

Background & Aims

Ecological Context: Larval behavioral plasticity in *Drosophila melanogaster* acts as a crucial, evolutionarily conserved adaptive mechanism for survival, enabling the precise selection of optimal foraging and pupation sites ^{1,2}.

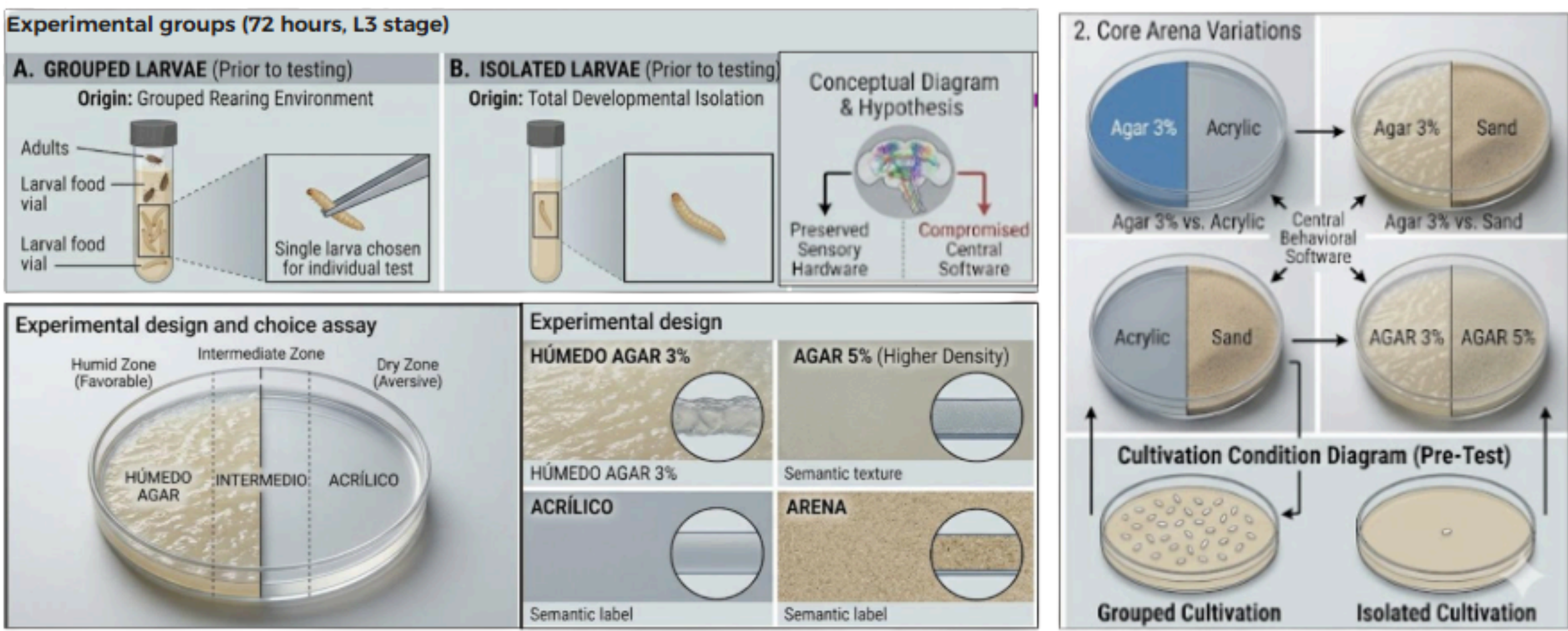
The Stressor: While social aggregation functions as a natural developmental and behavioral scaffold, total social deprivation represents a severe, chronic environmental stressor linked to systemic cellular stress and increased biological vulnerability ^{3,4}.

Classical Foundations: Baseline locomotor dynamics, feeding rates, and the structural etograms that define normal larval foraging behavior rely on a tightly linked genetic and ontogenetic architecture ^{5,6,7}.

Aim: We test whether developmental social isolation selectively impairs central behavioral integration ("**Software**": CNS processing and transition dynamics) while preserving peripheral sensory function ("**Hardware**": peripheral receptor integrity and immediate aversive detection).

Hypothesis: Early-life social isolation reduces behavioral plasticity, causing a "**Phenotype of Stereotyped Rigidity or Exploratory Restriction**" where the peripheral mechanosensory and texture-discriminating Hardware remains morphologically intact (allowing aversive avoidance) ⁸, but the central processing and motor-stabilizing Software is compromised due to an early developmental stress debt (reducing locomotor frequency and transition complexity) ⁹.

