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Microbiota-dependent increase in δ-valerobetaine affects neuronal synchronicity and mediates age-related cognitive decline

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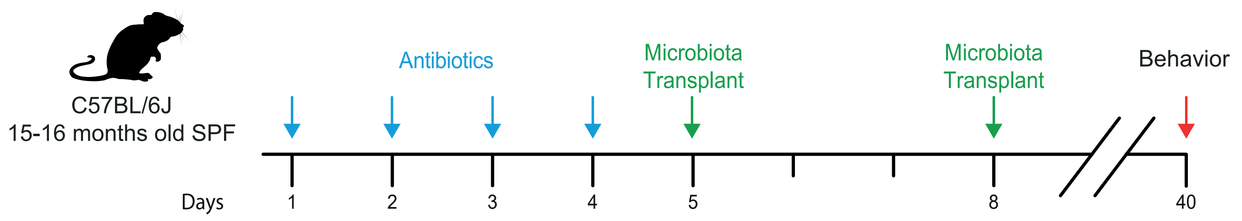
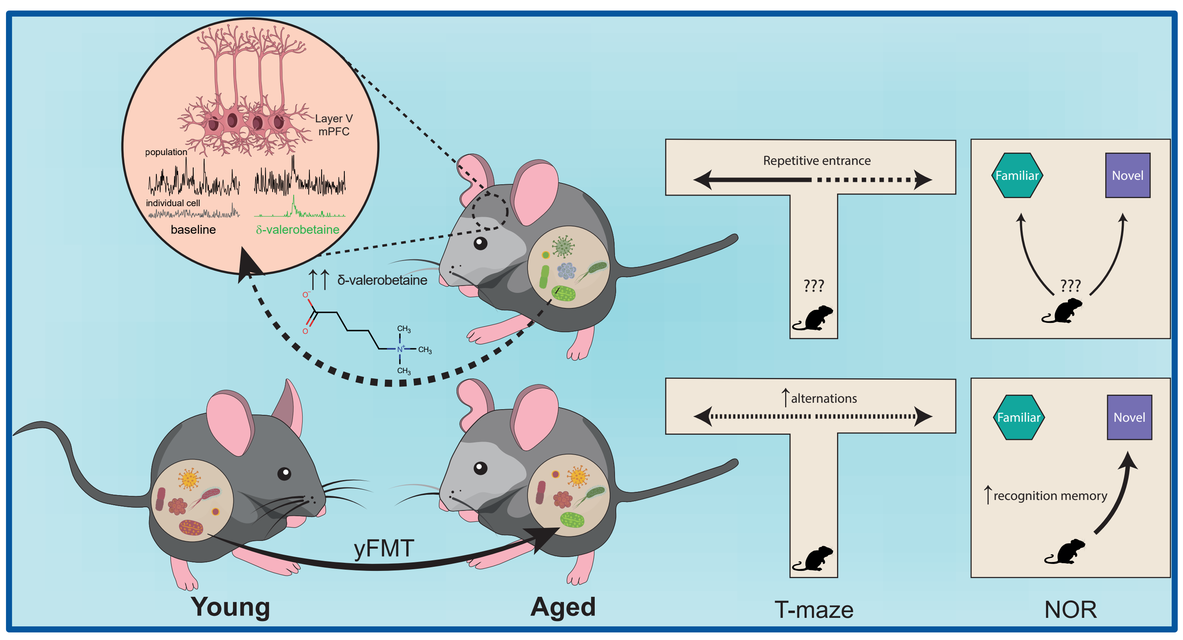
Introduction

