Neuron

Article

Reorganization of adolescent prefrontal cortex circuitry is required for mouse cognitive maturation

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Reorganization of adolescent prefrontal cortex circuitry is required for mouse cognitive maturation

Mouse medial prefrontal cortex exhibits an inverted U-shaped trajectory of high-frequency activity fluctuations, with gamma power peaking in early (peri)adolescence. This adolescent peak in gamma mirrors adolescent peaks in dendritic arborization and spine density on layer 2/3 pyramidal neurons; subsequent gamma reductions coincide with pyramidal pruning from adolescence to adulthood that emerges due to phagocytic microglia activity.

Article framing

- Prefrontal circuit assembly is protracted, required for development of cognitive functioning, but also enhances vulnerability to mental disorders

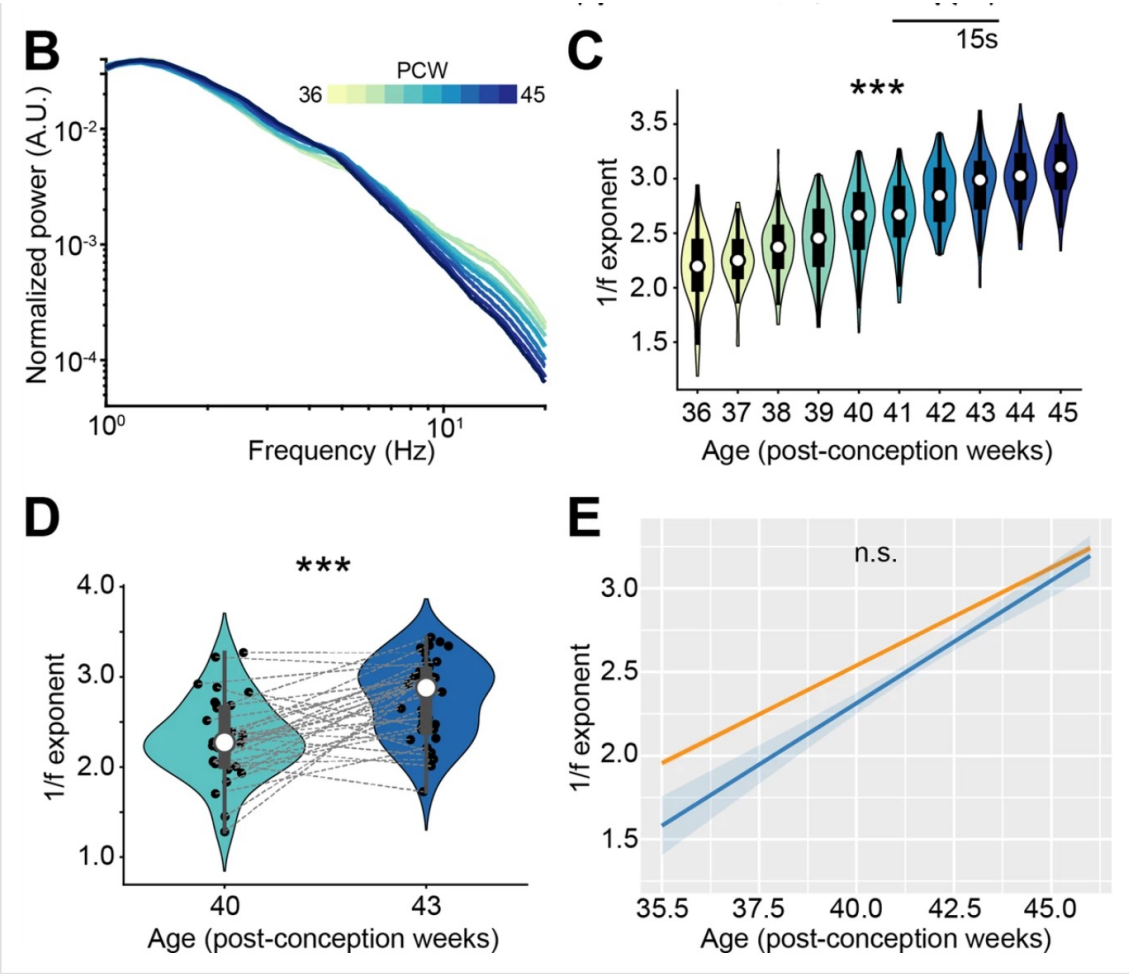
- We need mechanistic knowledge of late prefrontal development
  - Changes in neuromodulatory systems
  - Microglia cell activity
  - Changes in strength of afferent projections
  - Changes in gene expression
  - Pubertal hormones

- We need to understand how these things affect **activity-dependent refinement and assembling of prefrontal circuitry**

Prior work from the Hanganu-Opatz Lab

An increase of inhibition drives the developmental decorrelation of neural activity

Mattia Chini ✉, Thomas Pfeffer, Ileana Hanganu-Opatz



1/f exponent of EEG recordings increases with age in newborn babies.

Prior work from the Hanganu-Opatz Lab

Article

Neuron

A transient developmental increase in prefrontal activity alters network maturation and causes cognitive dysfunction in adult mice

Sebastian H. Bitzenhofer,[1,2,3,*] Jastyn A. Pöpplau,[1,2] Mattia Chini,[1] Annette Marquardt,[1] and Ileana L. Hanganu-Opatz[1,4,*]
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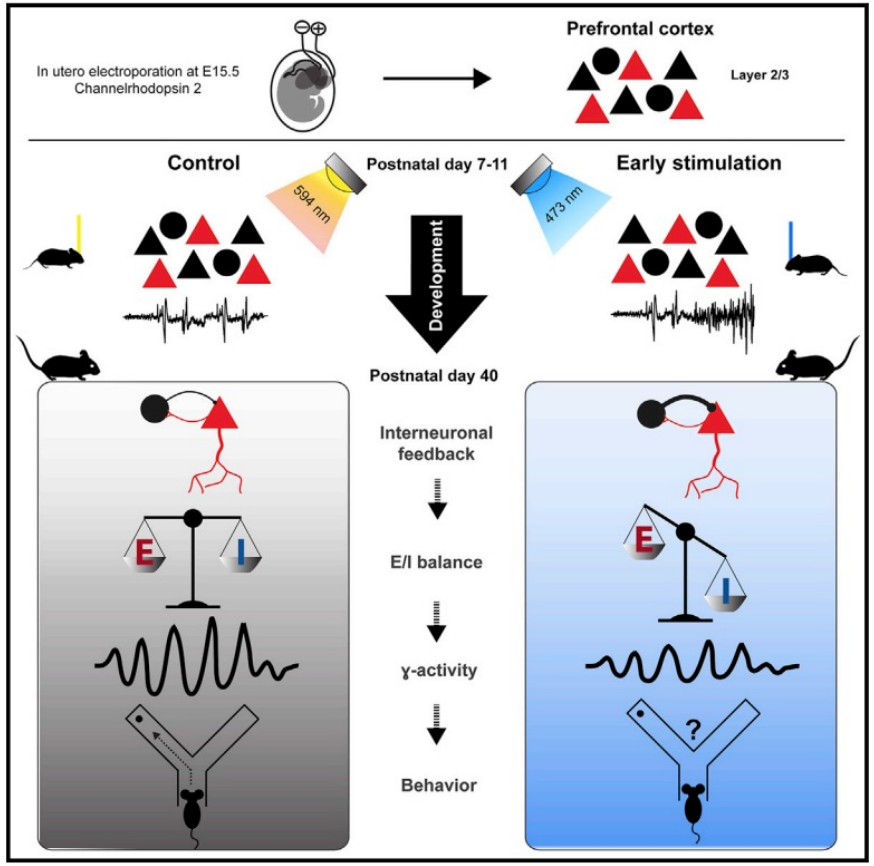
Highlights