Methods



Results

Preferencia de Sustrato / Substrate Preference

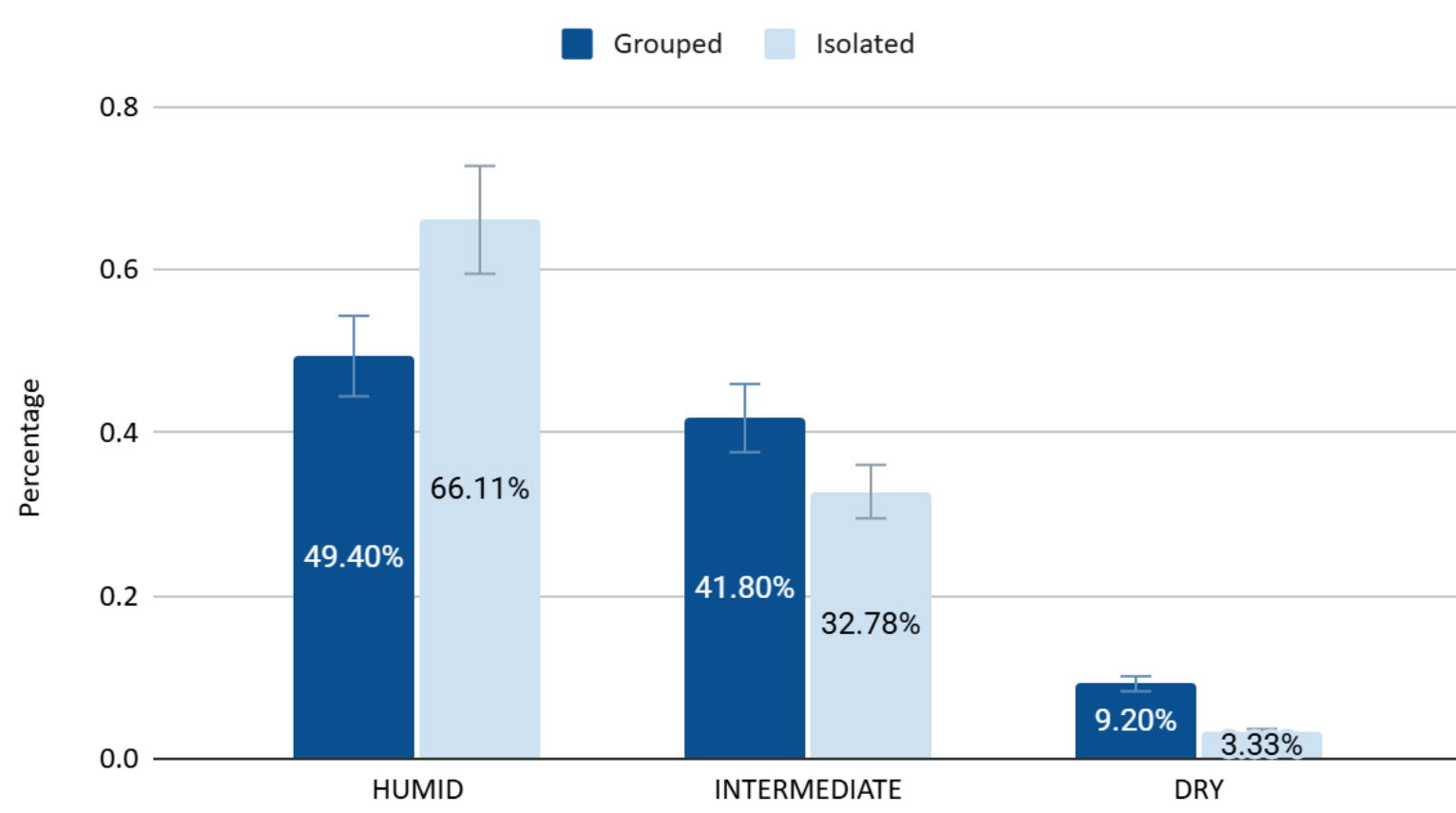


Figure 1: Comparison of Humid (Agar) , Dry (Acrylic) and intermediate preference (Grouped N=50 vs. Isolated N=18)