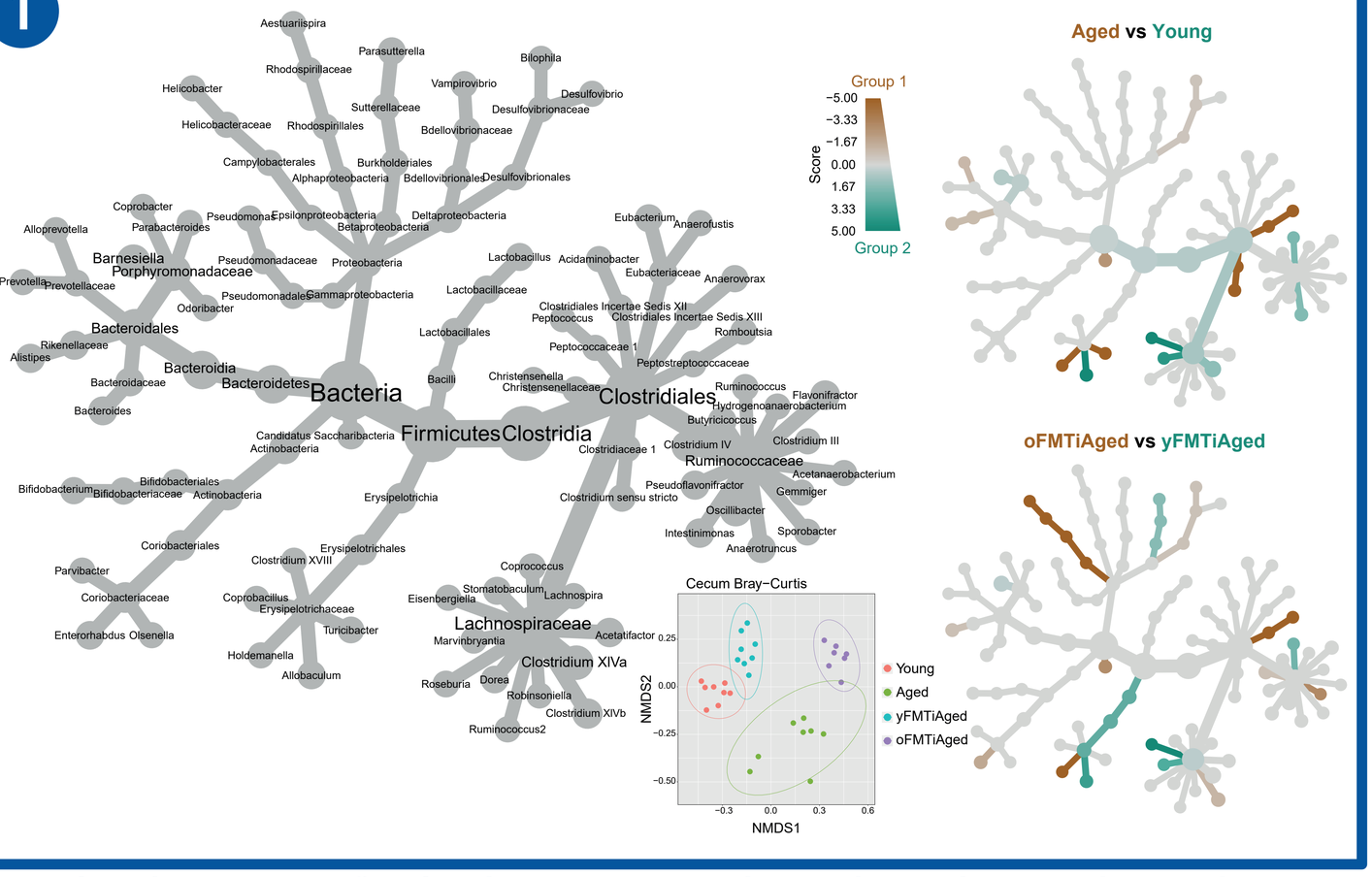
Age-related changes in the gut microbiota composition have recently been associated with several human diseases and conditions, involving age-related decline of brain function. Here, we identify δ-valerobetaine as a decisive microbiota-dependent metabolite, which displays elevated levels with increasing age, and contributes to the age-related cognitive decline.