- Increasing neonatal coordinated activity causes transient dendritic surge in mPFC
- Increasing neonatal activity disrupts gamma synchrony in adult prefrontal circuits
- Increasing neonatal activity causes excitation/inhibition imbalance in adult mPFC
- Increasing neonatal prefrontal activity disrupts adult cognitive abilities

Graphical Abstract



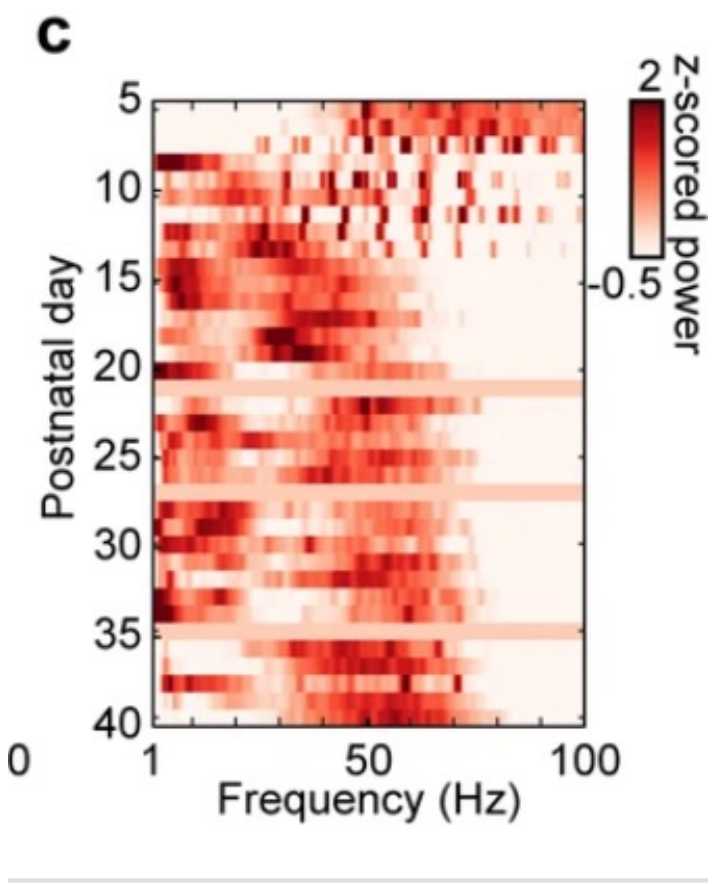
Prior work from the Hanganu-Opatz Lab

Gamma activity accelerates during prefrontal development

Sebastian H Bitzenhofer, Jastyn A Pöpplau, Ileana Hanganu-Opatz

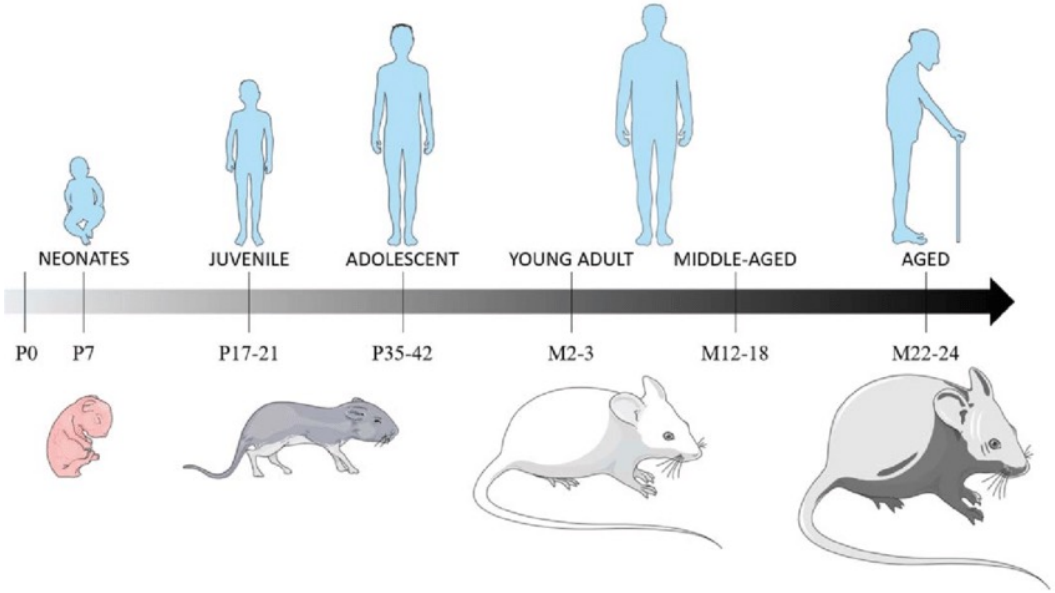
Abstract

Gamma oscillations are a prominent activity pattern in the cerebral cortex. While gamma rhythms have been extensively studied in the adult prefrontal cortex in the context of cognitive (dys)functions, little is known about their development. We addressed this issue by using extracellular recordings and optogenetic stimulations in mice across postnatal development. We show that fast rhythmic activity in the prefrontal cortex becomes prominent during the second postnatal week. While initially at about 15 Hz, fast oscillatory activity progressively accelerates with age and stabilizes within gamma frequency range (30–80 Hz) during the fourth postnatal week. Activation of layer 2/3 pyramidal neurons drives fast oscillations throughout development, yet the acceleration of their frequency follows similar temporal dynamics as the maturation of fast-spiking interneurons. These findings uncover the development of prefrontal gamma activity and provide a framework to examine the origin of abnormal gamma activity in neurodevelopmental disorders.



