Circadian dysregulation links social isolation to neurodegenerative risk: A translational study in Drosophila melanogaster

Javiera Palma 1,2 Christine Gierke 1,2,3,4 **Martina Morales 1,2**, Millaray Pizarro 1,2, Rocio Diaz 1,2,6 Vicente Iturriaga 1,2, Alfonso Valderrama 1,2, 5 Fernanda Cabrera 1,2,5 , Walthers Diaz-Gierke1,2,7 Carlos F. Navarro 1,2 & Francisco Del Pino 1,2,8.

1 Social Isolation Research Center (SIRC), Santiago, Chile, 2. ISOFLY Lab NiBG, Biomedical Sciences Institute, University of Chile, Santiago, Chile, 3. Neurology and Neurosurgery Service, Clinical Hospital University of Chile (HCUCH), 4. School of Psychology, Diego Portales University (UDP), Santiago, Chile. 5. School of Psychology, Silva Henriquez University, 6. Pontifical Catholic University (PUC), Santiago, Chile. 7. School of Psychology, Adolfo Ibañez University, Santiago, Chile. 8. Biomedical Sciences Institute (ICBM), NiBG , Faculty of Medicine University of Chile, Santiago, Chile.

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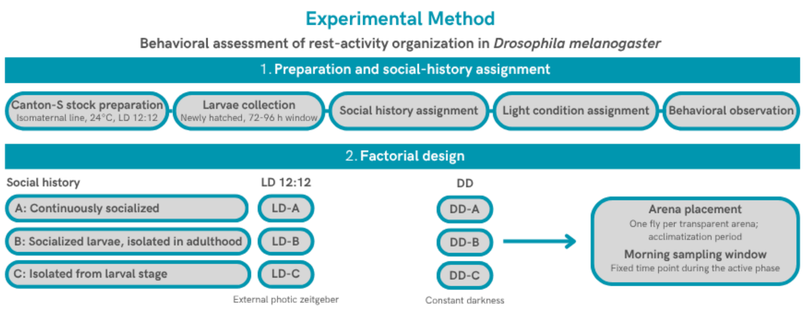
Introduction

The Clinical Paradigm: Social isolation is recognized by the Lancet Commission as a modifiable risk factor for cognitive decline and dementia, accounting for roughly 4% of global cases. Clinically, across neurodegenerative diseases, circadian disruption frequently manifests as fragmented sleep, altered rest-activity rythms, nocturnal agitatipn, and impaired behavioral timing.

Social Isolation as a Circadian Stressor: In *Drosophila melanogaster*, chronic social isolation has been shown to reduce sleep and alter sleep architecture, particularly through shorter and more fragmented rest bouts. These behavioral changes suggest that the absence of social context can destabilize sleep–wake organization.

Neurobiological Rationale: In *Drosophila melanogaster*, social isolation has been shown to reduce and fragment sleep, suggesting that disrupted rest is not only a behavioral outcome but also a potential biological stressor. Brown et al. (2017) demonstrated that isolation-induced sleep loss activates cellular stress pathways, particularly endoplasmic reticulum stress and the unfolded protein response (UPR), reflected by increased BiP/GRP78 expression. Together with evidence linking circadian disruption to oxidative imbalance and neuronal vulnerability, this supports a translational pathway connecting social isolation, sleep fragmentation, cellular stress, and neurodegenerative risk.

Methods





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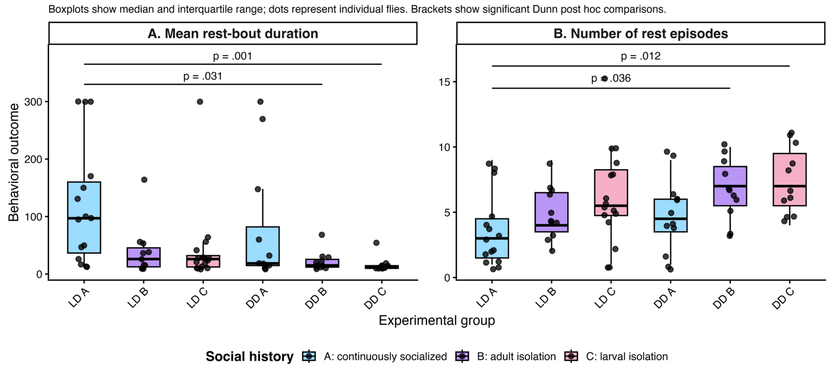
Social Isolation Research Center (SIRC)
christinegierke@uchile.cl
fdelpino@med.uchile.cl
javiera .palma.1@ug.uchile.cl
martina.morales.s@ug.uchile.cl

References

Results

Figure 1. Rest organization differs across experimental groups

Boxplots show median and interquartile range; dots represent individual flies. Brackets show significant Dunn post hoc comparisons.



Sources: *LD (Light-Dark cycle (12:12 hours)); DD (Constant Darkness).*

Figure 1. Rest organization differs across experimental groups.

Mean rest-bout duration was significantly higher in LD A compared with DD B and DD C, whereas the number of rest episodes was significantly lower in LD A compared with DD B and DD C. These findings suggest more consolidated rest in socially enriched flies under light–dark conditions and greater rest fragmentation under constant darkness combined with isolation.