Preferencia de Sustrato / Substrate preference

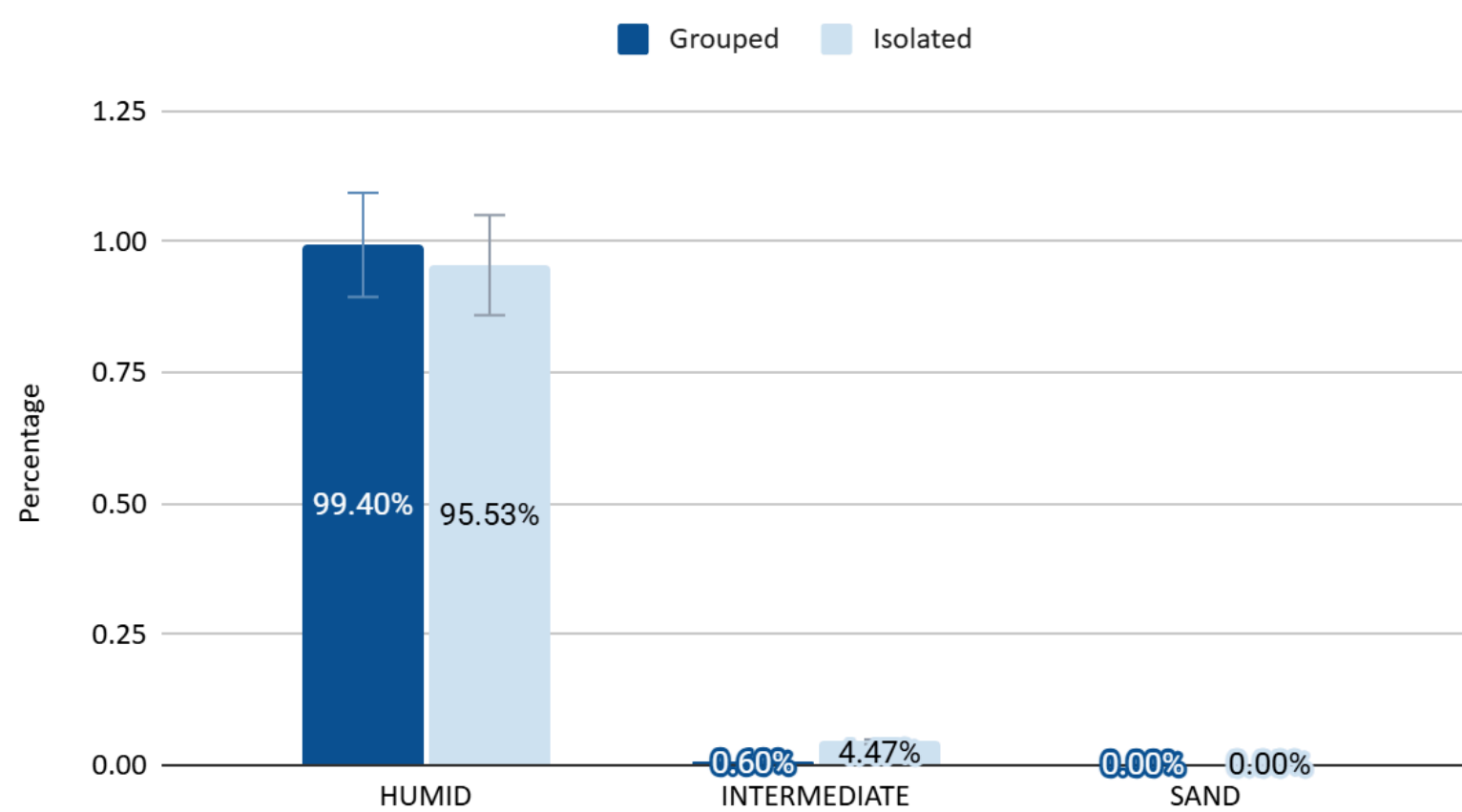


Figure 2: Comparison of Humid (Agar) , Dry (Acrylic) and intermediate preference (Grouped N=50 vs. Isolated N=38)