Methodological approach

- Chronic extracellular monitoring of prefrontal activity combined with optogenetic manipulations from P16 – 60
- Microglia ablation during adolescence and adulthood
- Cognitive tasks



Methodological approach

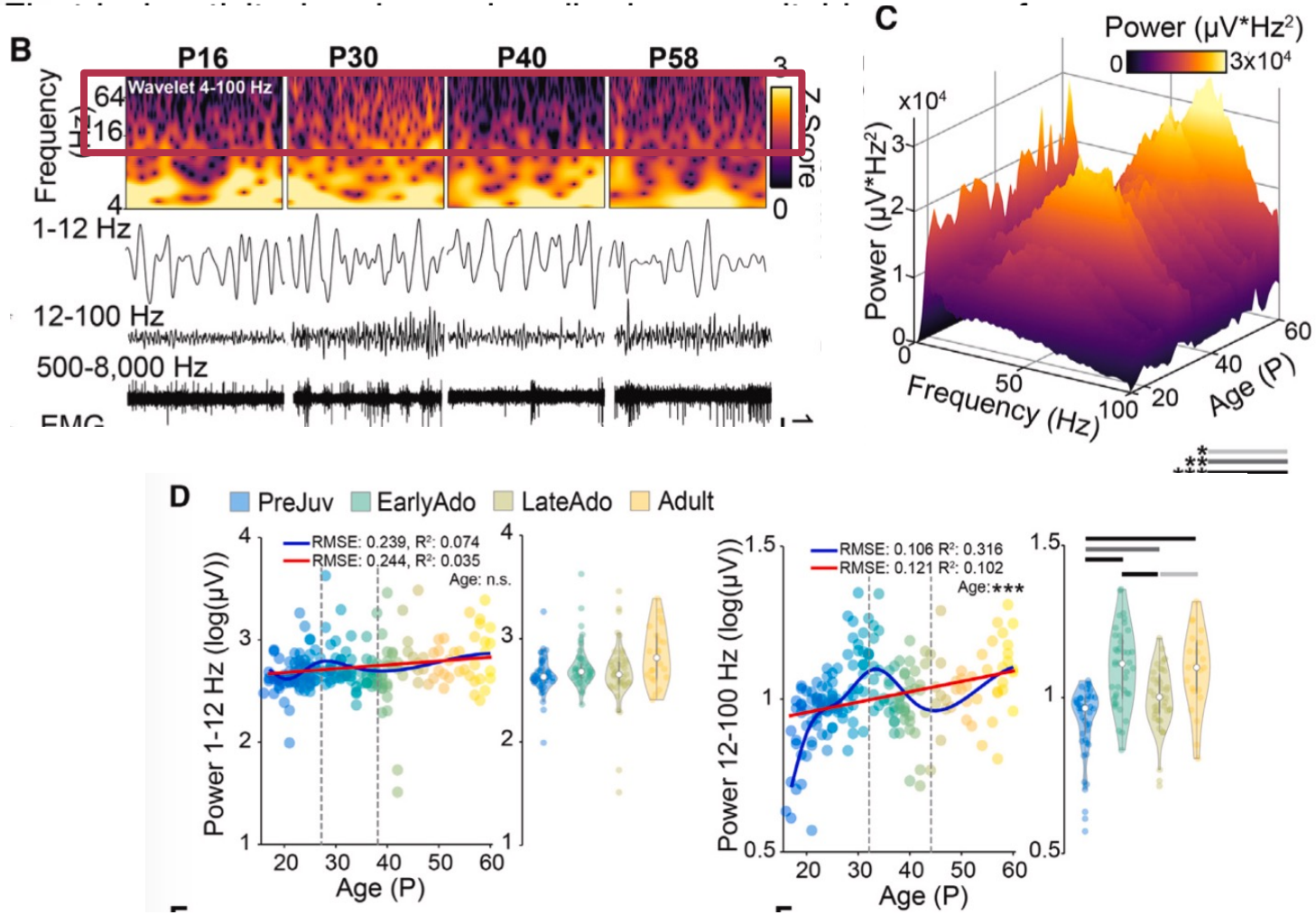
Chronic extracellular monitoring of prefrontal activity combined with optogenetic manipulations from P16 – 60

- Multisite extracellular head-fixed recordings were performed unilaterally in the mPFC (prelimbic cortex) or S1 of P16–60 and P98–102 mice
- In mPFC: one-shank, A1x16 recording sites, 100 mm spacing, 2.0 mm deep
- Recorded for 30-60 minutes
- Recorded the same mice up to 18 times
- Analyzed LFPs from L2/3
- Mice were freely moving or resting on a spin plate: main results are resting; sensitivity are moving

Slow activity in mPFC is largely age-independent.

Power in the fast frequency range shows a progressive increase until early adolescence, followed by a reduction in late adolescence.

