Synaptic dysfunction in rare neuroimmune diseases

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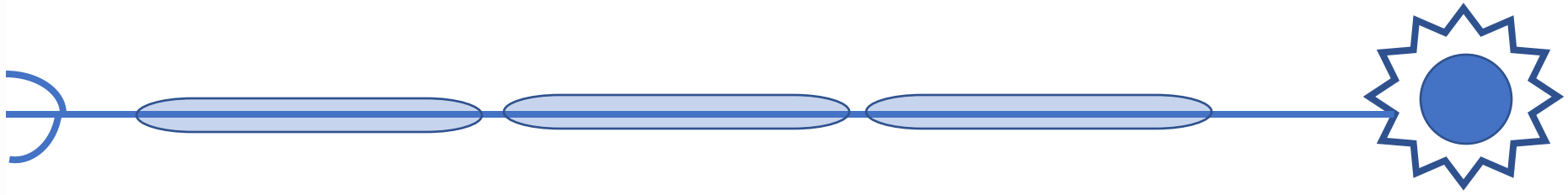
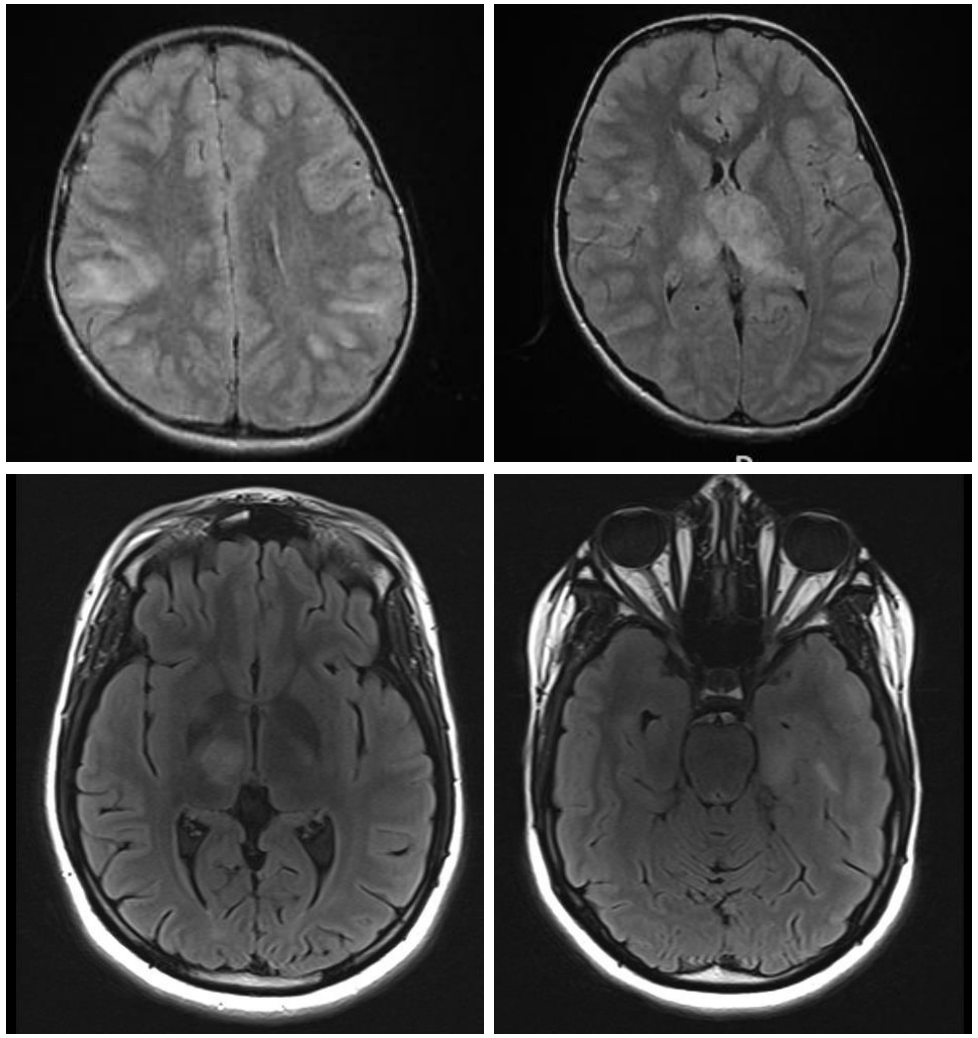


Rare neuroimmune diseases in children

MOGAD

NMOSD



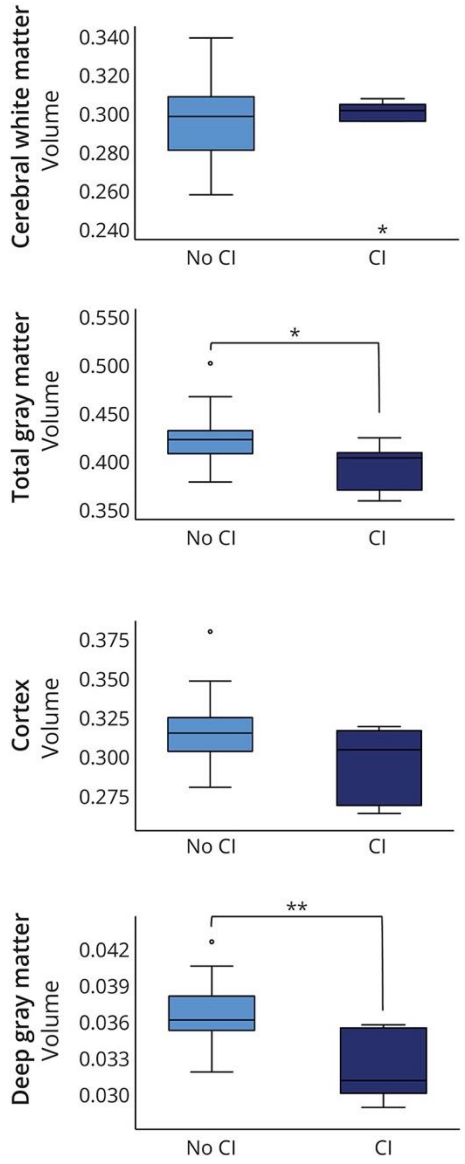
- Global incidence of acute demyelinating syndrome estimated to be 0.87/100,000 children per year
- Myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD): 30-40%
- Aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder (AQP4-NMOSD): <5%
- Multiple sclerosis (MS): 20%

Fadda et al (2021) Lancet Neurology

Cognitive impairment in MOGAD patients is associated with gray matter volume loss

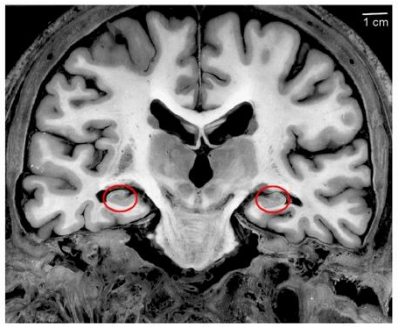
Table 2 Frequency of Cognitive Dysfunction in Various Domains and Overall Cognitive Impairment, Fatigue, and Depression

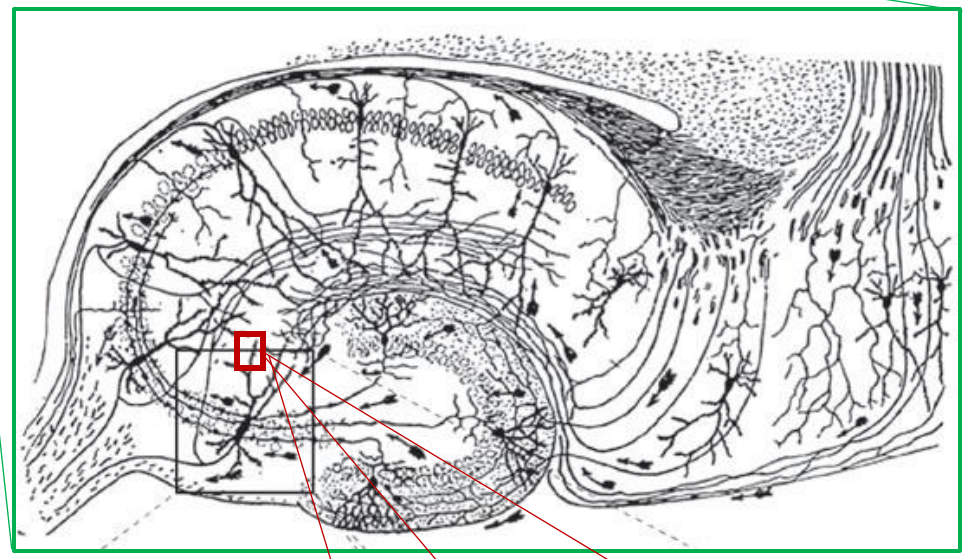
Cognitive function	Test	Abnormal cognitive performance,[a] %
Mental flexibility	RWT, phonematic category change	16.7
Attention		
Phasic alertness	TAP, subtest alertness	14.8
Tonic alertness	TAP, subtest alertness	11.1
Verbal working memory	WMS-R, subtest digit span backwards	10.3
Mental rotation	LPS 7	8.3
Visual short-term memory	WMS-R, subtest visual reproduction	8.3
Verbal learning	VLMT, recall 5	6.5
Verbal short-term memory	WMS-R, subtest digit span forwards	6.3
Verbal (long-term) memory	VLMT, recall 7	3.2
Cognitive impairment[b]		21.9