Results

Actividad locomotora / Locomotor Activity - Grouped Larvae

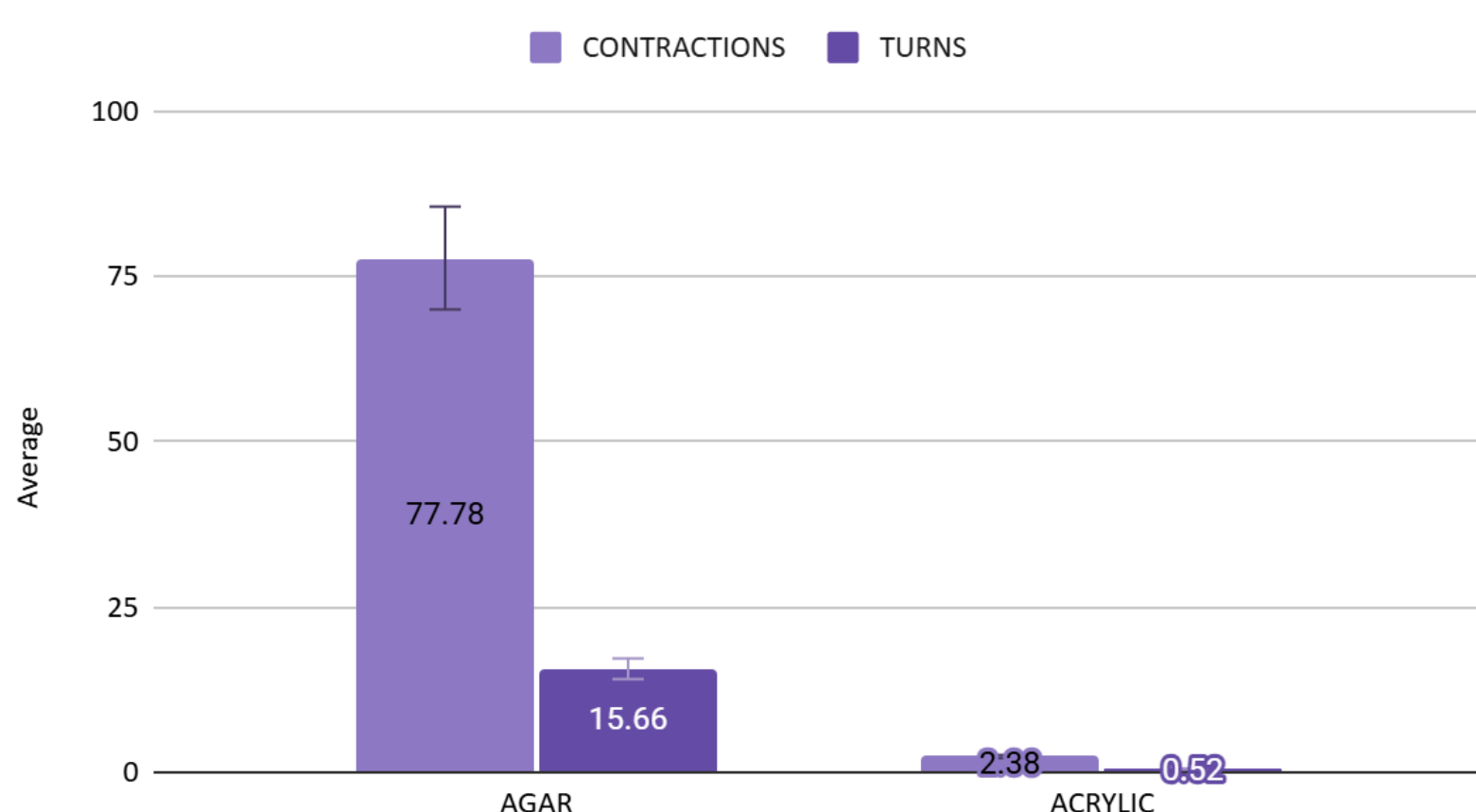


Figure 3: Average locomotor activity of grouped larvae in Agar and Acrylic during the 2-minute trial (Grouped on Agar N=50 vs. Grouped on Acrylic N=50)