Prefrontal activity undergoes a nonlinear reorganization during adolescence

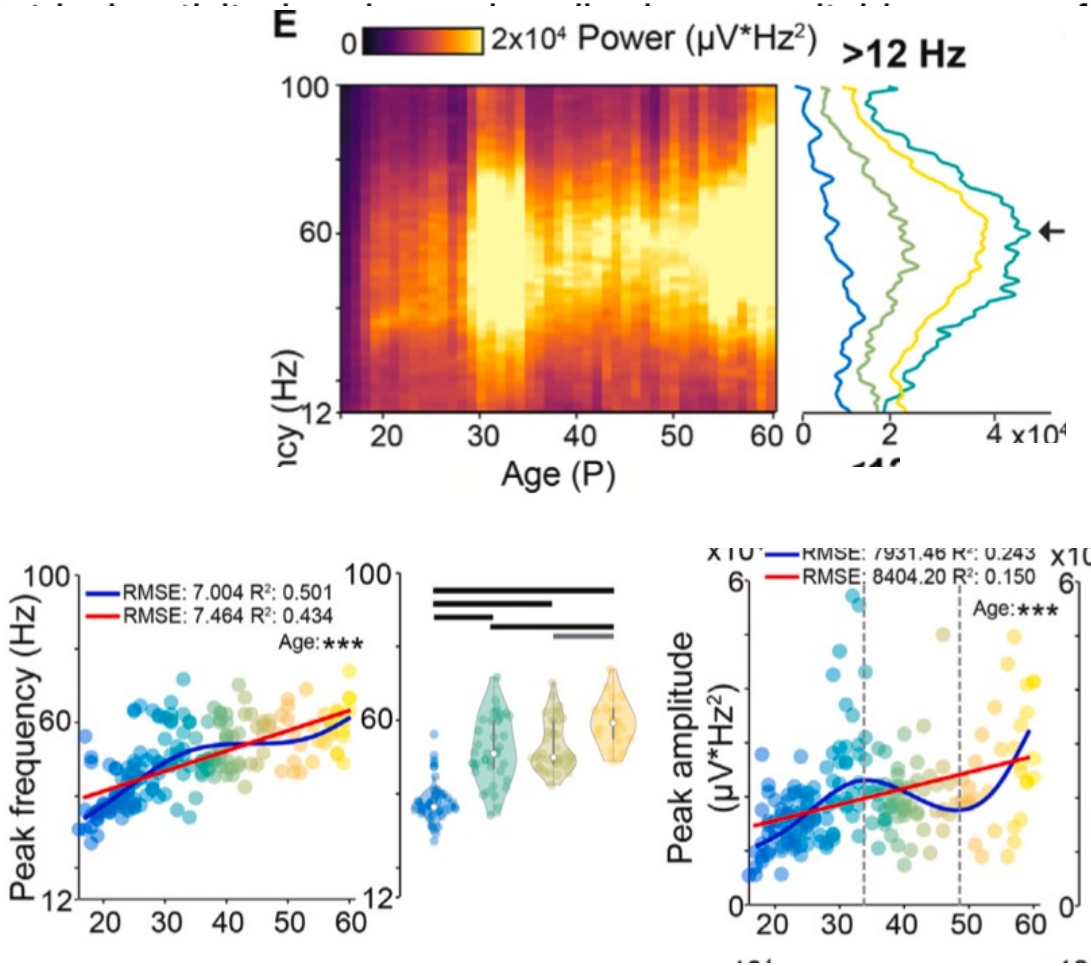


PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Peak frequency of gamma band activity increases with age.

Peak amplitude of gamma band activity shows a peak in early adolescence.

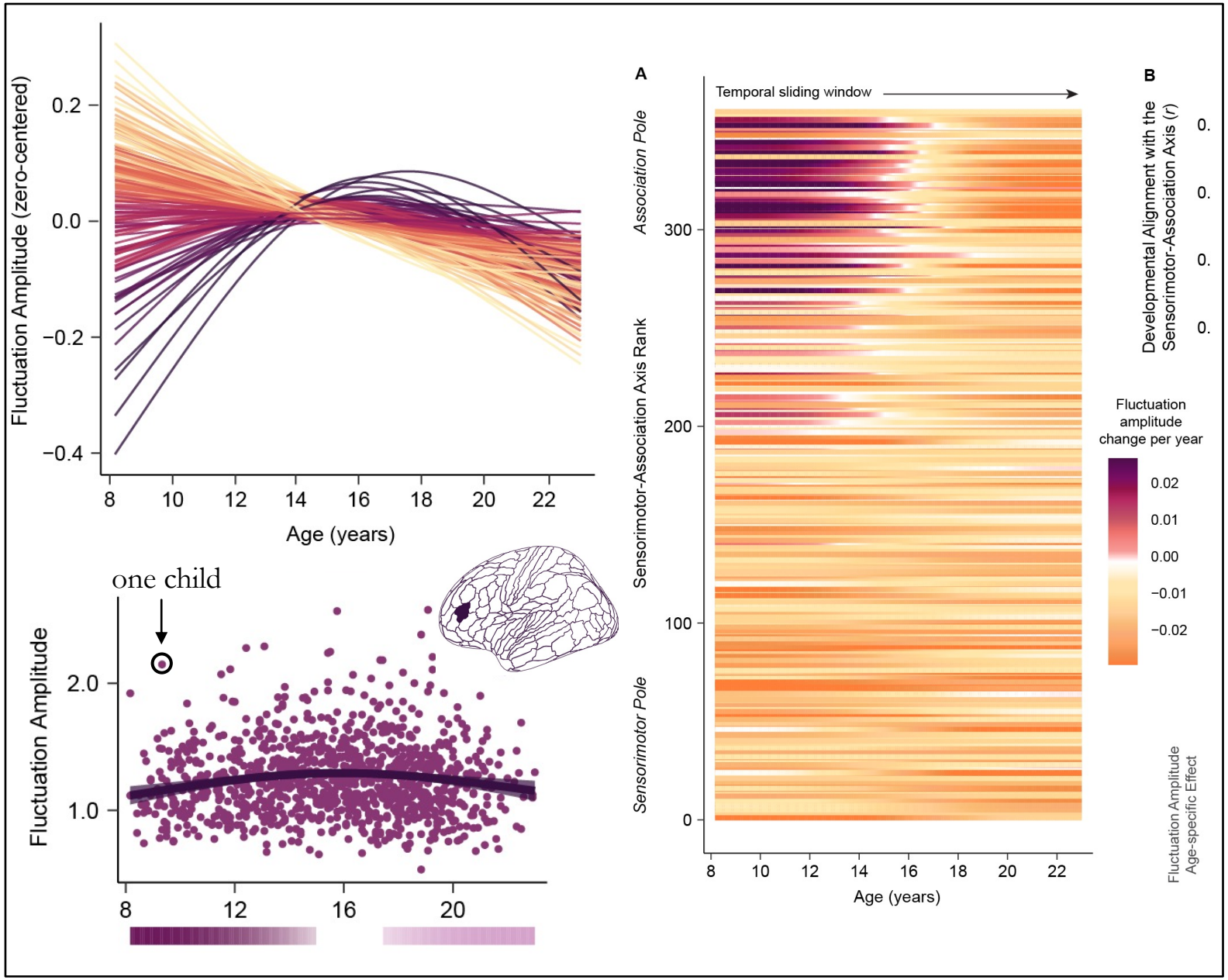
Prefrontal activity undergoes a nonlinear reorganization during adolescence



Gamma band = 30-80 Hz

PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Fluctuation Amplitude Development Varies Across the Cortex

