***eLife’s* transparent reporting form**

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**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
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All information on sample sizes are reported in the methods of the paper.

**Replicates**

* You should report how often each experiment was performed
* You should include a definition of biological versus technical replication
* The data obtained should be provided and sufficient information should be provided to indicate the number of independent biological and/or technical replicates
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* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

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All reagents and data sets used in this study can be found in the Key Resources Table. The RNA-sequencing performed on *Drosophila* HD models and corresponding controls is available in GEO, both link and token are provided in the manuscript at the end of the methods section (Data and Software Availability, page 34). A detailed description of experiments can be found in the methods section. The statistical test used to analyze data is stated in the figure legend that corresponds to that data.

**Statistical reporting**

* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
* For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
* Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

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Statistical tests are referenced in figure legends when appropriate. Statistical tests are described in greater detail in the methods section. Due to the large number of experiments performed for *Drosophila* behavior exact p-values for results summarized in Figures 3-6 in Table S4 and Table S6.

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
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Information on group allocation of *Drosophila* for climbing assay is provided in the methods section.

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* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
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* Include model definition files including the full list of parameters used
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Please indicate the figures or tables for which source data files have been provided:

Source codes and data have been provided for Figures 1-6 and relevant supplemental information. A list of source codes and data has been provided at the end of the manuscript before References (pg. 46-47).