

How do synapses acquire their identity

The role of **Unc-5** in synaptic heterogeneity during *Drosophila* development

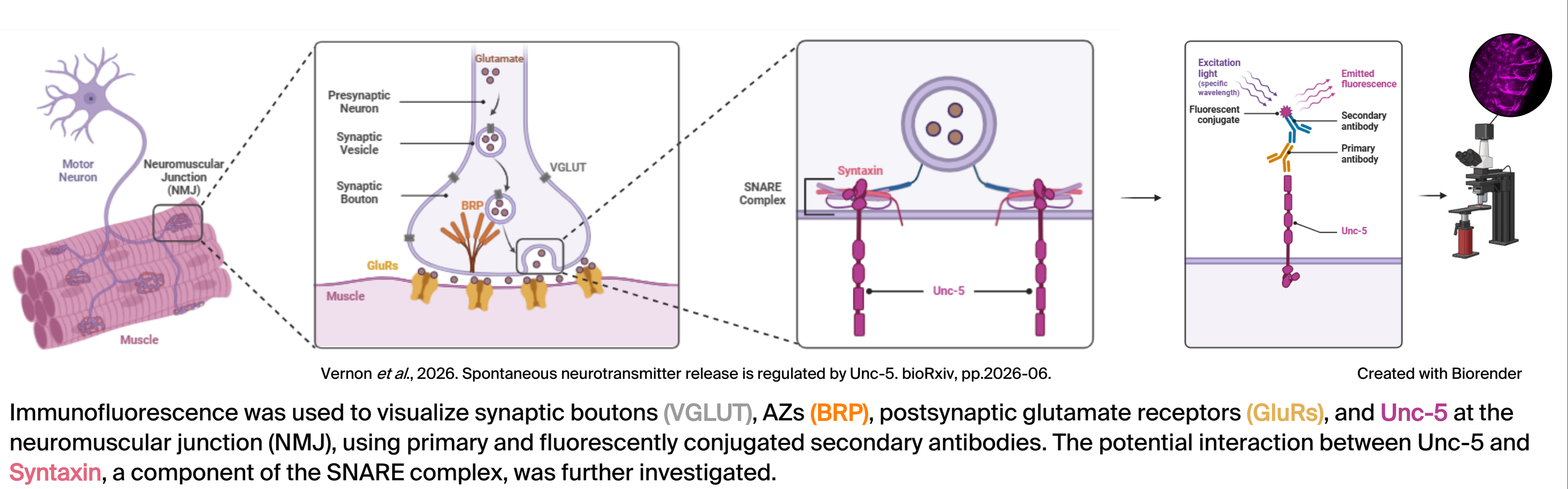
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INTRODUCTION

