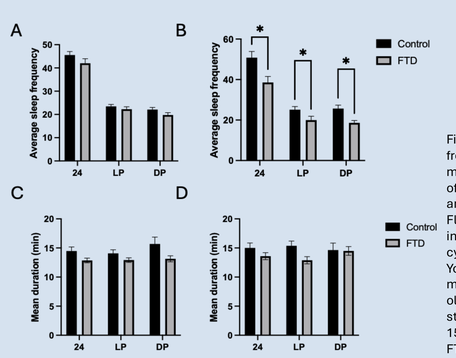


Fig. 2. Average sleep frequency (A, B) and mean duration (C, D) of young flies (A,C), and old flies (B,D). Flies were monitored in 12-hour light/dark cycle for four days. Young flies started monitoring at 1 day old, and old flies started monitoring at 15 days old. Viability of FTD flies is ~21 days.

FTD flies have altered sleep structure

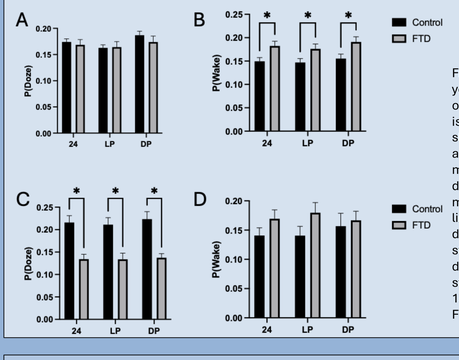


Fig. 3. Sleep quality of young flies (A, B) and old flies(C, D). P(Doze) is a measurement of sleep pressure (A,C) and P(Wake) is a measurement of sleep depth (B,D). Flies were monitored in 12-hour light/dark cycle for four days. Young flies started monitoring at 1 day old, and old flies started monitoring at 15 days old. Viability of FTD flies is ~21 days.

FTD flies are arrhythmic

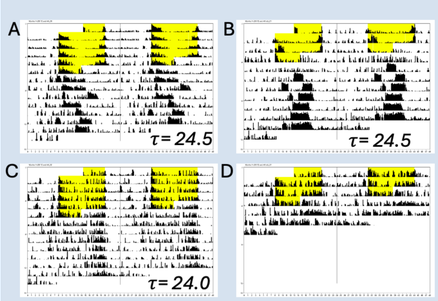


Fig 4. Activity plot and tau value of young flies (A, C) and old flies (B, D). Flies were monitored in 12-hour light/dark cycle (yellow= light, white= dark) and then in constant darkness (free running) as indicated. Young flies started monitoring at 1 day old, and old flies started monitoring at 15 days old. Viability of FTD flies is ~21 days.

Clock gene expression is altered in FTD flies

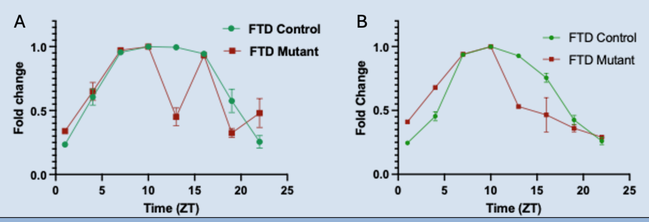


Fig 5. Quantitative PCR analysis of *per* (A) and *tim* (B) over 24-hour period in 7-day old flies, normalized with *beta-tubulin*.

Conclusions

1. Flies expressing the C9orf72 hexanucleotide repeat expansion (FTD) under the control of the ELAV enhancer have an average survival time of 21 days at 25 °C.
2. FTD young flies display normal activity frequency but increased mean activity duration.
3. Older FTD flies display decreased activity frequency but still have elevated activity duration.
4. FTD young flies have normal sleep frequency and mean duration.
5. Older FTD flies display decreased sleep frequency but normal mean duration.
6. FTD flies have poor sleep quality, with decreased sleep pressure and increased sleep depth.
7. Young FTD flies can be entrained by 12-hour light/dark cycle and maintain this during free-running.
8. Older FTD flies are somewhat entrained by a 12-hour light/dark cycle and but do not maintain this during free-running.
9. *per* and *tim* gene expression is altered in FTD young flies.

Future Directions

1. Repeat activity and sleep experiments with additional biological replicates.
2. Repeat activity and sleep experiments with additional models of C9orf72-FTD with varying numbers of HRE.
3. Repeat qPCR experiments with additional biological replicates.
4. Analyze expression of *clock* and *cycle.*
5. Analyze gene and protein expression of other regulators of the central clock.

References

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Acknowledgements

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