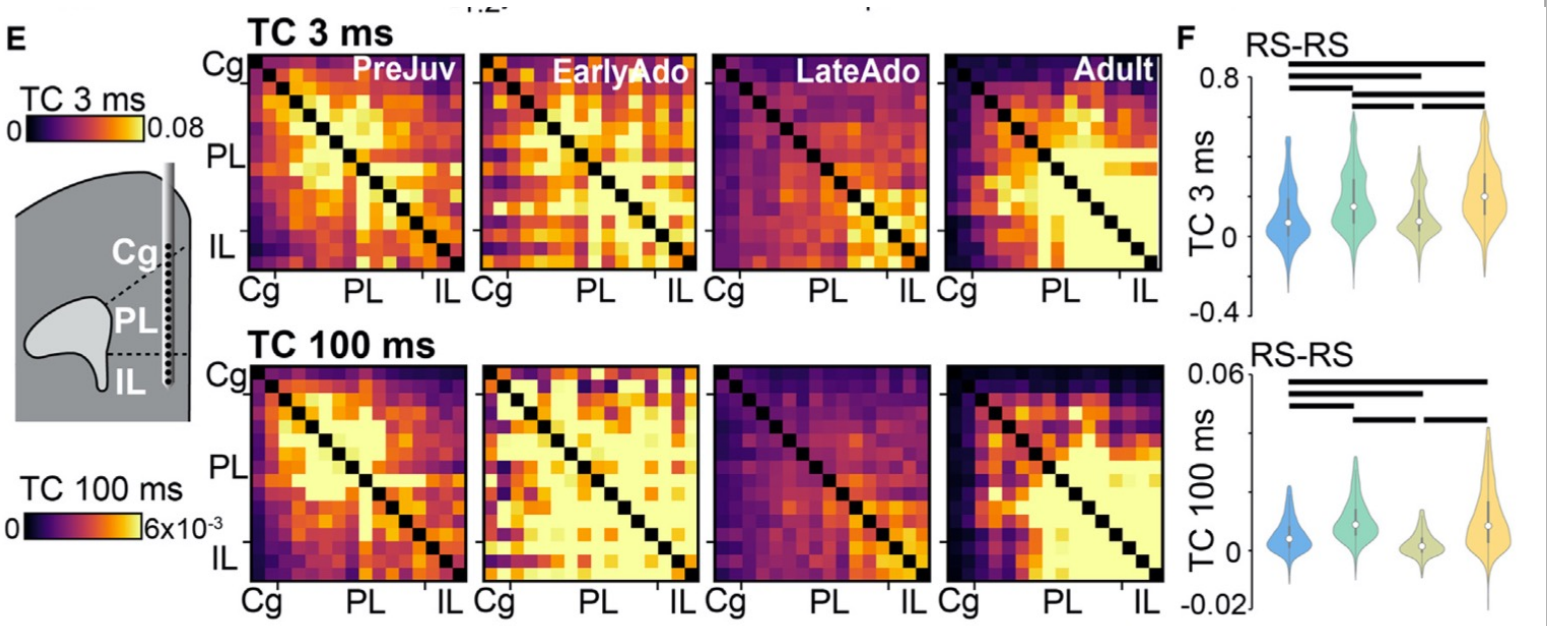


Firing of L2/3 pyramidal neurons increase is greatest in early adolescence, with second peak in adulthood. Correlated spiking activity is augmented in early adolescence and declines in late adol.

Firing of PV+ interneurons linearly changes.

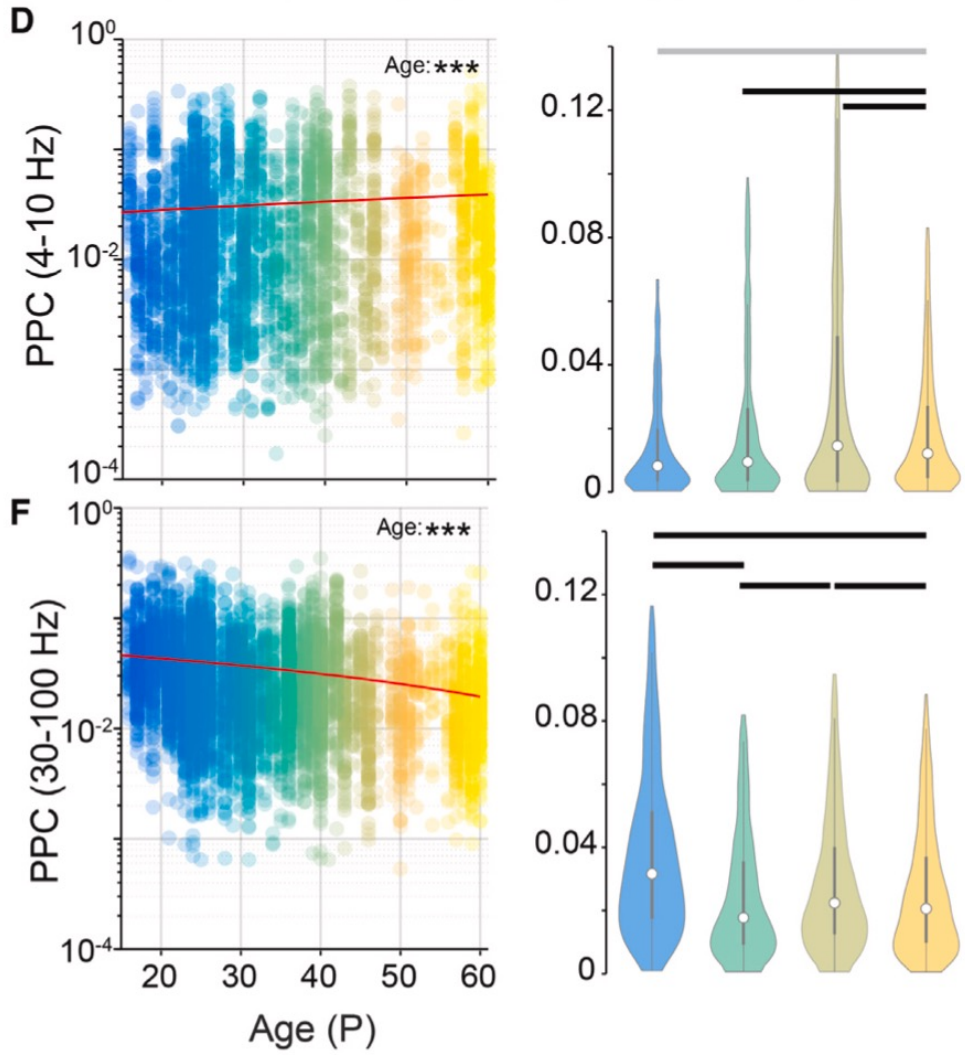
Spiking of putative prefrontal L2/3 PYRs resembles the age-dependent dynamics of gamma oscillations

TC = tiling coefficient, a firing rate-independent measure of correlated spiking activity



PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Phase locking of neuronal firing (from single unit activity) increases to theta oscillations with age but locking strength to gamma oscillations decreases with age