Figure 3. Statistical summary of behavioral outcomes

Kruskal-Wallis tests across six experimental groups; Dunn post hoc comparisons are shown for significant outcomes.

Outcome	Kruskal-Wallis	p-value	Main post hoc finding	Statistical interpretation
Crossings	K-W H(5) = 7.44	.190	ns	Not statistically significant
Mean rest-bout duration	K-W H(5) = 17.41	.004	LD A > DD B, DD C	**Statistically significant**
Rest episodes	K-W H(5) = 15.32	.009	LD A < DD B, DD C	**Statistically significant**

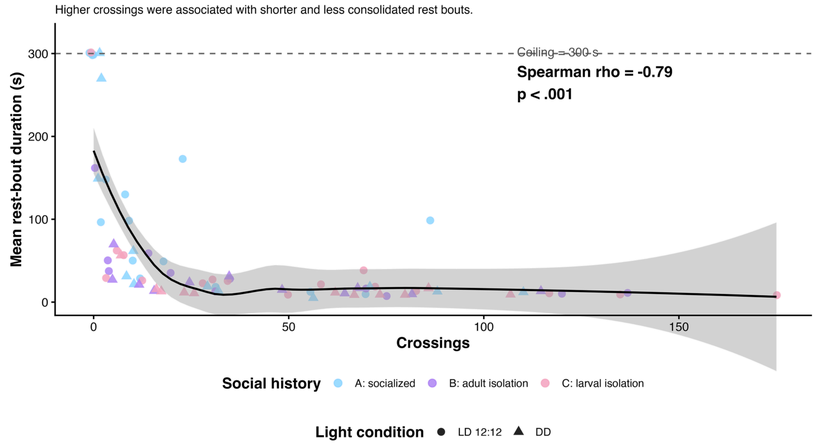
Sources: *LD (Light-Dark cycle (12:12 hours)); DD (Constant Darkness).*

Figure 3 summarizes the inferential analyses across the six experimental groups.

Significant group differences were observed for mean rest-bout duration and rest episodes, but not for crossings, indicating that the experimental conditions primarily affected rest organization rather than gross locomotor activity.

Figure 2. Activity is inversely associated with rest-bout duration

Higher crossings were associated with shorter and less consolidated rest bouts.



Sources: *LD (Light-Dark cycle (12:12 hours)); DD (Constant Darkness).*

Figure 2. Higher locomotor activity was strongly associated with shorter rest-bout duration.

Spearman correlation showed a strong negative association between crossings and mean rest-bout duration, ρ = −0.79, p < .001, suggesting that more active flies tended to show shorter and less consolidated rest episodes.

Discussion

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Rest fragmentation pattern: LD A showed longer rest-bout duration and fewer rest episodes compared with DD B and DD C, **indicating a more consolidated rest structure**. In contrast, flies exposed to constant darkness combined with social isolation showed shorter and more fragmented rest bouts.

Consistency with prior Drosophila findings: This pattern is consistent with previous work showing that socially isolated *Drosophila* **exhibit reduced and fragmented slee**p, with increased sleep-bout number and decreased sleep-bout duration. Brown et al. further linked isolation-induced sleep loss to cellular stress through UPR activation, including increased BiP/GRP78 expression.

Light as an external temporal cue: The stronger fragmentation observed in DD groups suggests that the absence of photic entrainment may reduce the stability of rest–activity organization, particularly when social context is also disrupted. In this sense, LD cycles may act as an external temporal scaffold that partially buffers isolation-related rest fragmentation.

Alzheimer's disease relevance: **Sleep–wake and rest–activity disturbances are increasingly recognized as early and clinically relevant features of Alzheimer's disease**. Although this behavioral phase did not measure AD pathology directly, the observed **rest fragmentation provides an AD-relevant phenotype through which social isolation and circadian instability may converge on impaired brain homeostasis.** In future work, combining continuous circadian monitoring with cellular stress markers such as BiP/UPR and ROS could help test whether **isolation-induced sleep fragmentation represents an early behavioral proxy of neurodegenerative vulnerability.**

Conclusions

The present study provides partial behavioral evidence that social isolation disrupts **rest–activity organization in *Drosophila melanogaster***. The effect was expressed primarily in rest structure, **with significant differences in mean rest-bout duration and number of rest episodes**, while gross locomotor activity did not significantly differ between groups. Flies maintained under socialized light–dark conditions showed the most consolidated rest pattern, whereas isolated flies exposed to constant darkness showed shorter and more fragmented rest bouts.

These findings support rest fragmentation as an **AD-relevant behavioral phenotype linking social isolation, circadian instability, and neurodegenerative vulnerability.** However, several limitations must be acknowledged, including the relatively small group sizes, the 300-s ceiling effect in rest-bout duration, the use of a single 5-minute manual observation window, and the absence of continuous circadian monitoring or direct cellular stress markers. Future work should incorporate automated 24-hour activity monitoring and molecular measures such as BiP/UPR and ROS to directly test the mechanistic pathway between social isolation, sleep fragmentation, cellular stress, and Alzheimer's disease-related vulnerability.