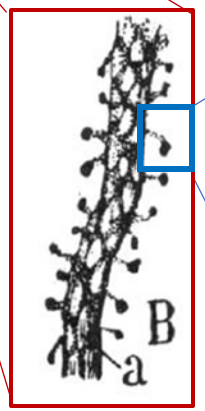


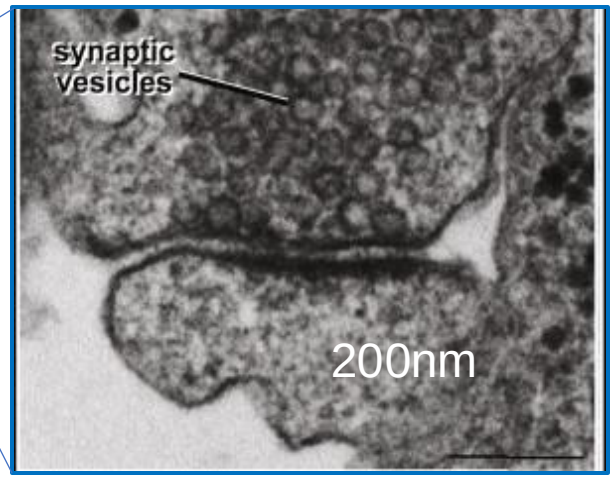
Kogel et al (2024) Neurology Neuroimmunology & Neuroinflammation

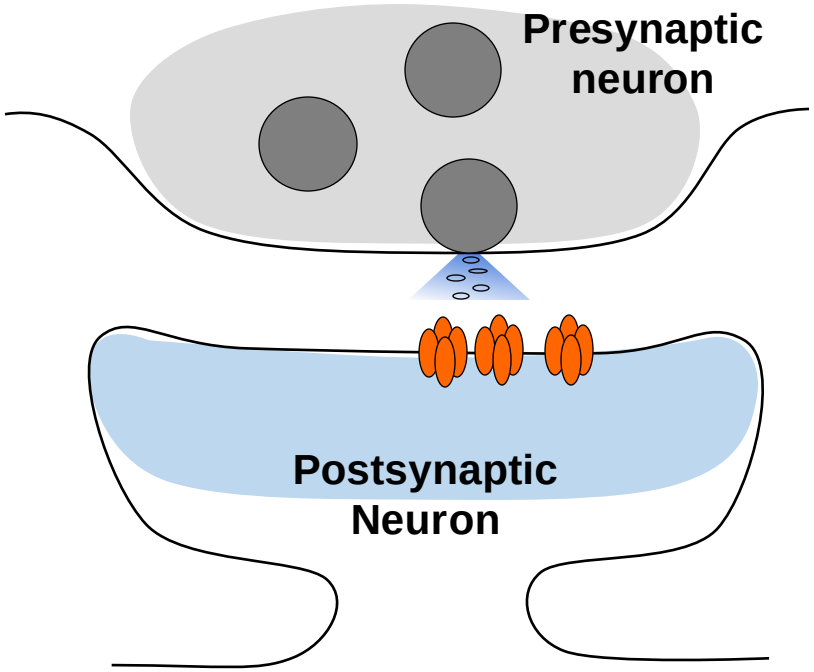
Synapses are the fundamental units for cognition

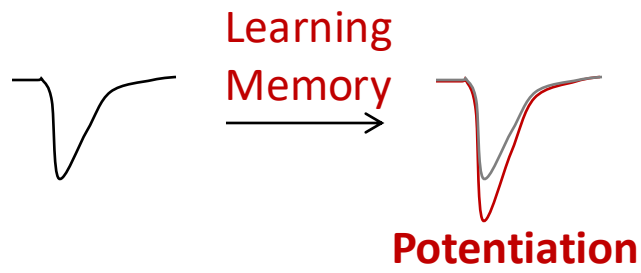






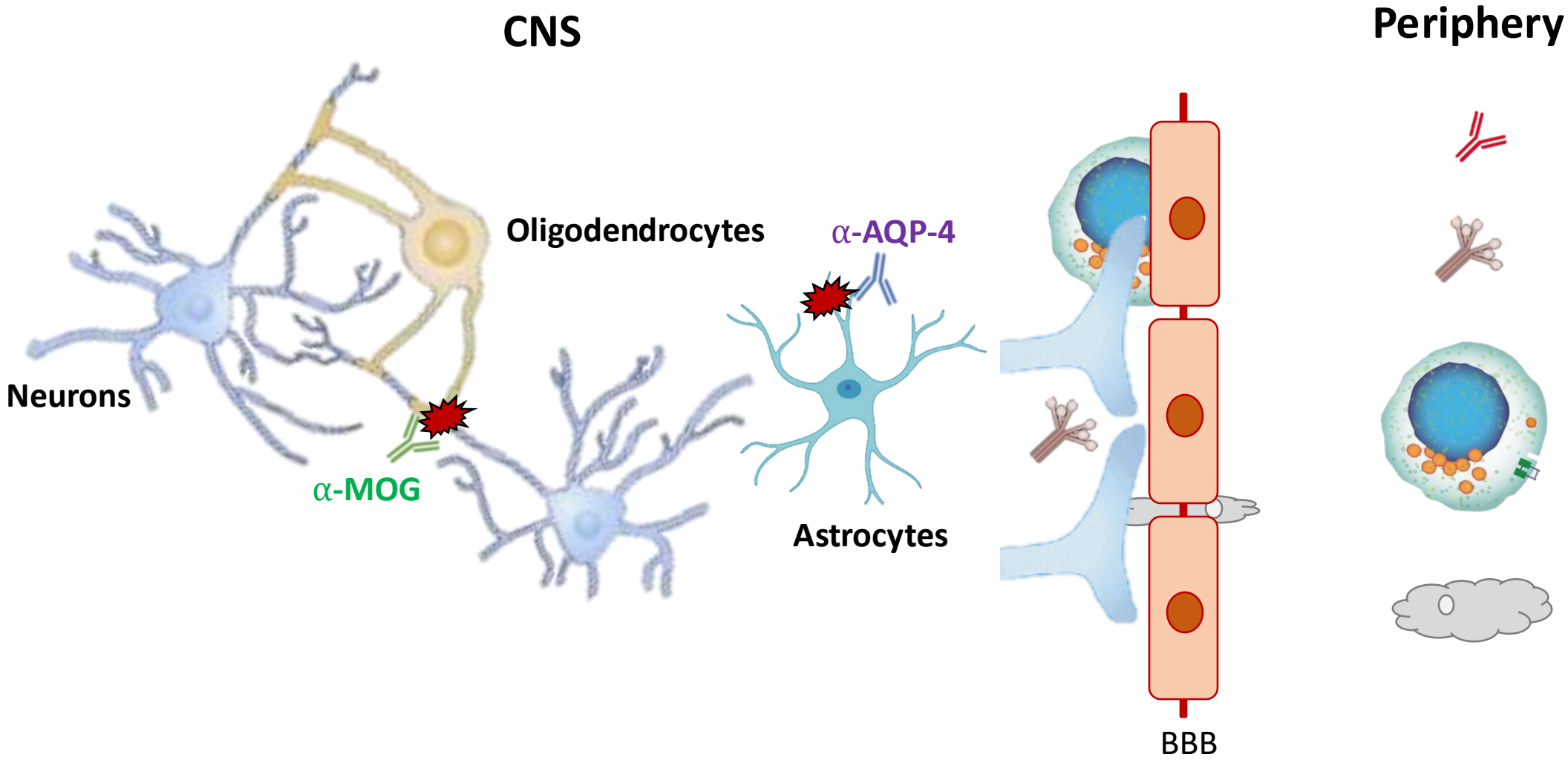




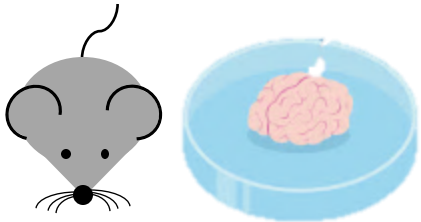


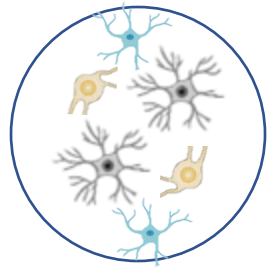
Ramon y Cajal (c1900), Sudhof (2012) *Neuron*