Methods

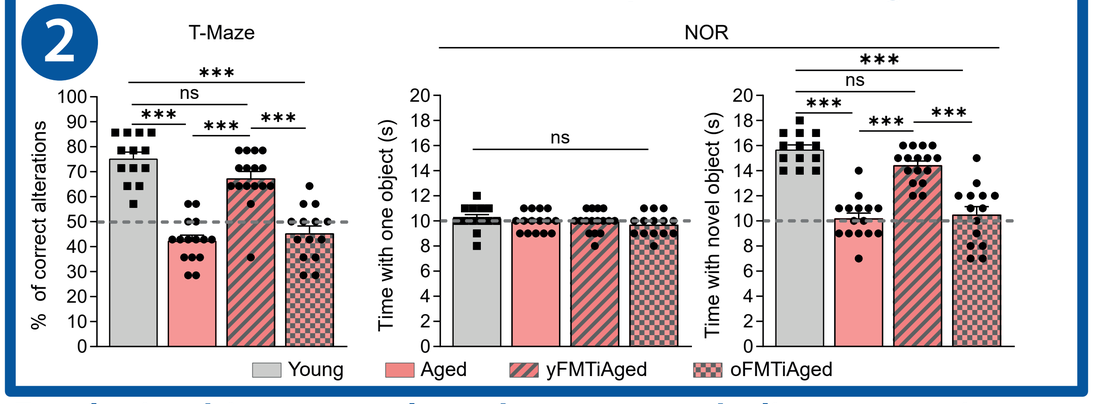




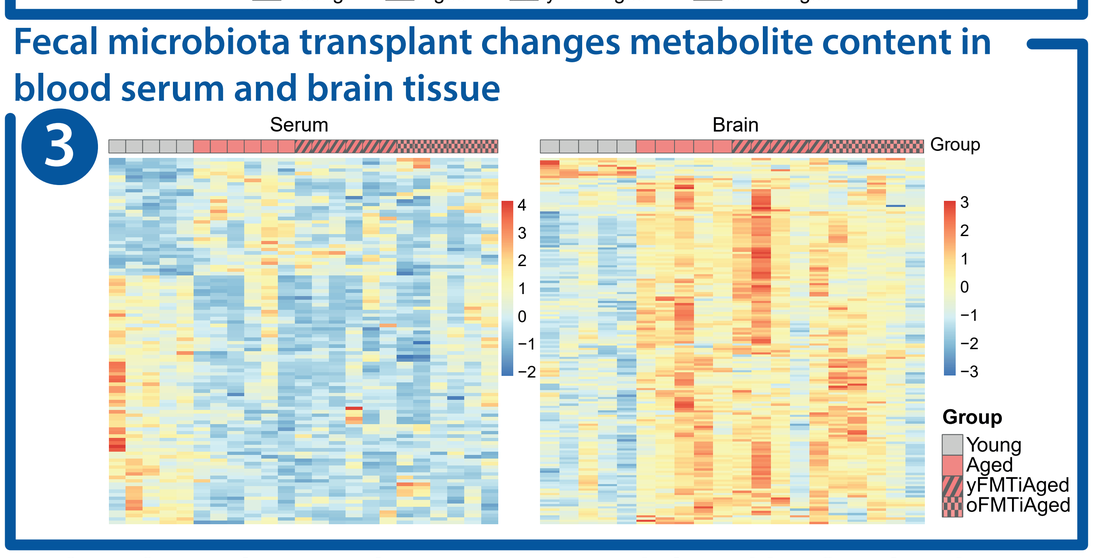
Restoring young microbiota by fecal microbiota transplant (FMT)



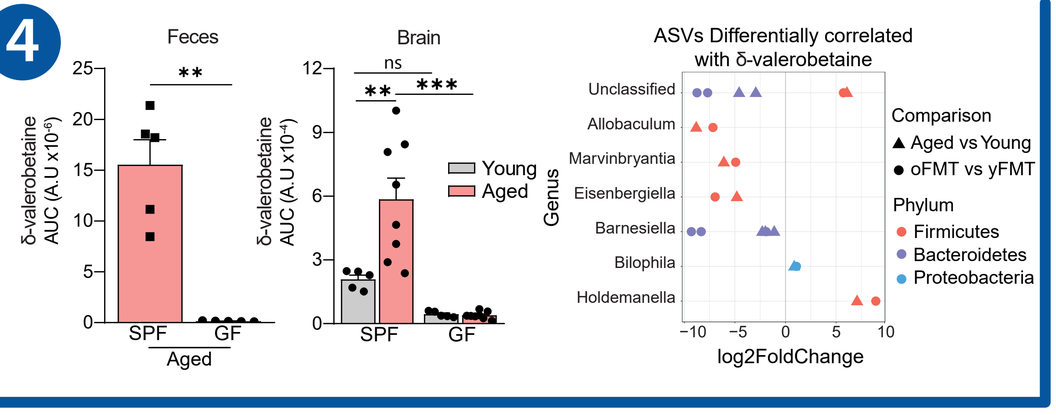
Heterochronic fecal microbiota transplant directs cognition