Locomotor Activity in agar - Grouped vs Isolated Larvae

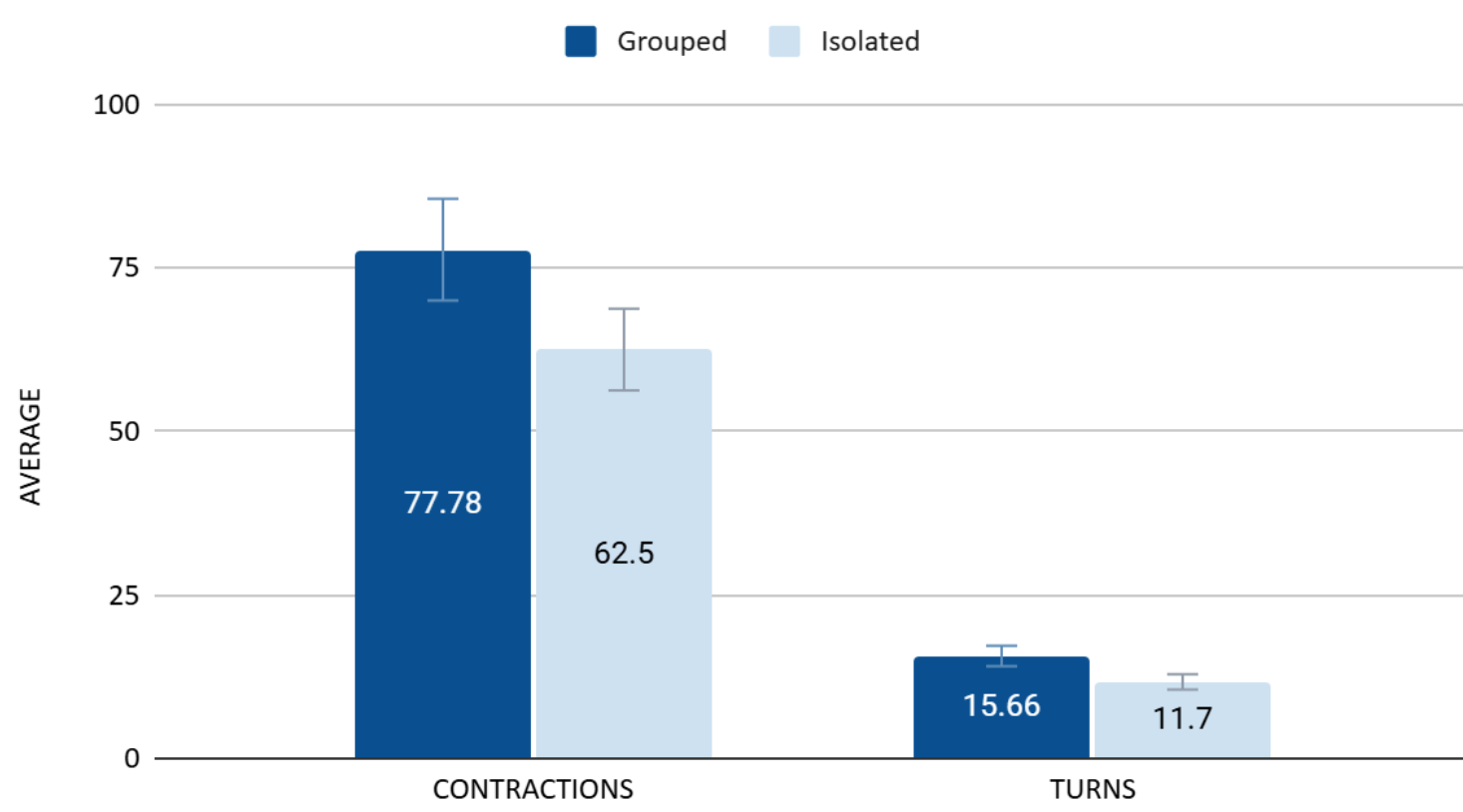


Figure 4: Average locomotor activity of grouped and isolated larvae in Agar during the 2-minute trial (Grouped N=50 vs. Isolated N=10)