Synaptic dysfunction as a mechanism of injury in rare neuroimmune diseases

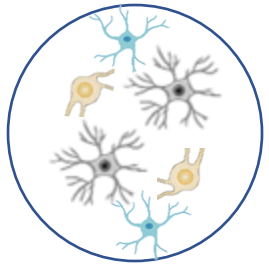


How do neuroimmune diseases disrupt synapses?



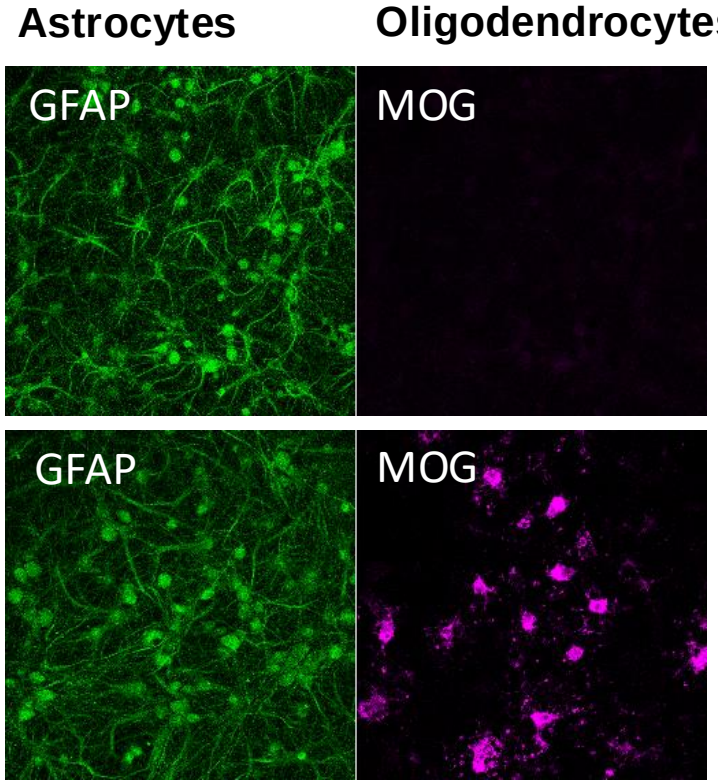


Primary Cultures



Neu
Neurons, Astrocytes

OL
Neurons, Astrocytes,
Oligodendrocytes

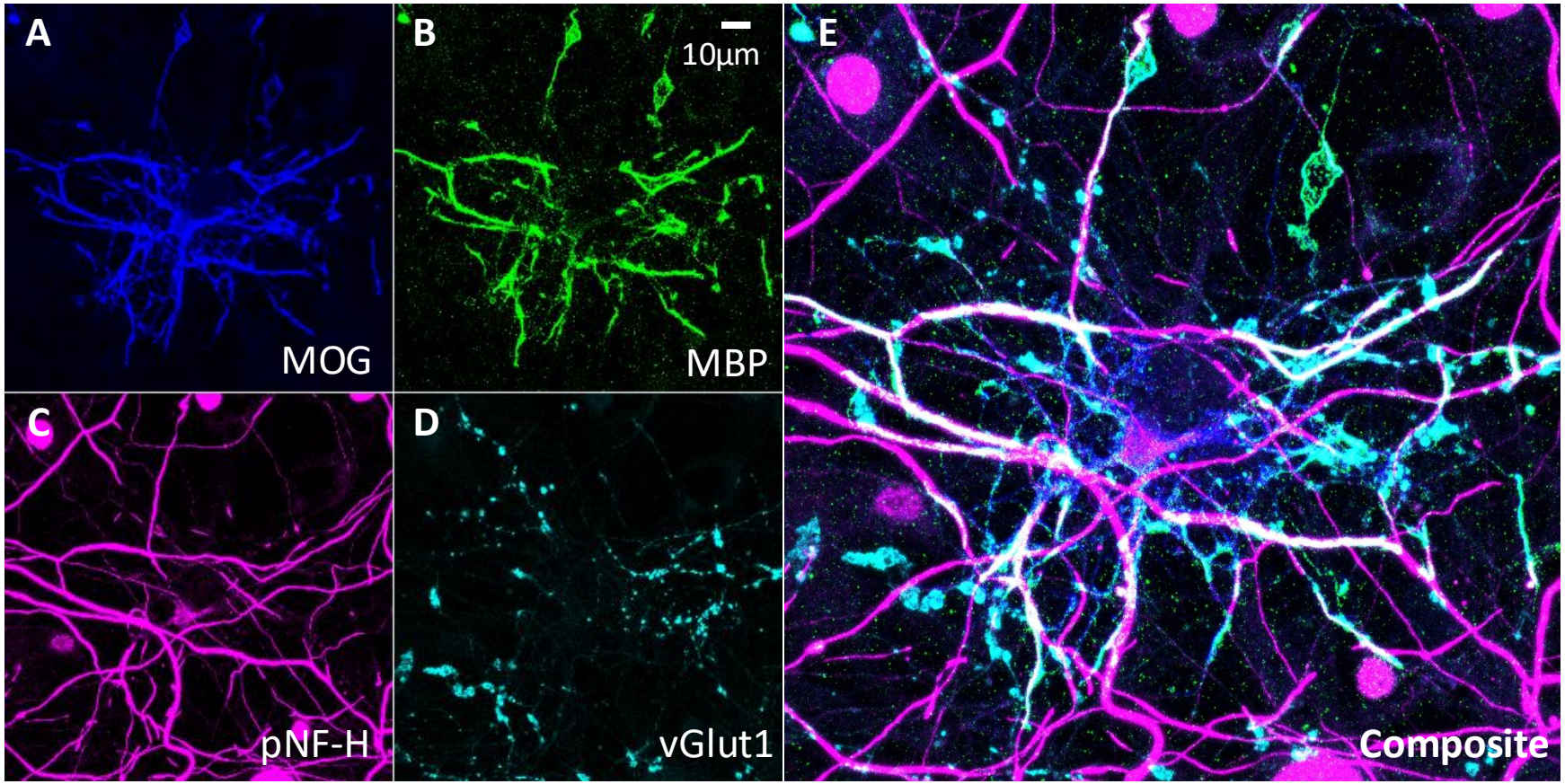


Evaluate synapses

Structure

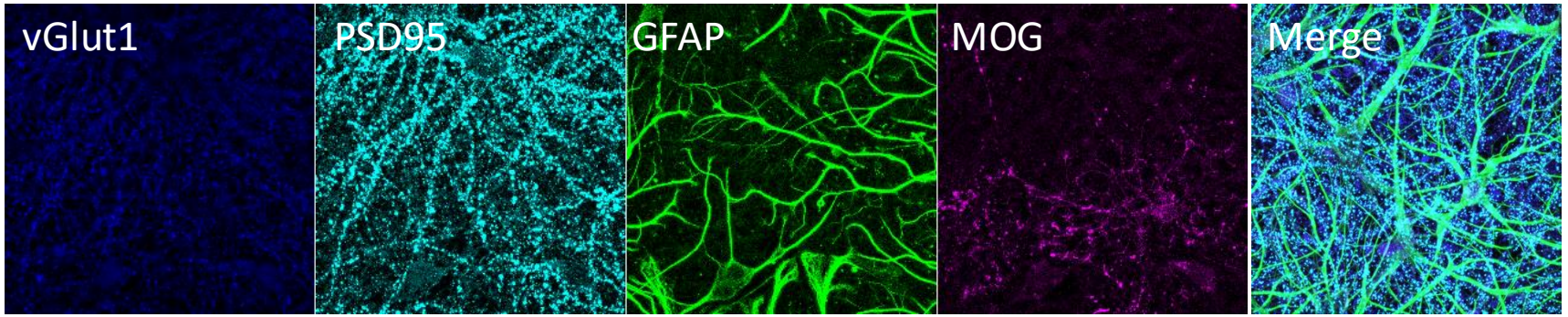
Function

Establishing an in vitro model system for neuronal-glial interactions