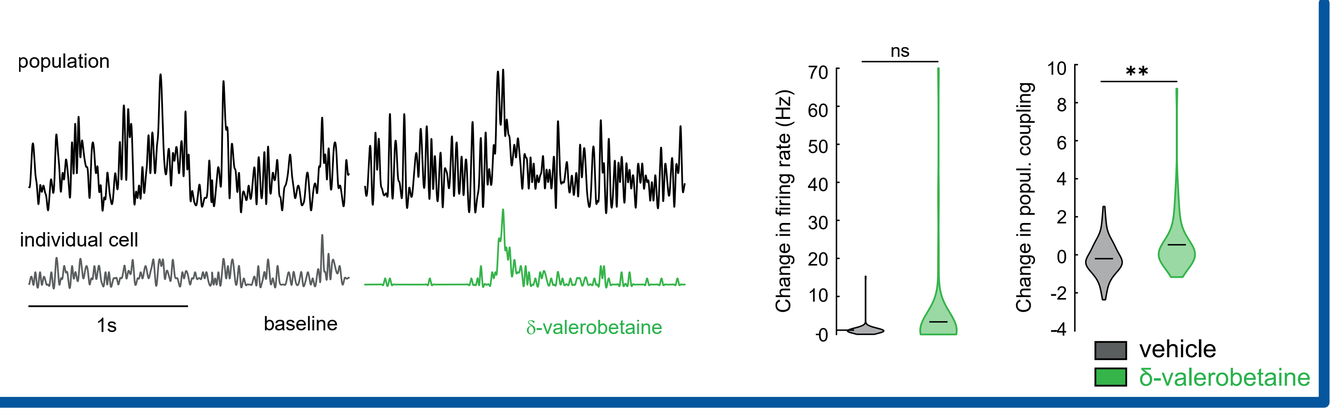
Fecal microbiota transplant changes metabolite content in blood serum and brain tissue



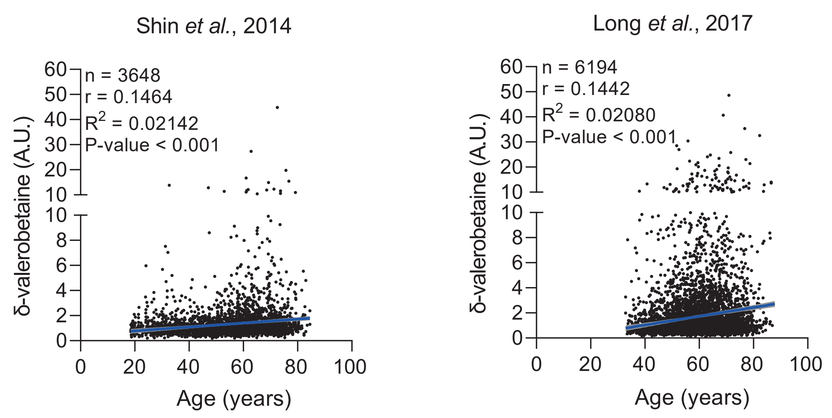
Age-related increase in δ-valerobetaine is microbiota-dependent



Spike synchronization of prefrontal cortical neurons is modulated by δ-valerobetaine



Serum δ-valerobetaine positively correlates with age in humans



Summary

- Young fecal microbiota transplantation (FMT) into aged mice efficiently improves their cognitive abilities.
- Untargeted metabolomics from serum and brain tissue following the FMT experiments identified δ-valerobetaine as a decisive microbiota-dependent metabolite, which displayed elevated levels with increasing age.
- *In vivo* electrophysiological recordings from the prefrontal cortex of δ-valerobetaine-treated mice showed a distinct change in action potential synchronization, which represents a critical process underlying memory formation.
- We identified prospective bacteria that correlate with δ-valerobetaine levels in the brain.
- δ-valerobetaine exhibits an age-related increase in δ-valerobetaine in human serum.
- δ-valerobetaine is a potential target for combating age-related memory loss.

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