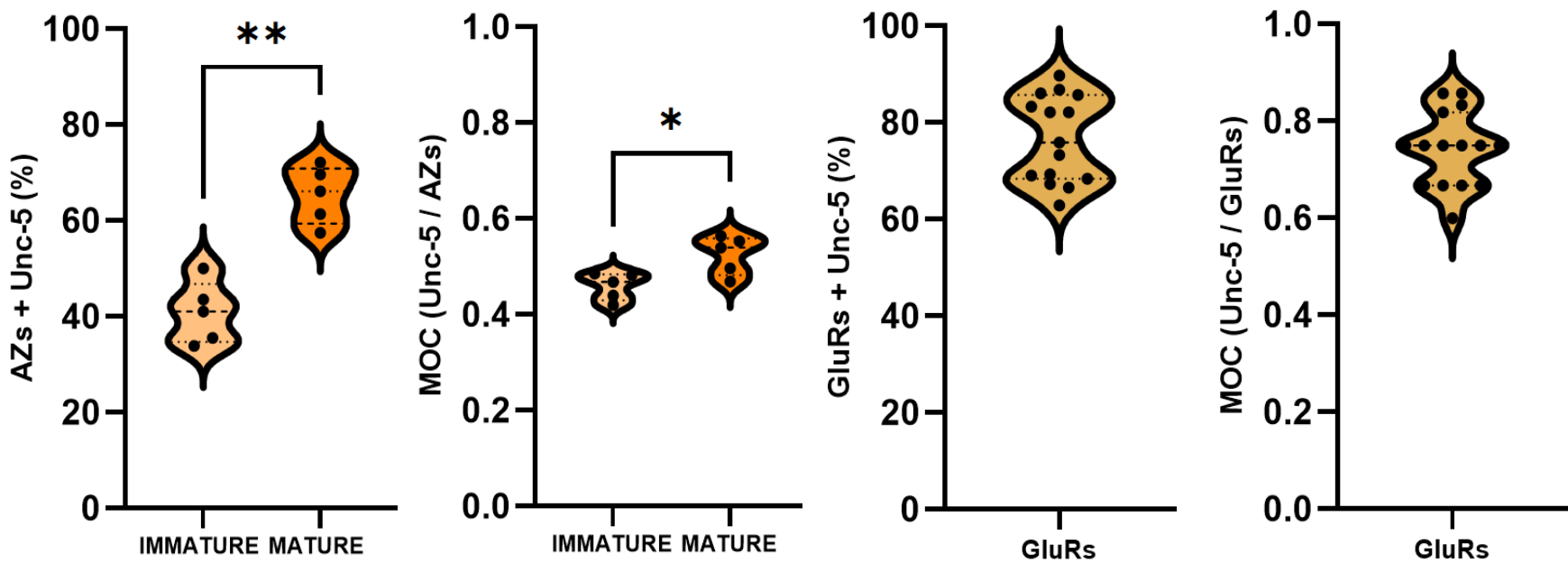
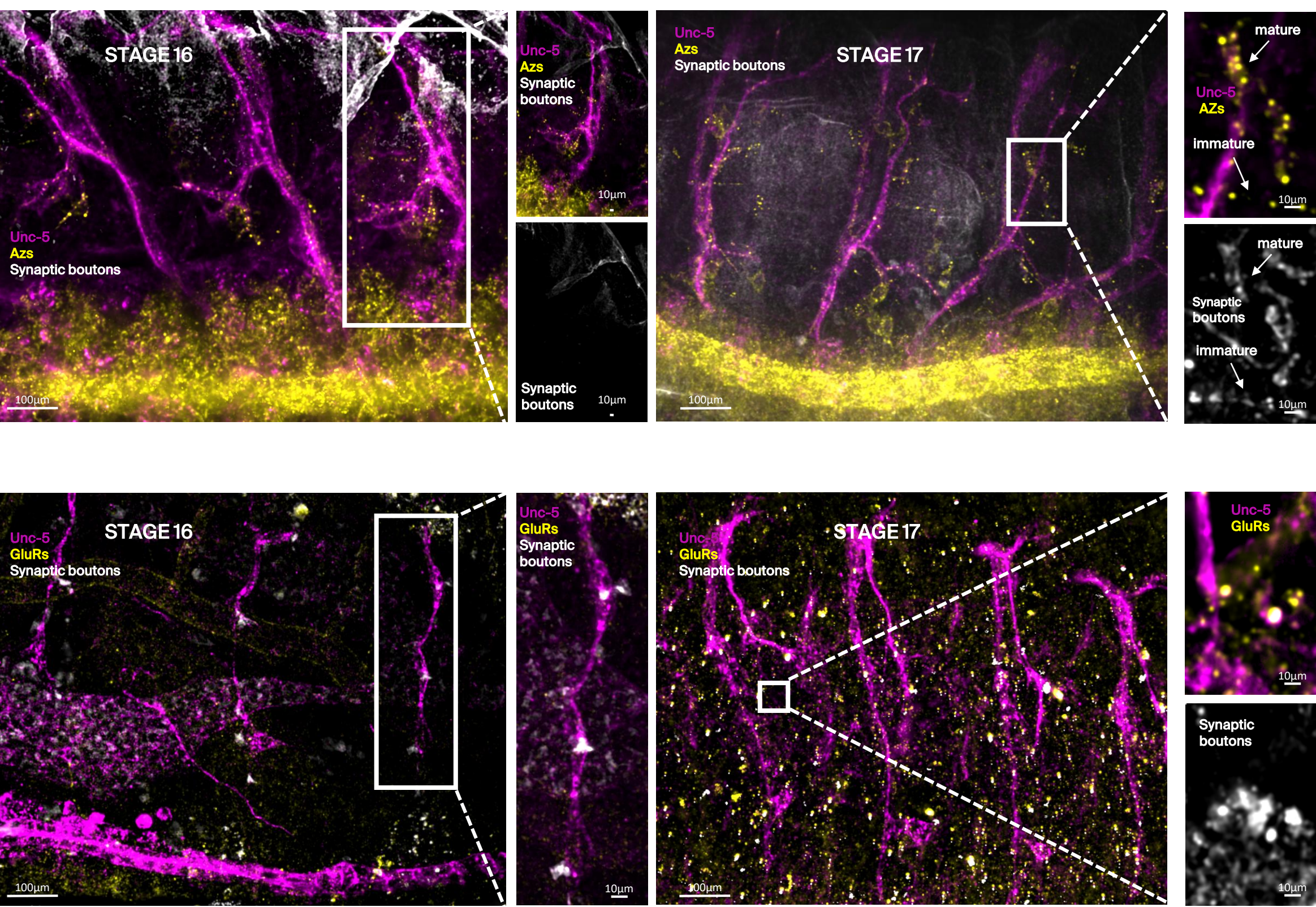
The developmental protein **Unc-5** was initially characterized for its role in **axon guidance**. However, it has recently been shown to locally promote distinct forms of **neurotransmission** at ~40% of release sites, termed **active zones (AZs)**, in adult *Drosophila* (Vernon *et al.*, 2026).