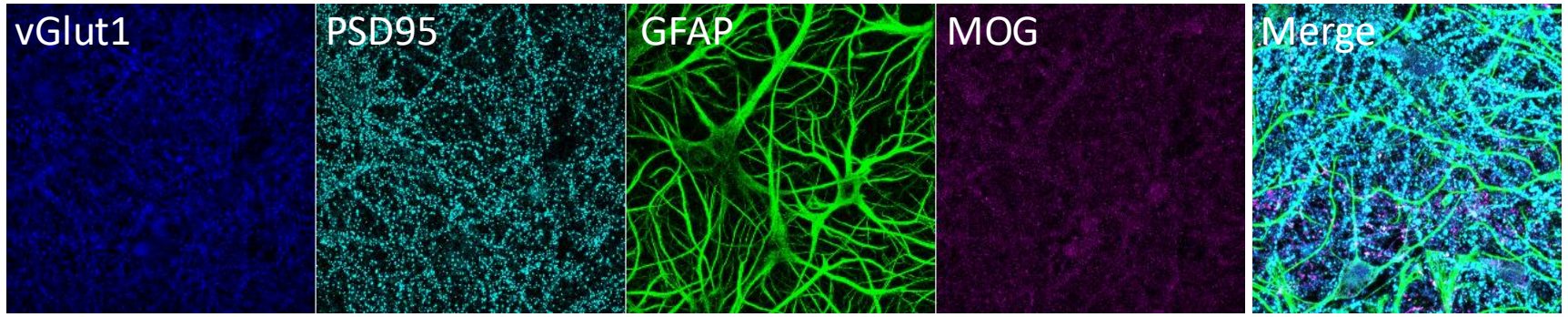


Oligos may influence synapse composition over development

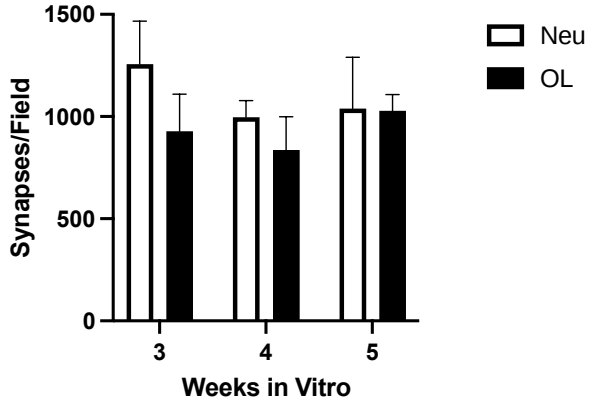
OL

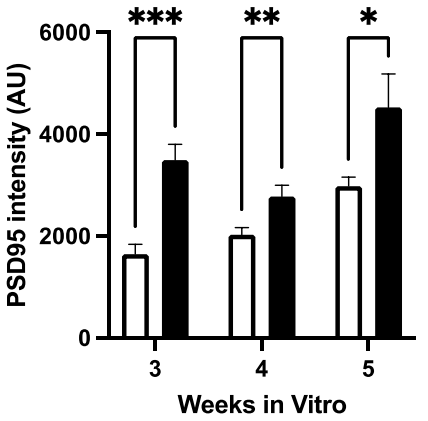


Neu

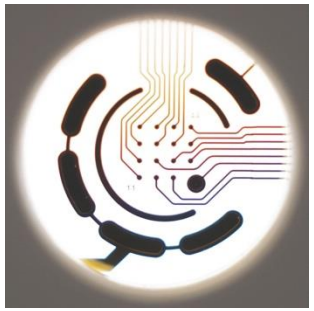


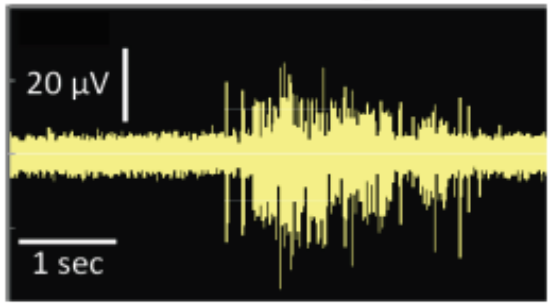
10µm

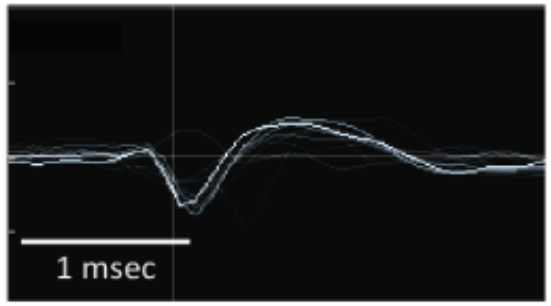


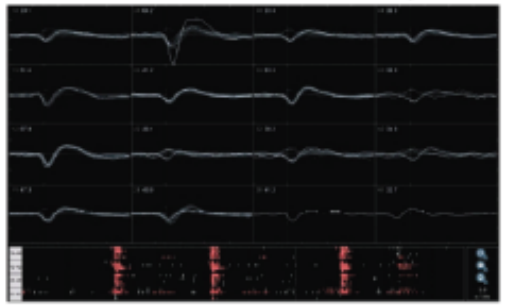


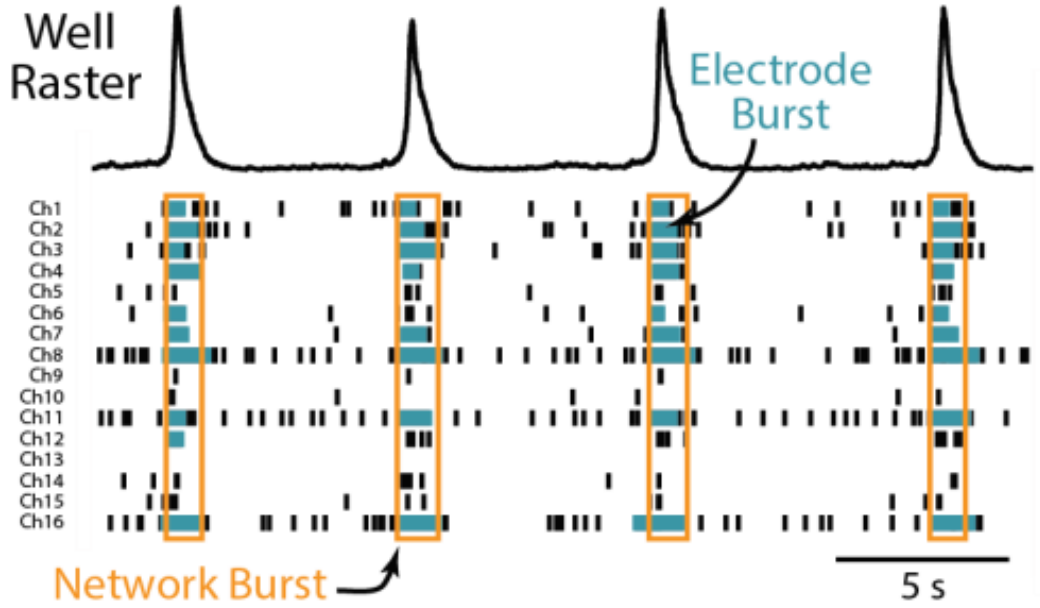
Measuring synaptic activity using Multi-Electrode Arrays (MEA)