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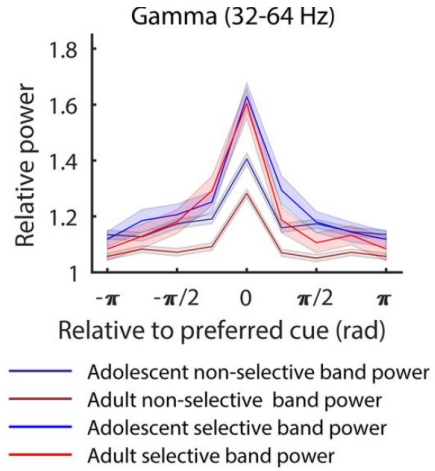
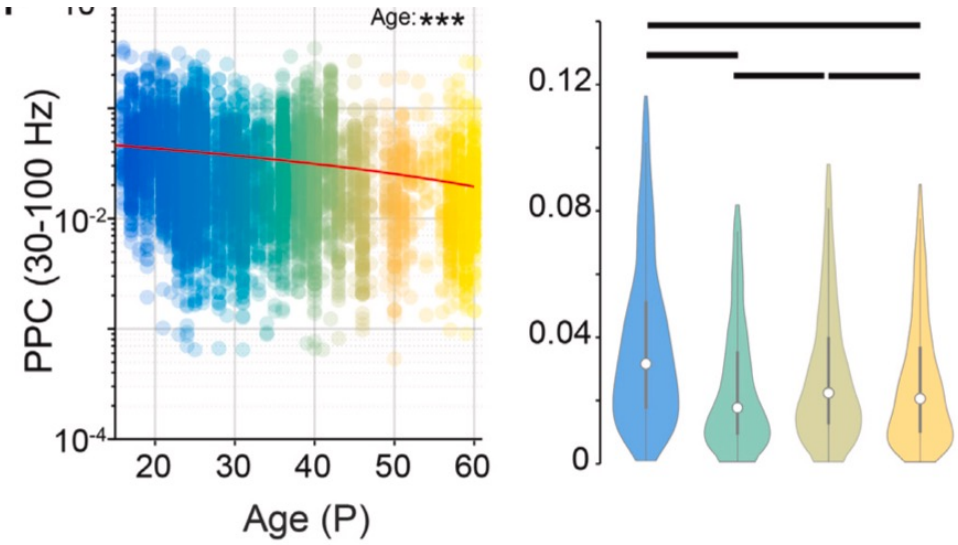
Strong Gamma Frequency Oscillations in the Adolescent Prefrontal Cortex

Zhengyang Wang, Balbir Singh, Xin Zhou, and Christos Constantinidis

Journal of Neuroscience 6 April 2022, 42 (14) 2917-2929; DOI: https://doi.org/10.1523/JNEUROSCI.1604-21.2022

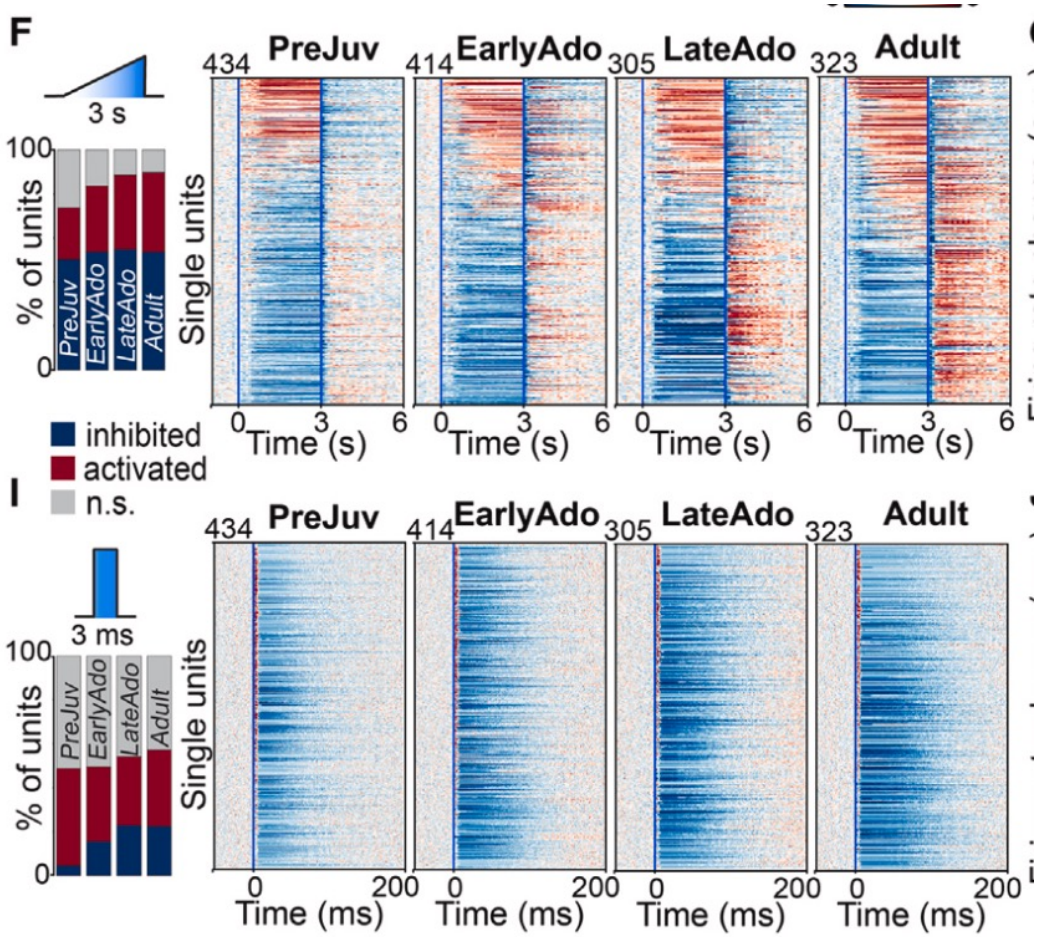


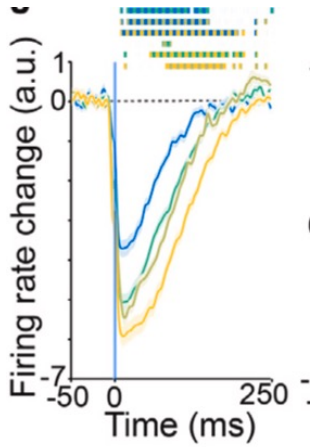


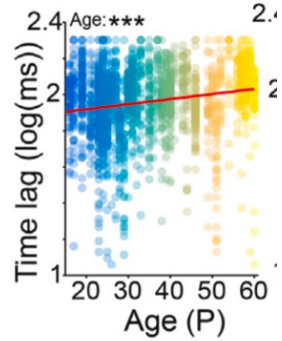
PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Inhibitory drive and firing rate of prefrontal interneurons onto L2/3 pyramidal cells increases linearly in development

The inhibitory effect of interneuronal firing in the mPFC gradually increases with age