Temporal dynamics - Grouped Larvae

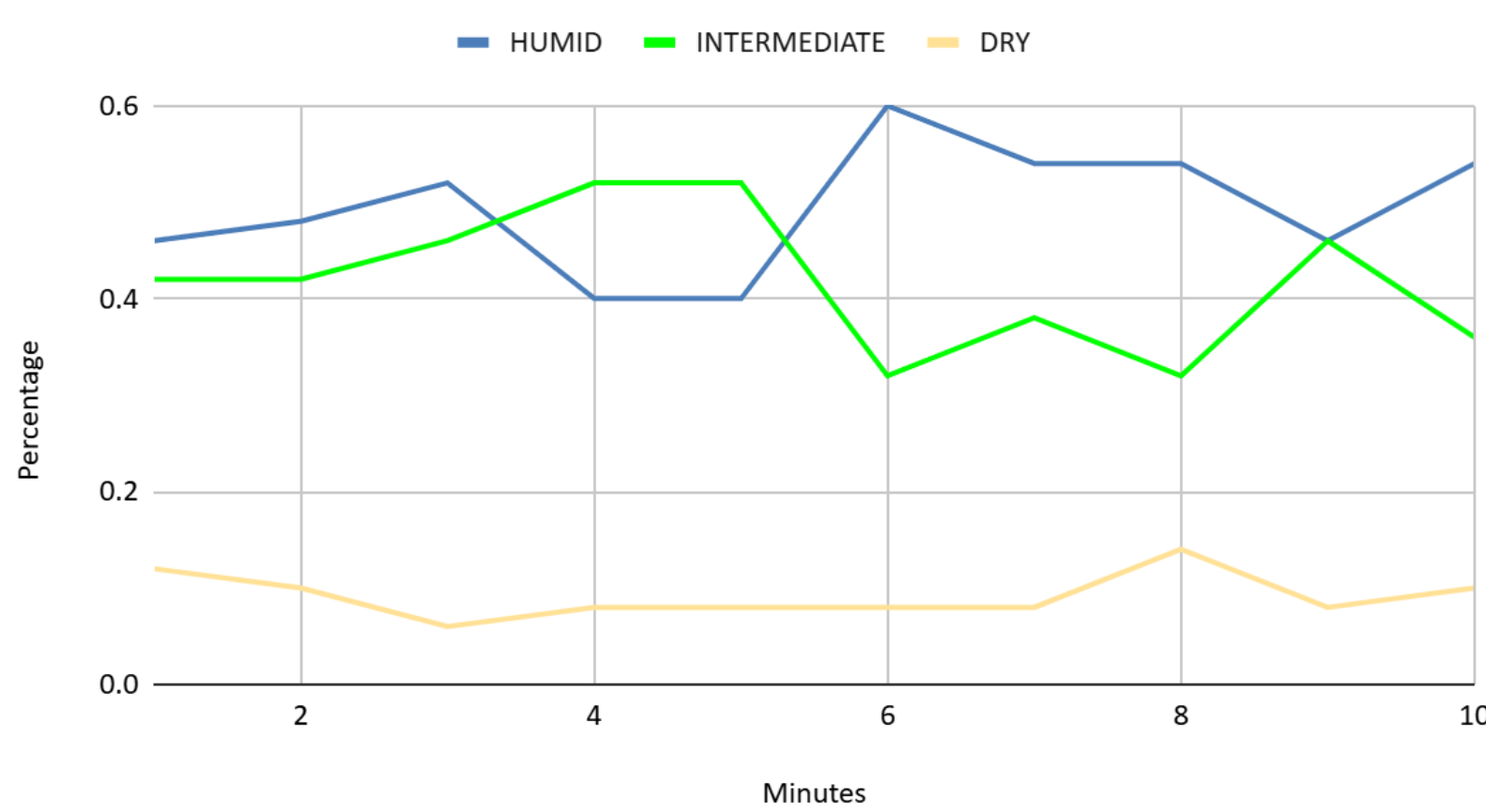


Figure 5: Percentage of grouped larvae in the different substrates (Agar and Acrylic) during the 10-minute trial (N=50)