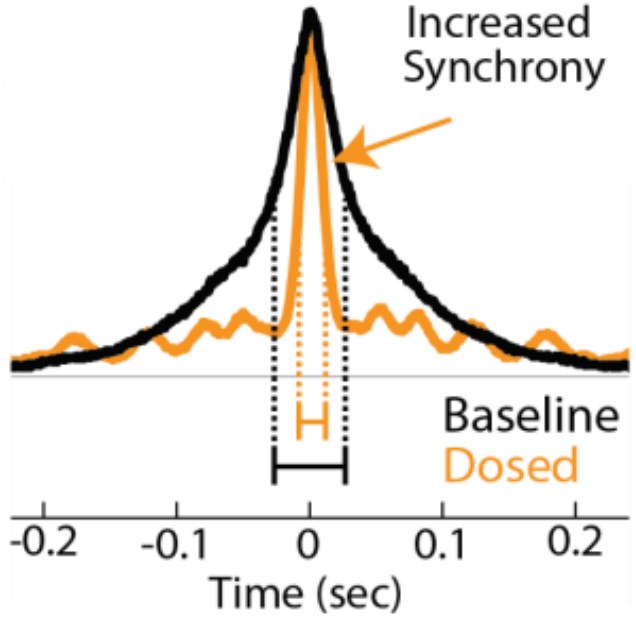






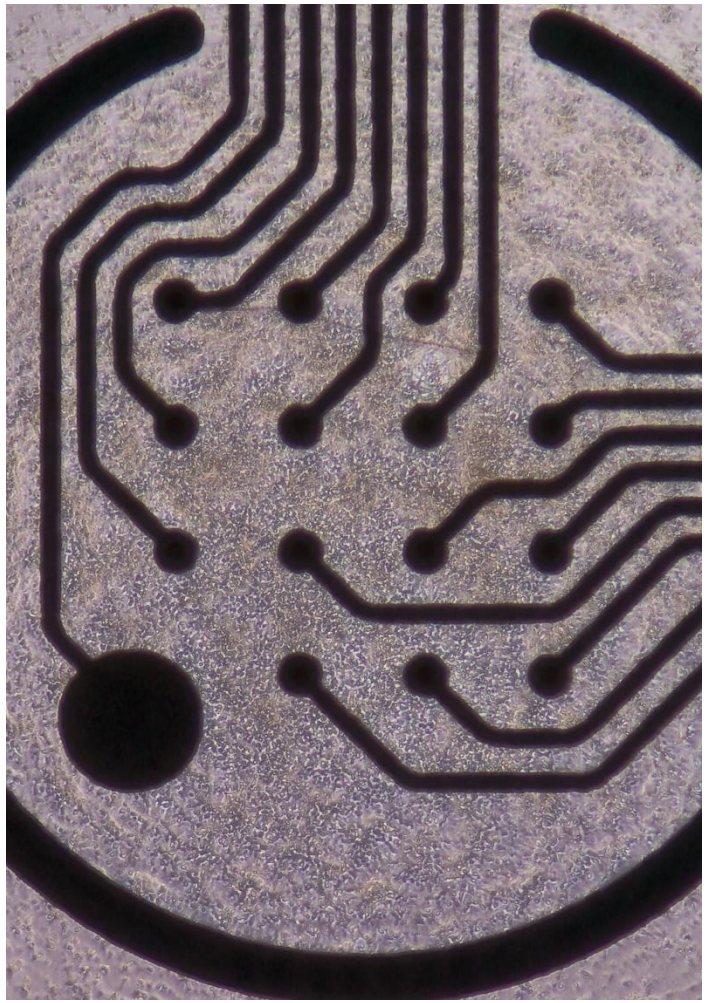






Axion Biosystems

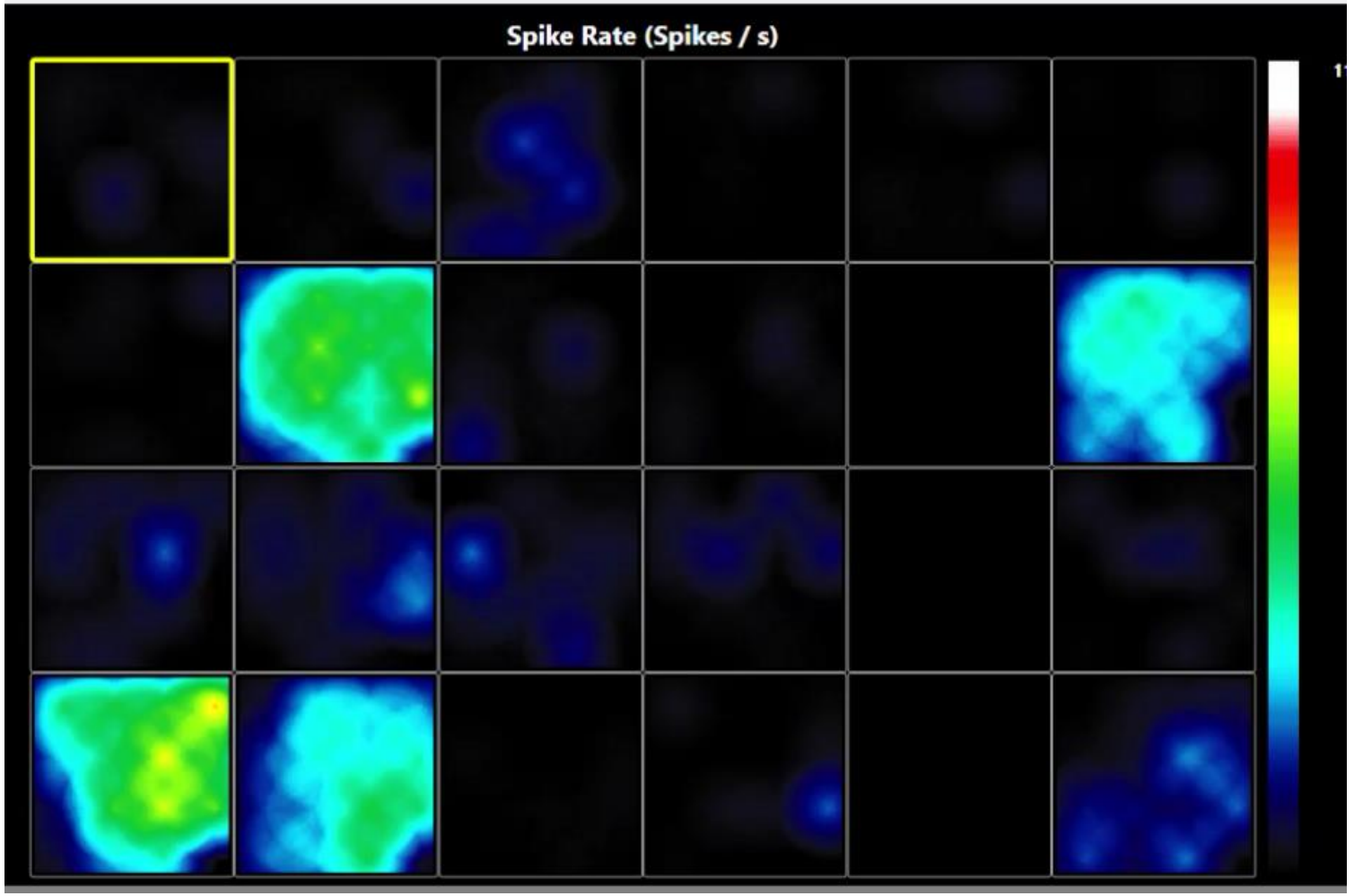
Oligos change the pattern of neuronal firing