This raises the question of whether **Unc-5** has an independent, **novel function** in the adult nervous system or a previously **unidentified role in development**. We utilised immunohistochemistry, electrophysiology and classic loss-of-function mutants in embryonic and early larval developmental stages, to investigate the **role and regulation** of **Unc-5** during earlier development.

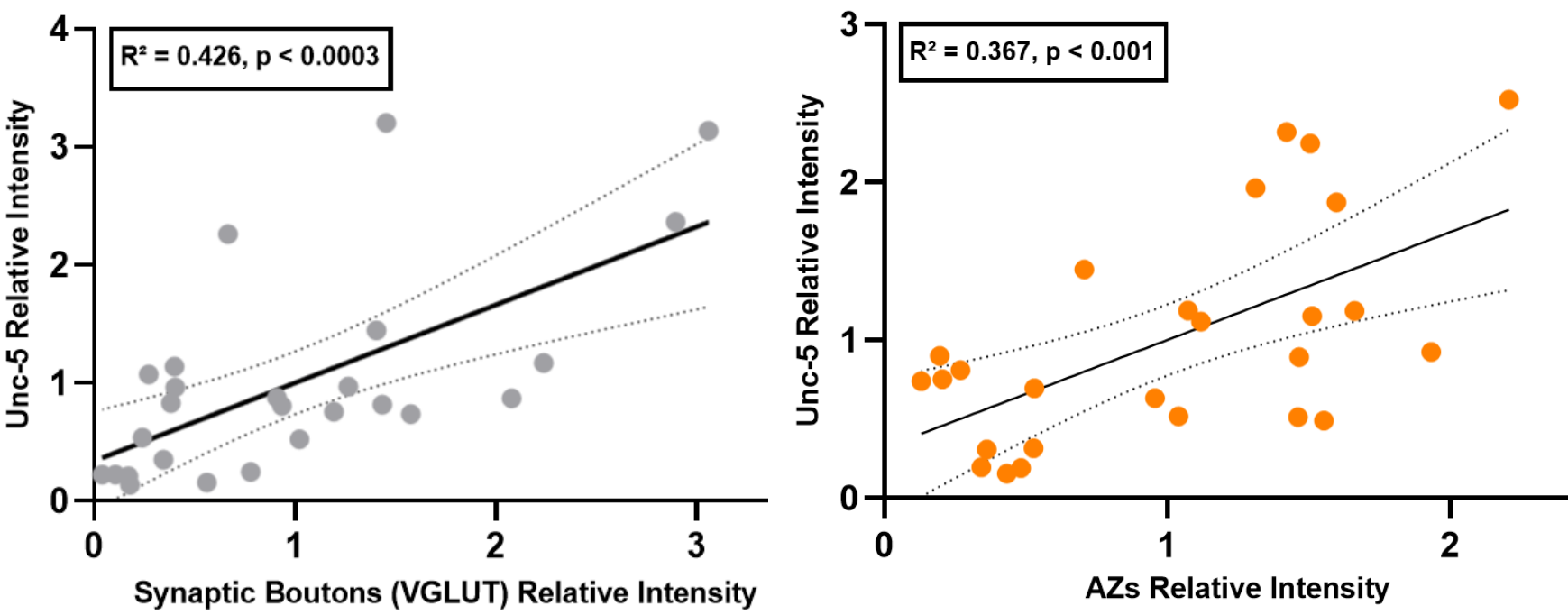
EXPERIMENTAL APPROACH



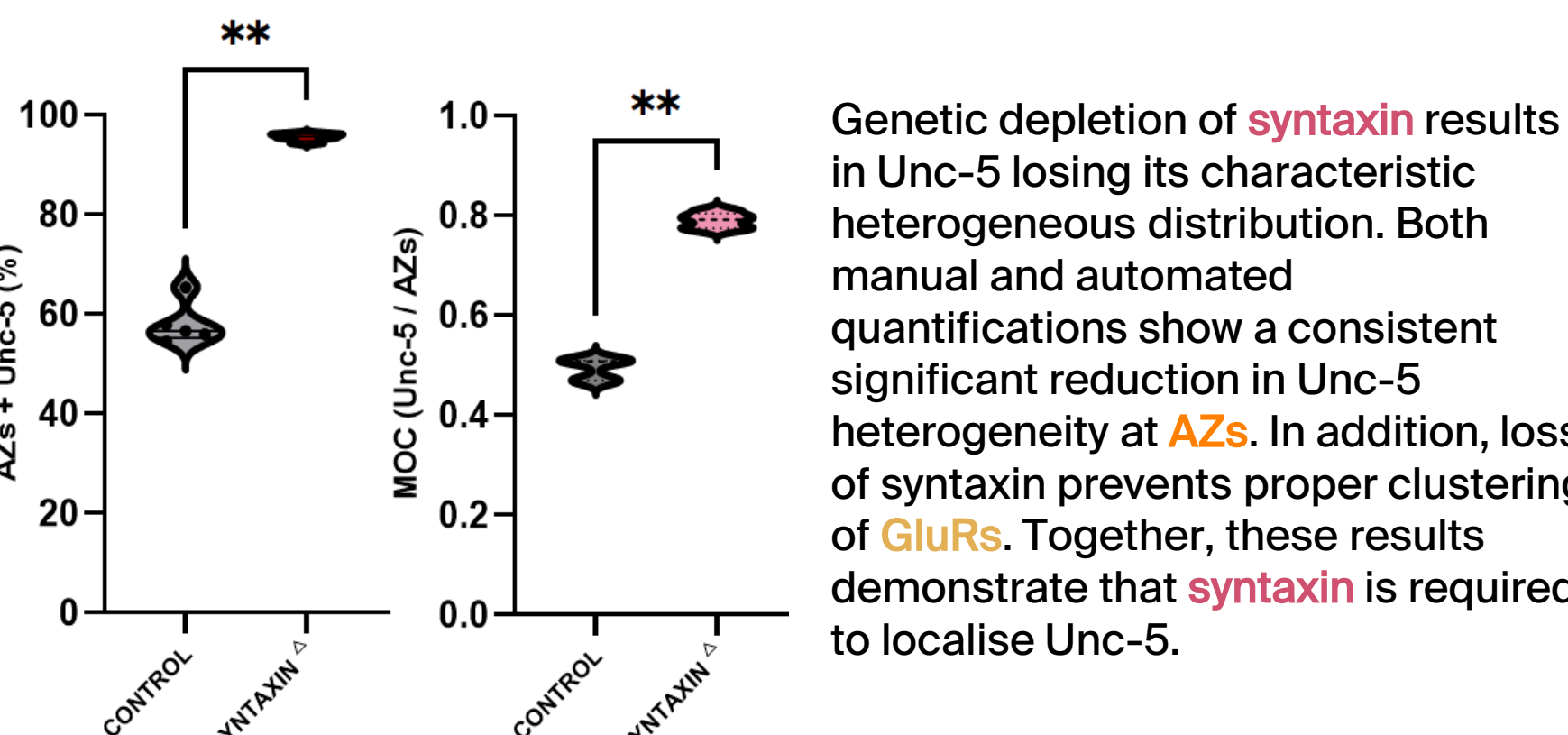
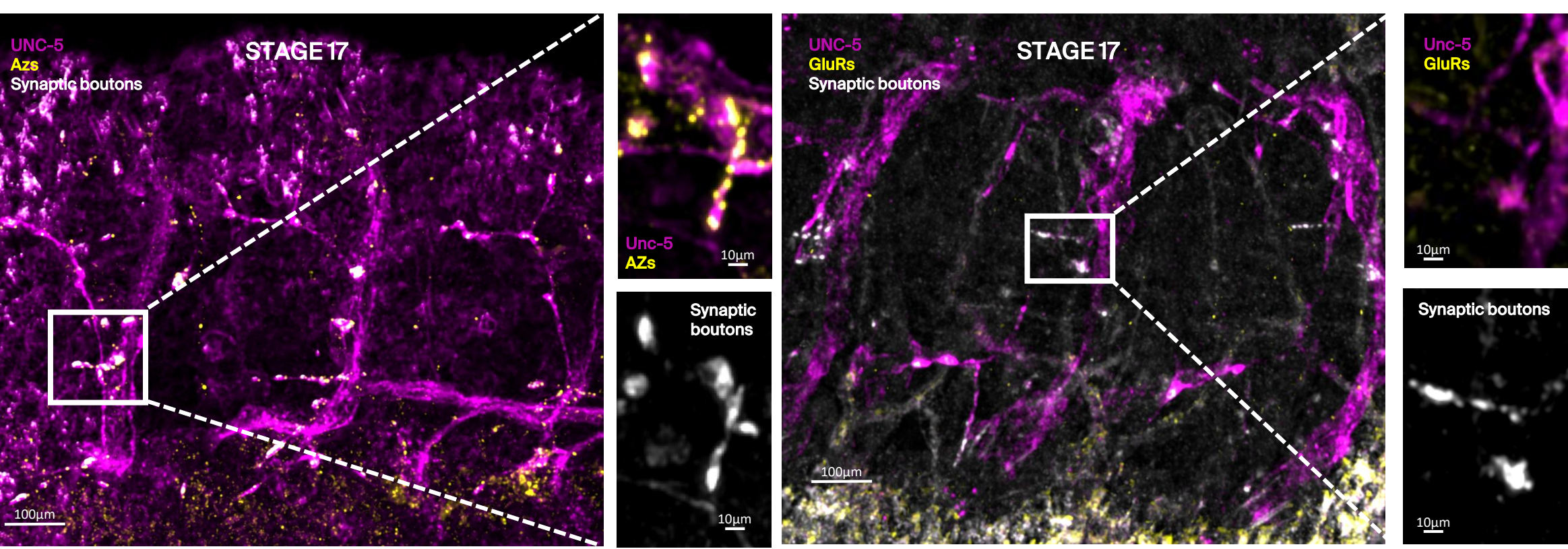
DEVELOPMENTAL EMERGENCE OF HETEROGENEOUS **UNC-5** LOCALIZATION