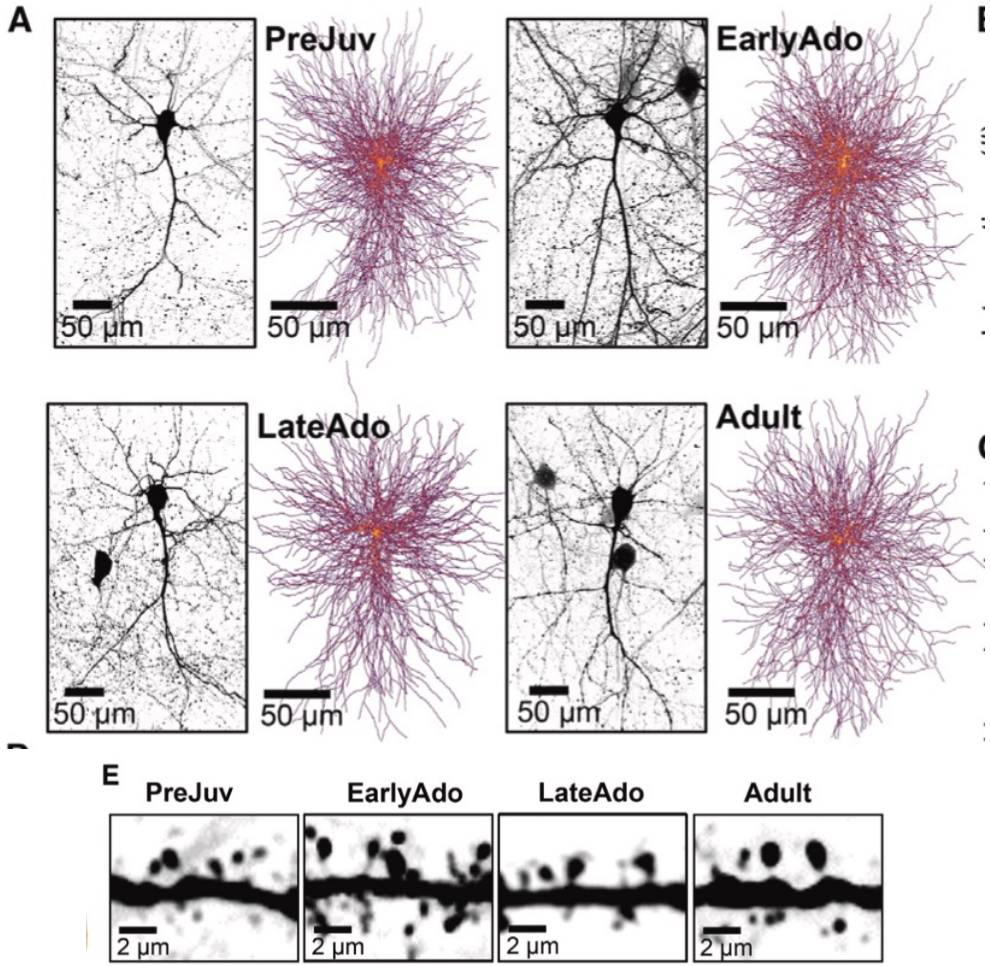
PreJuv
EarlyAdo
LateAdo
Adult

PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Dendritic arborization complexity, dendritic length, and spine density of L2/3 pyramidal neurons peaked during early adolescence.

Adolescence is likely characterized by increased excitatory connectivity in mPFC.

Prefrontal L2/3 PYRs experience microglia-mediated structural remodeling during adolescence



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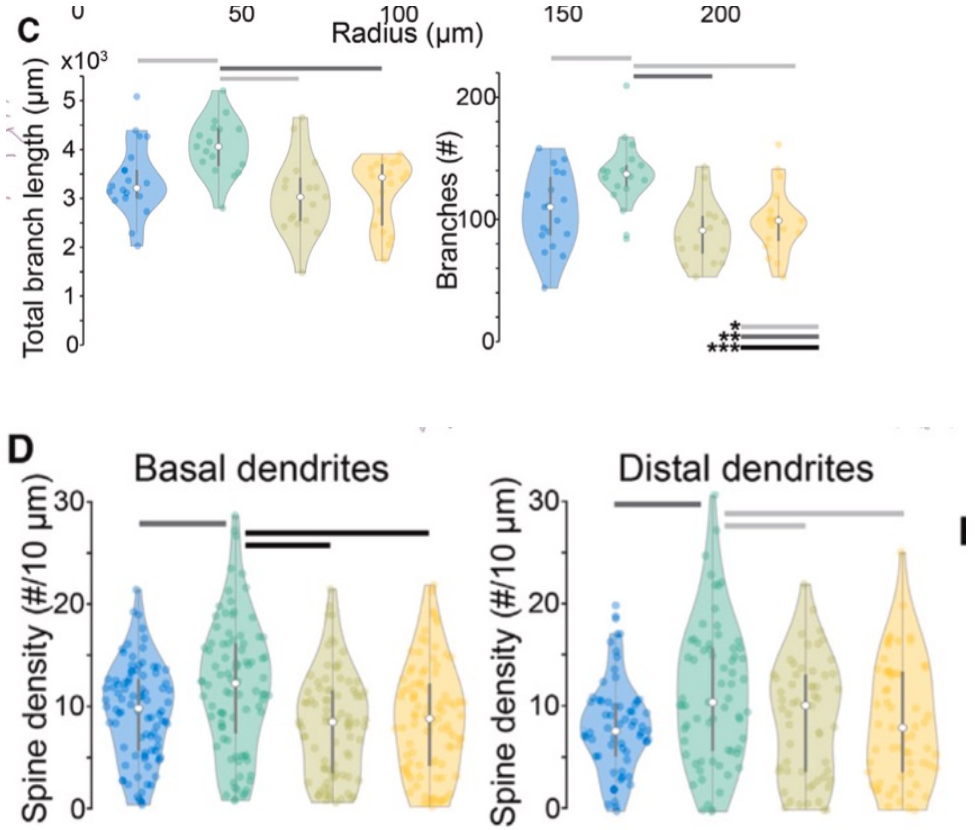

PreJuv: P16-P23; EarlyAdo: P28-P35; LateAdo: P36-P43; Adult: P53-P60

Microglia density decreased in late adolescence.

Microglia are more phagocytically active throughout adolescence.