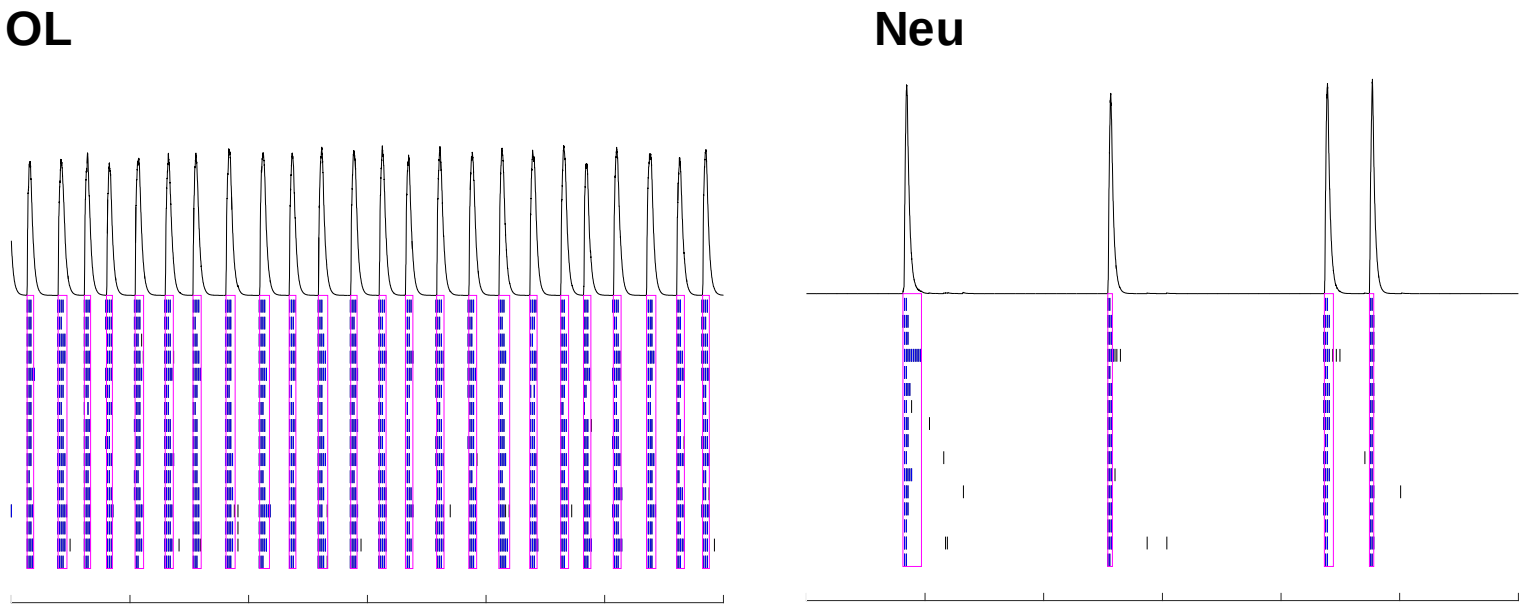
200µm

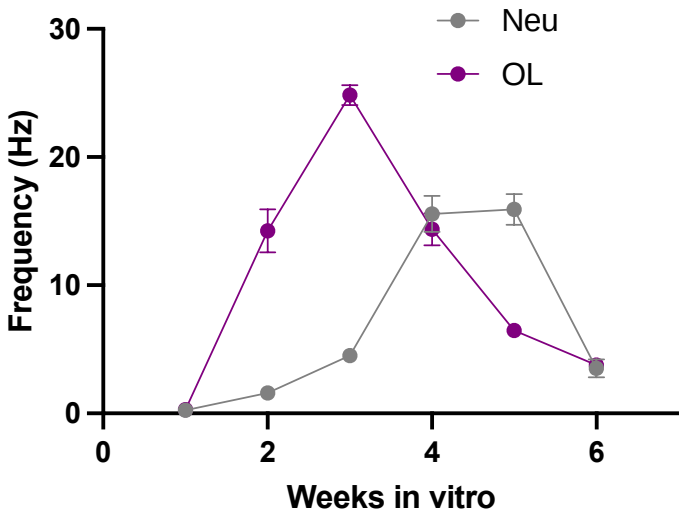
OL

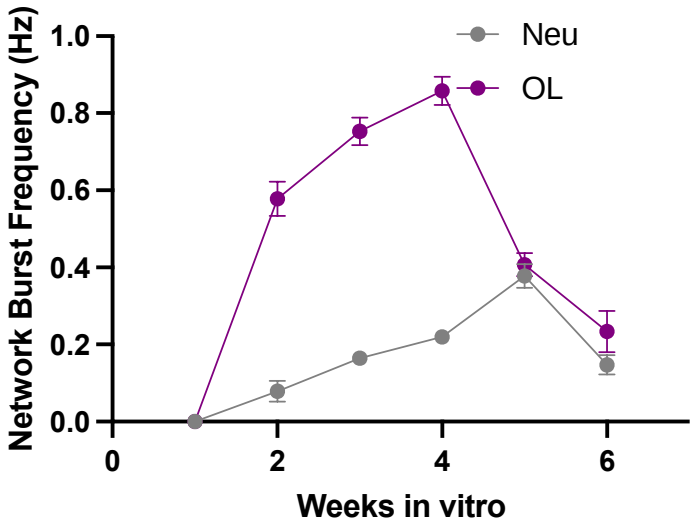
Neu



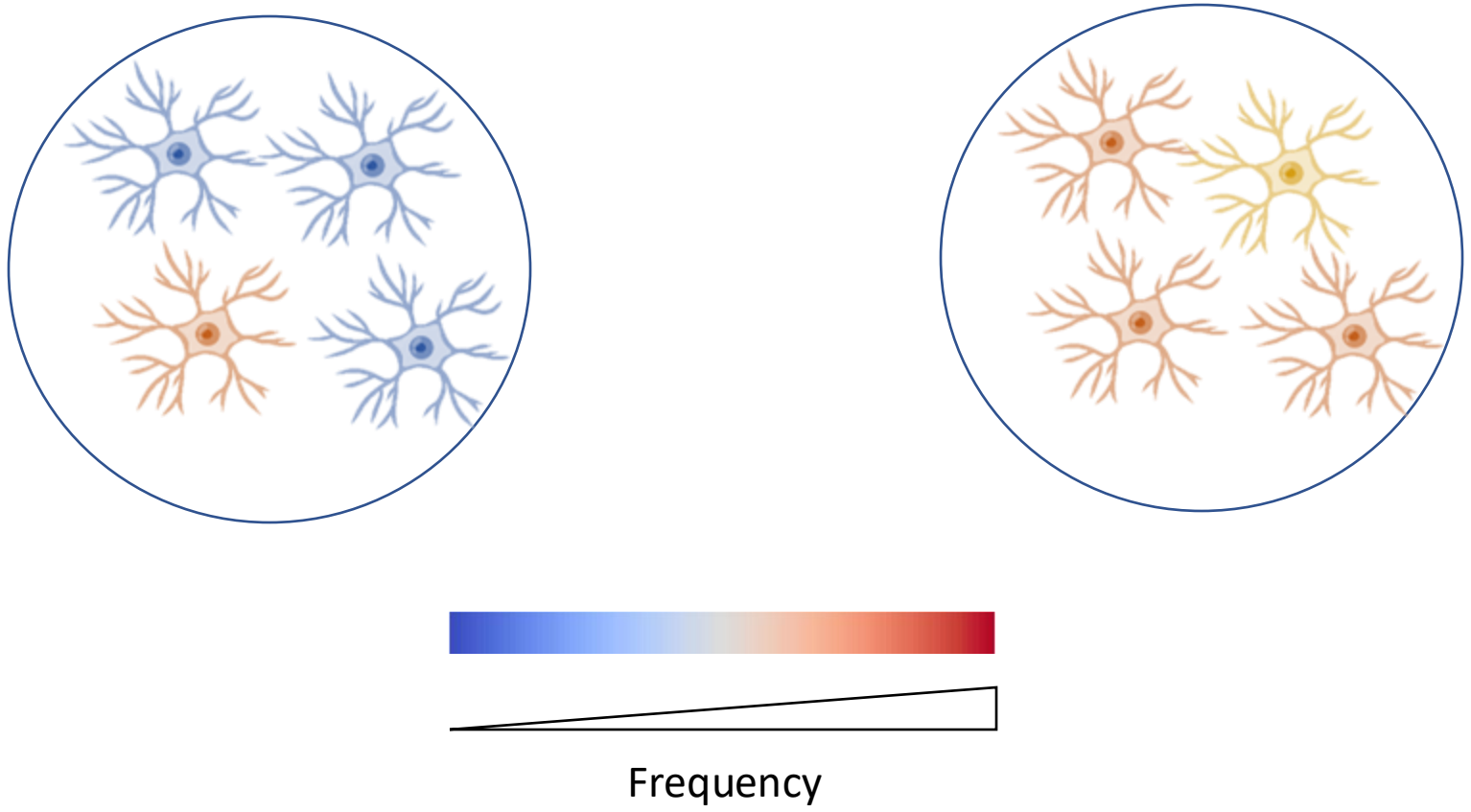
Oligos increase the frequency and synchrony of neuronal firing