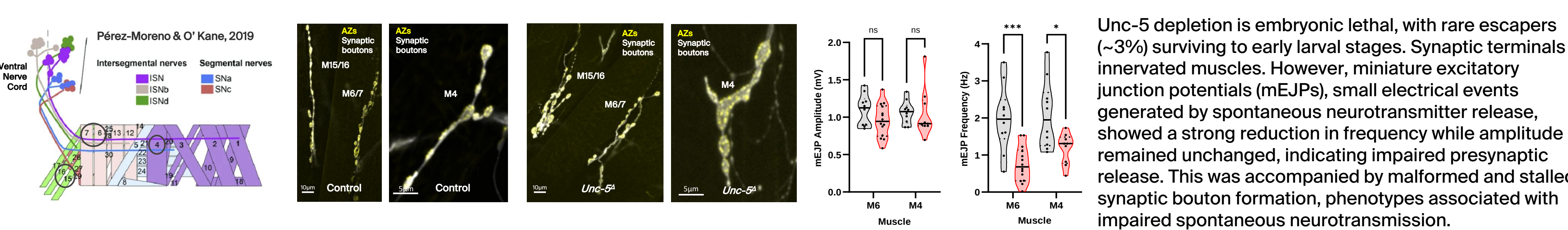
Manual and automated MOC quantification (based on Mander's overlap coefficient) at **AZs** and **GluRs** both reveal heterogeneous **Unc-5** localization. At **AZs**, both approaches show an increase in **Unc-5** association with mature boutons.



LOSS OF SYNTAXIN DISRUPTS **UNC-5** HETEROGENEITY



CONSERVED SYNAPTIC ROLE FOR **UNC-5** DURING SYNAPTIC DEVELOPMENT



CONCLUSION

These findings identify a **conserved synaptic role** for **Unc-5** in the **establishment and regulation of neurotransmission** during synaptic bouton and **AZ** maturation, and show that **Unc-5** levels can be **regulated** through manipulation of the canonical synaptic release machinery. These data further suggest that **AZ heterogeneity** does not simply emerge from stochastic differences between mature release sites, but can be **actively established during development** by molecular programmes that **spatially organize the release machinery**, a process that is **maintained during ageing**. This provides a basis for further investigating the roles and interactions of these proteins. Understanding how synapses acquire their identity may be the first step toward understanding how they lose it.