Temporal dynamics - Isolated Larvae

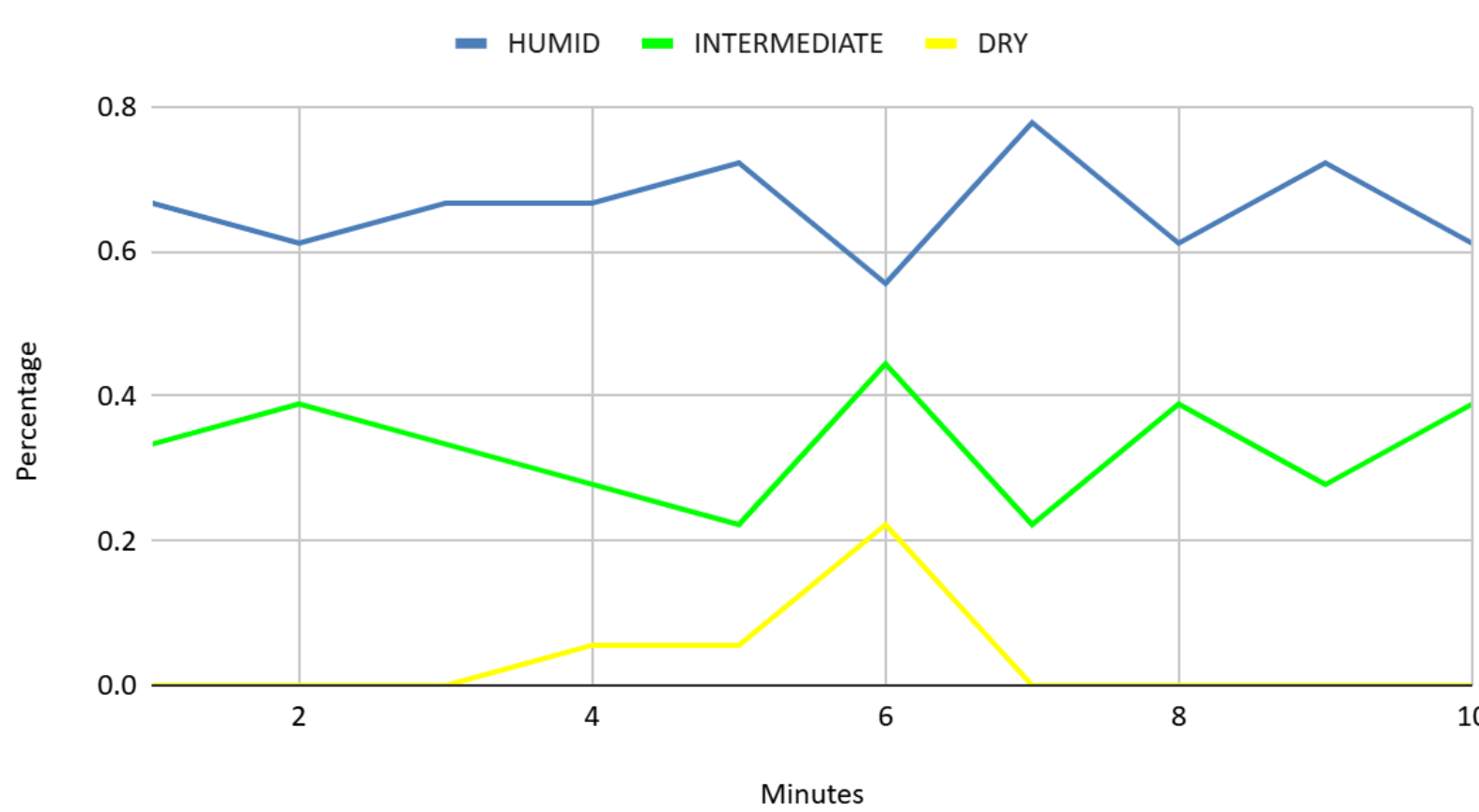


Figure 6: Percentage of isolated larvae in the different substrates (Agar and Acrylic) during the 10-minute trial (N=18)