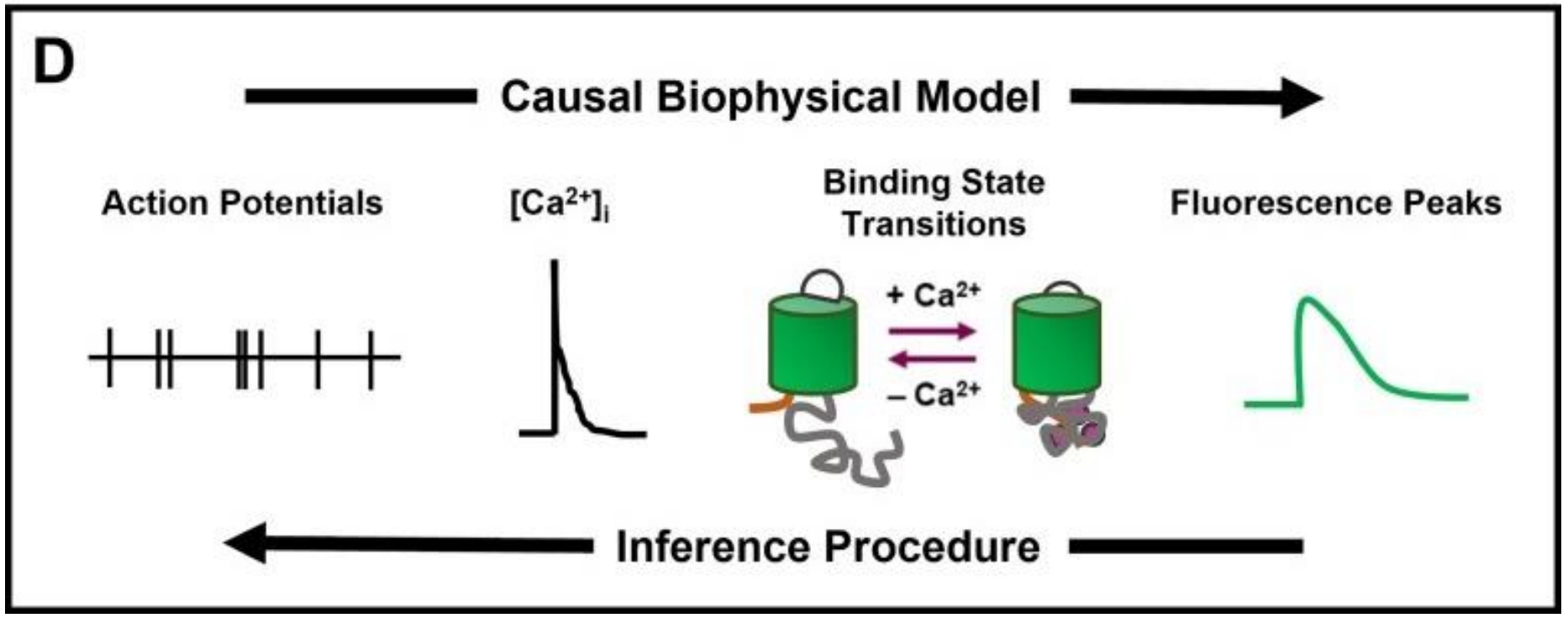




Is increased firing at the individual cell level or population level?



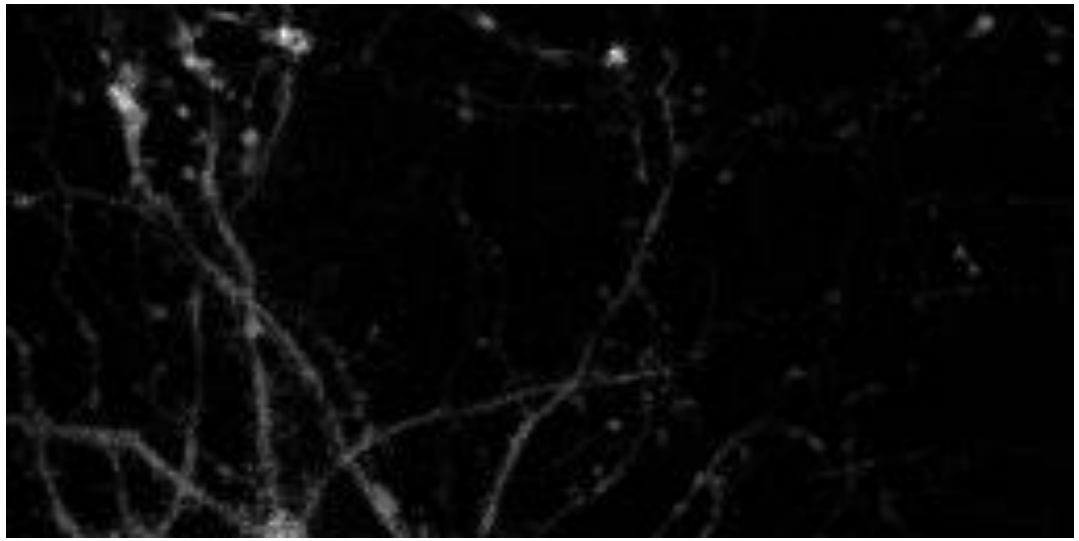
Calcium imaging as a tool to measure action potentials at an individual cell level