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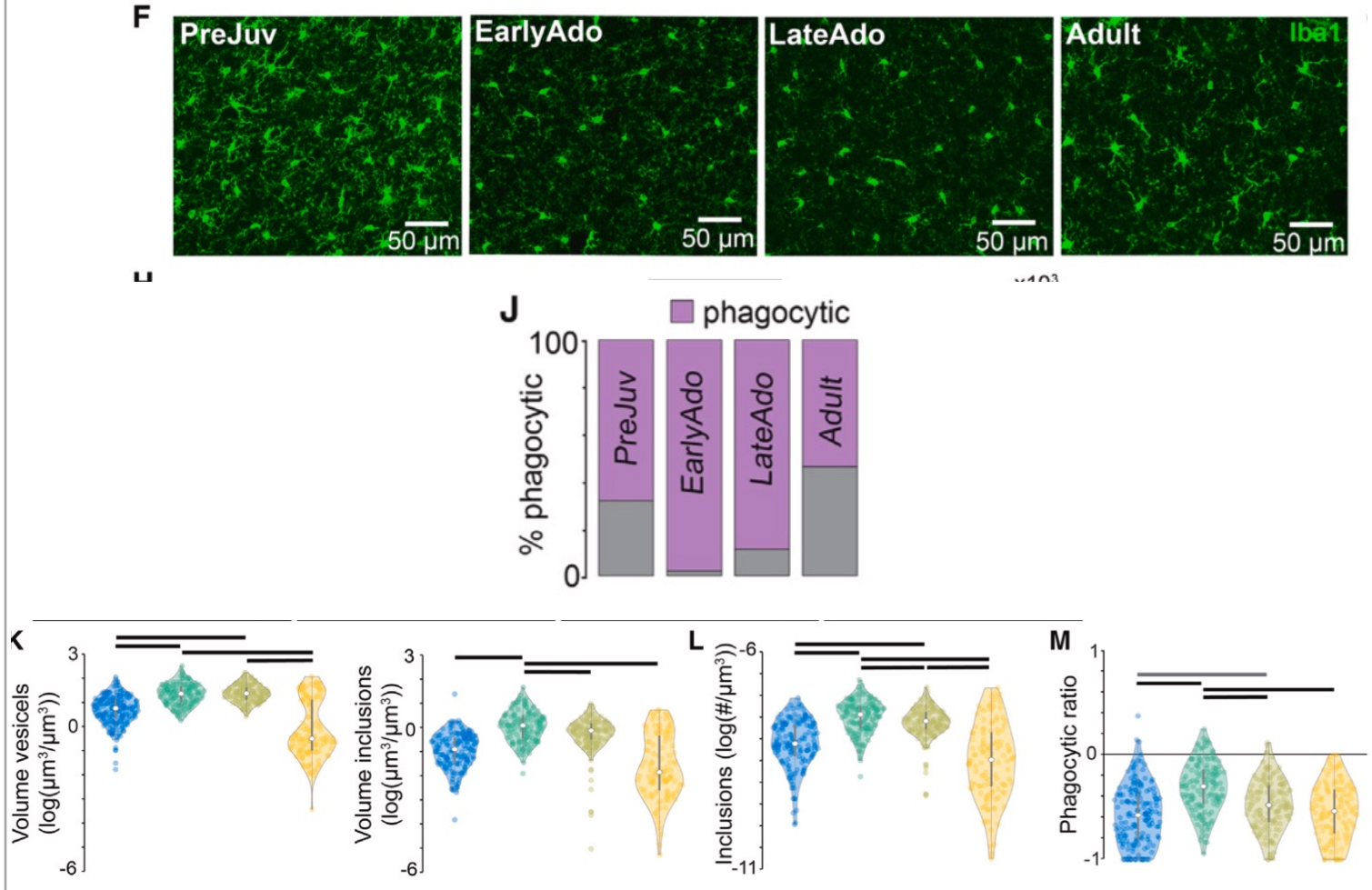

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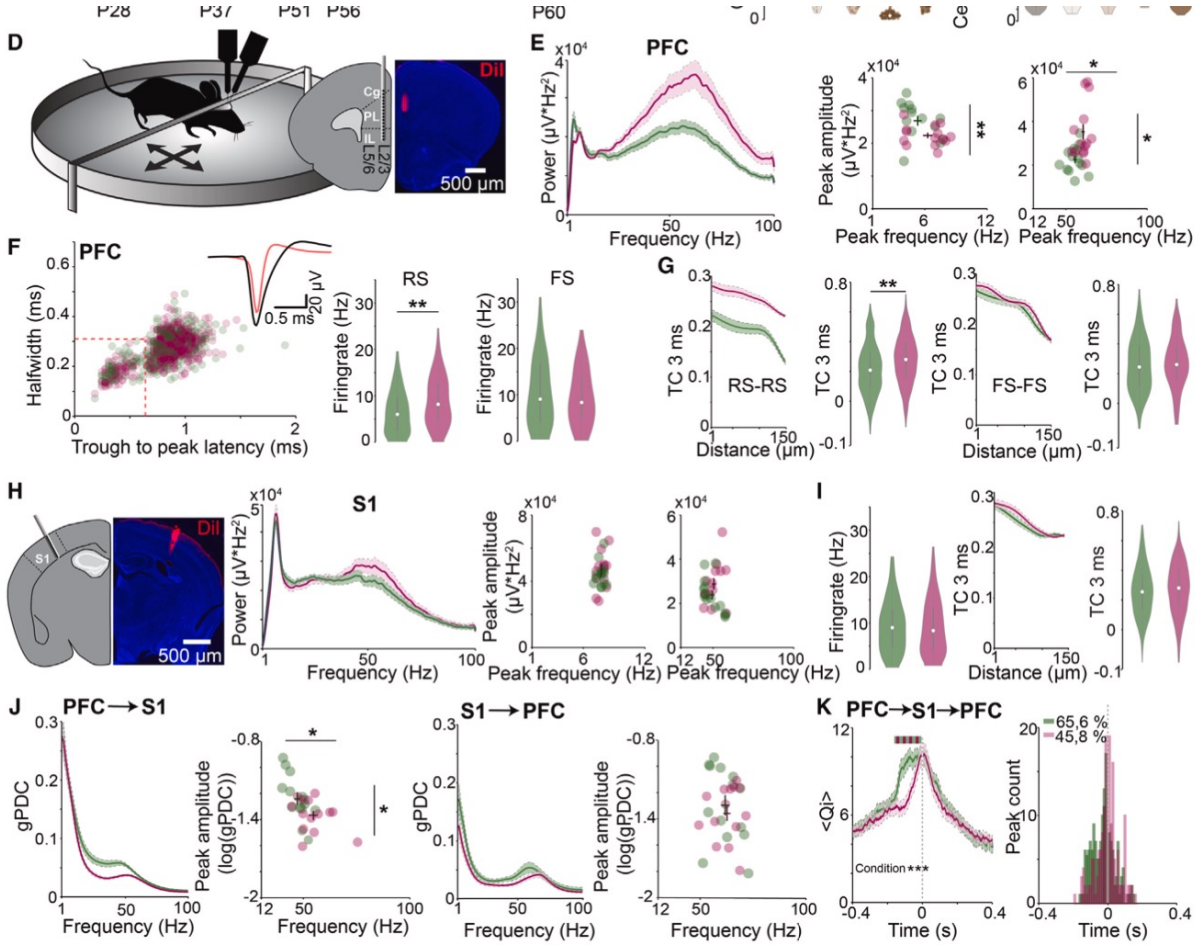

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