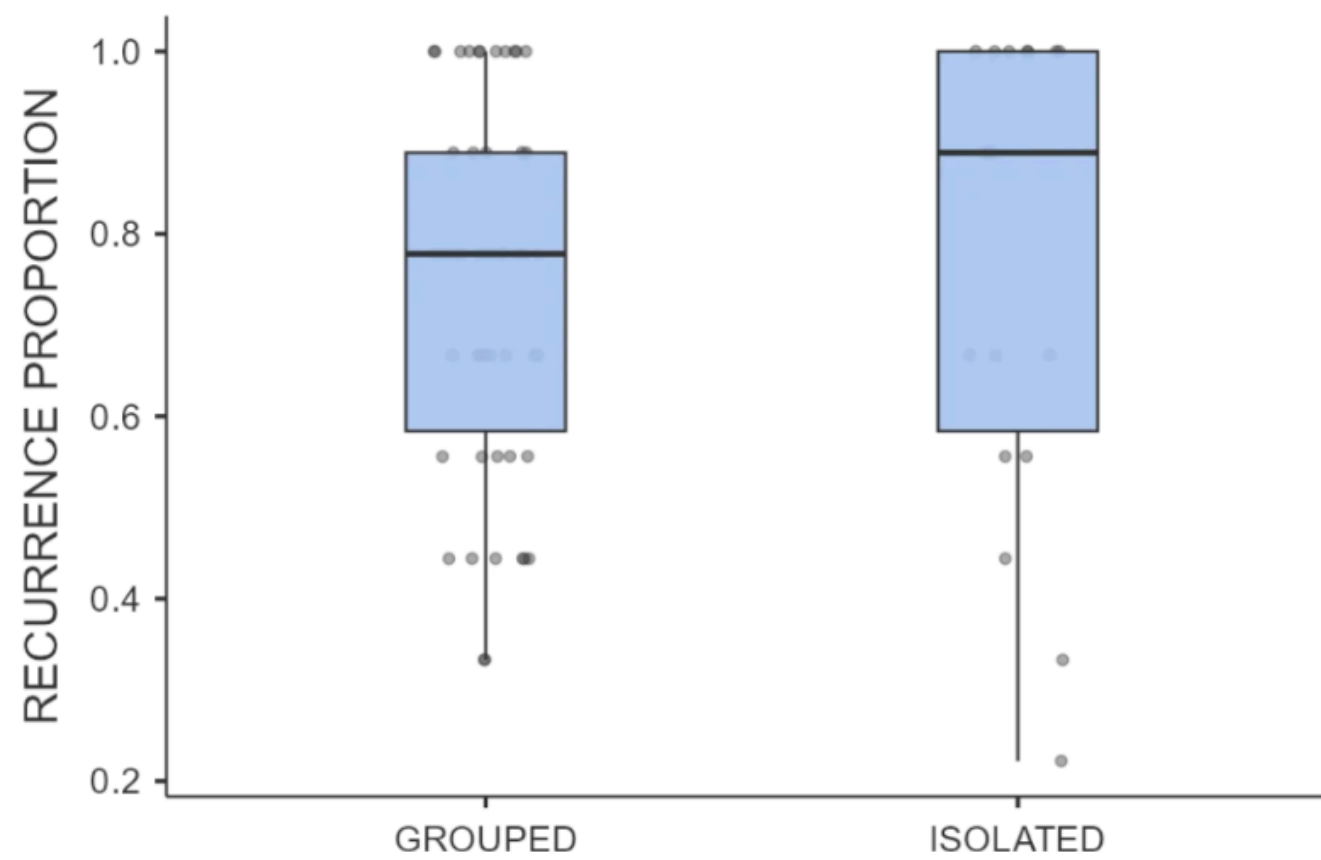


Figure 7: Recurrence proportion per larva in grouped (N=50) and isolated (N=18) conditions.

Discussion

Peripheral Integrity vs. Central Failure: Consistent with *Drosophila* sensory architecture maps ⁸, our data confirms that peripheral sensory mechanoreceptors ("Hardware") remain functionally intact under isolation, as larvae actively avoid unfavorable environments. However, the significantly altered transition structure and lower contraction rates reflect an impairment in central integration neuro-networks ("Software").

The Epigenetic Debt & Chromatin Remodeling: Following foundational developmental stress models ^{9,10}, chronic social deprivation acts as an environmental trigger for chromatin remodeling, matching known features of isolation like cellular stress, UPR activation, and sleep alterations ³. This structural phenotype is tied to global alterations in histone acetylation modifiers ¹¹ and aberrant DNA methylation of critical plasticity genes ¹⁰.

The Alzheimer's Disease (AD) Link: In mammalian models and human cohorts, social isolation stands out as a major non-genetic risk factor that accelerates AD pathology ^{4,12}. The epigenetic modifications observed under isolation directly parallel the transcriptional blockade and histone acetylation disruptions found in the early pathogenesis of Alzheimer's disease ^{11,13}.

Larval Drosophila as an AD Screening Platform: Because histone acetyltransferases (HATs) and DNA methyltransferases (DNMTs) are highly conserved between *Drosophila* and humans ¹⁰, our quantifiable "**Phenotype of Exploratory Restriction**" provides a high-throughput, non-mammalian behavioral platform to screen epigenetic drugs (like HDAC inhibitors) ¹⁰ designed to rescue neurodegenerative cognitive and behavioral latency.

Conclusions

- 1.Early-life social isolation induces a specific central integration deficit without damaging peripheral sensory structures, validating a localized neurodevelopmental stress phenotype.
- 2.The preserved average spatial stability (substrate recurrence) alongside a simplified, restricted transition profile represents a behavioral readout of an underlying epigenetic debt and cellular stress ^{3,9}.
- 3.This automated larval platform establishes a highly reliable, low-cost framework to model the silent epigenetic erosion caused by social isolation, a critical non-genetic risk factor accelerating Alzheimer's disease progression ¹².

References

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