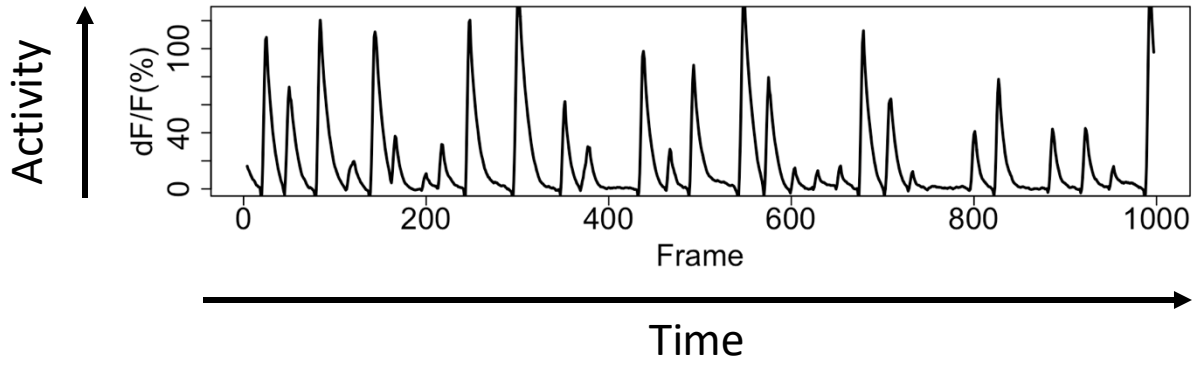


Iseppon et al (2022) Neurobio of Pain

Increased action potentials in individual neurons grown with oligodendrocytes

OL





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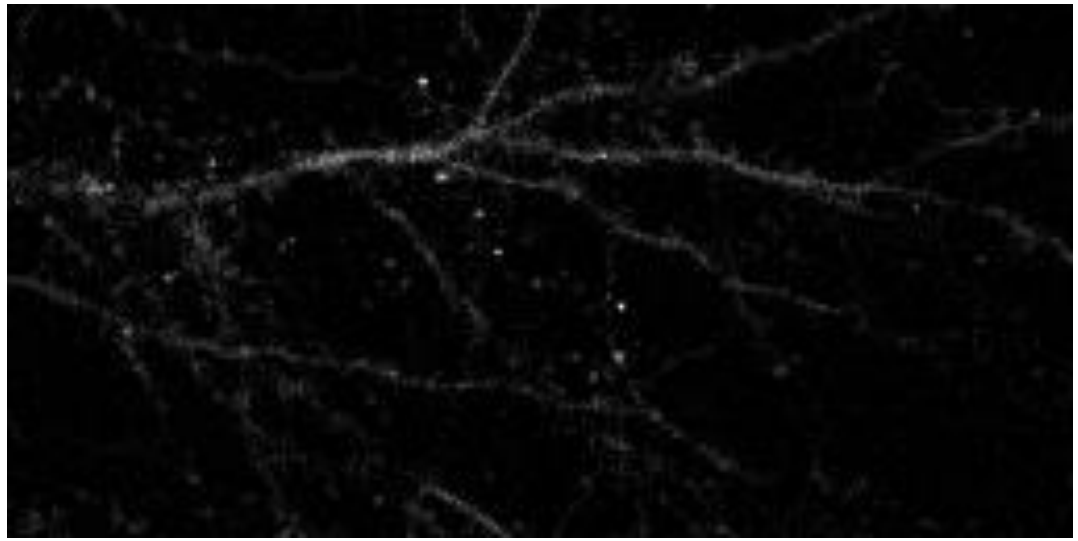
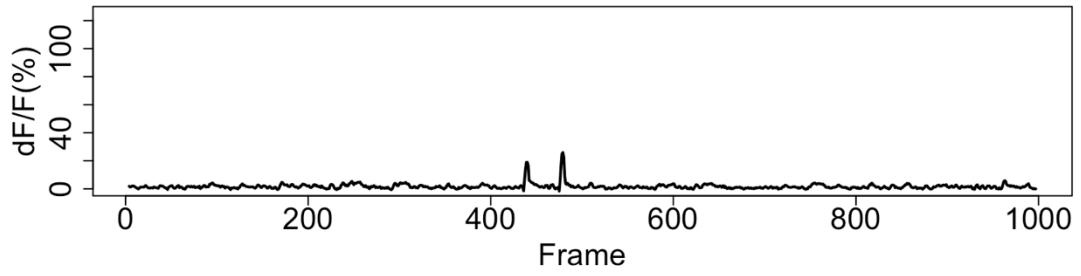
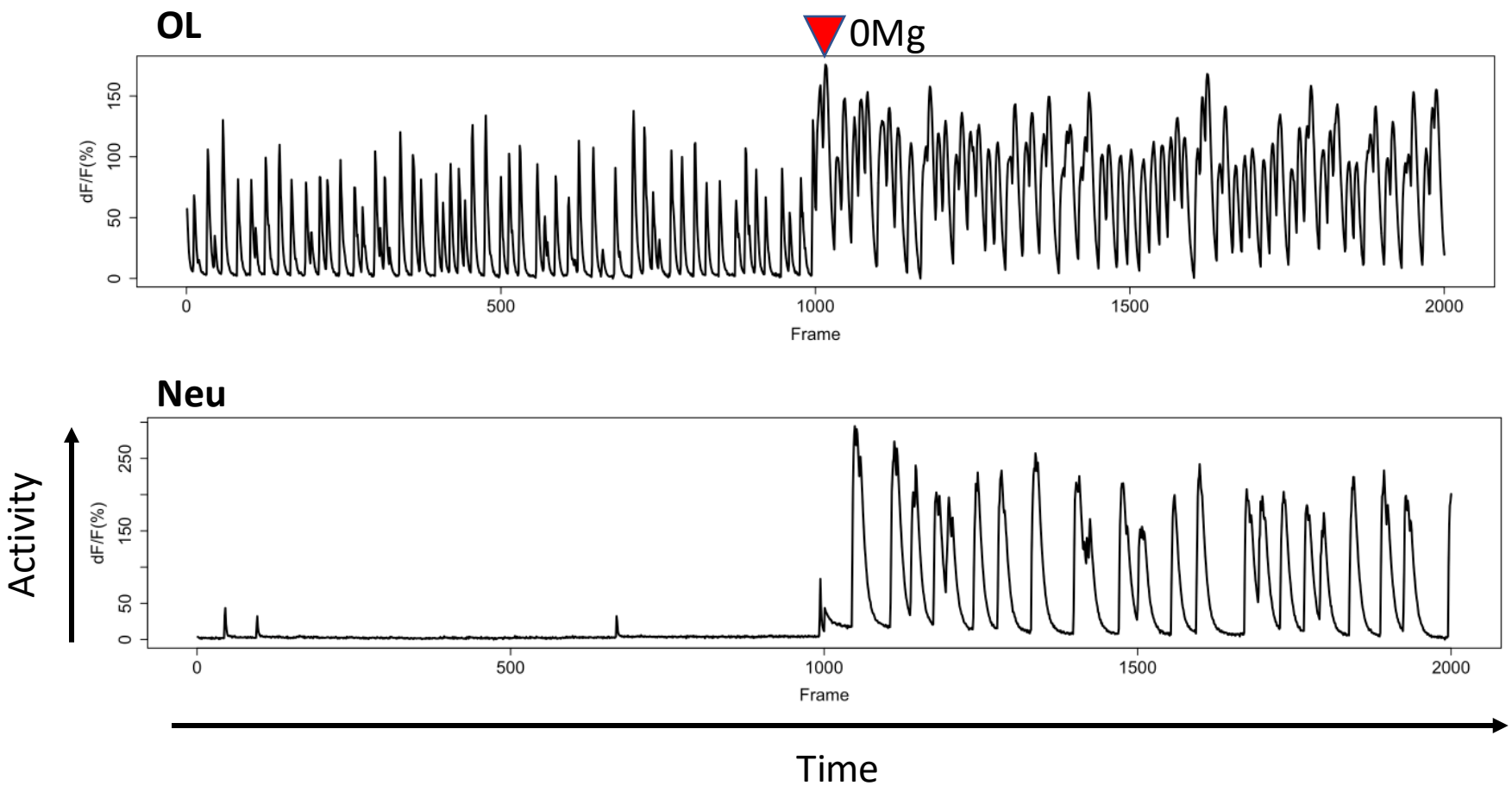
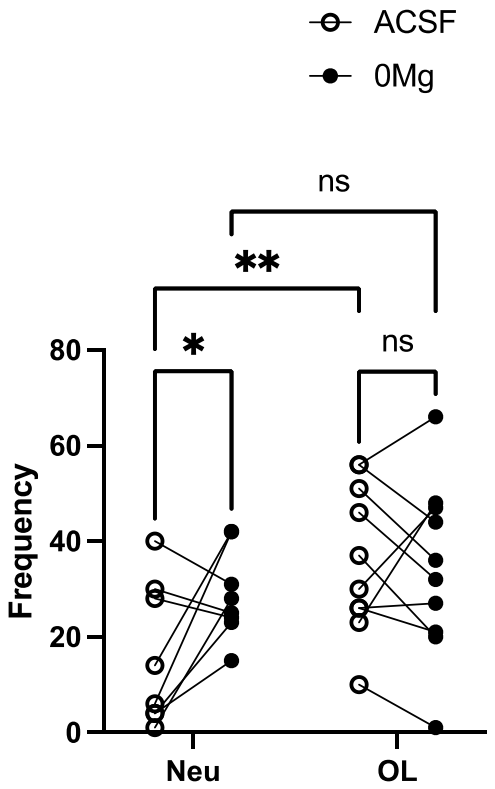


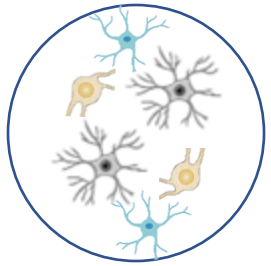


OL neurons shift toward higher activity levels than Neu neurons

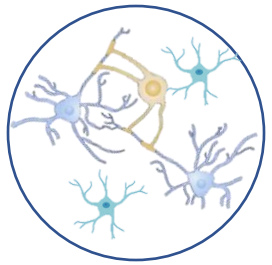




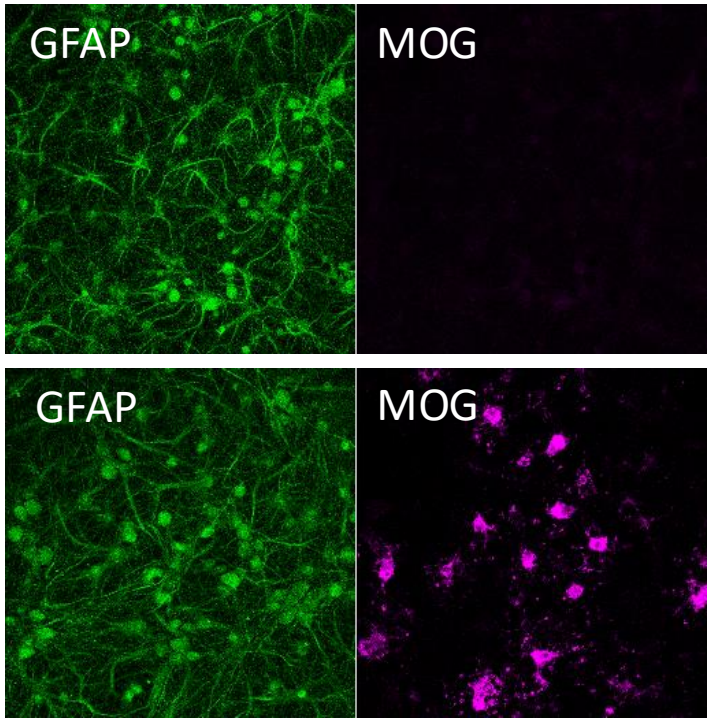
OL neurons have larger synapses and are more active



Neu
Neurons, Astrocytes



OL
Neurons, Astrocytes, Oligodendrocytes

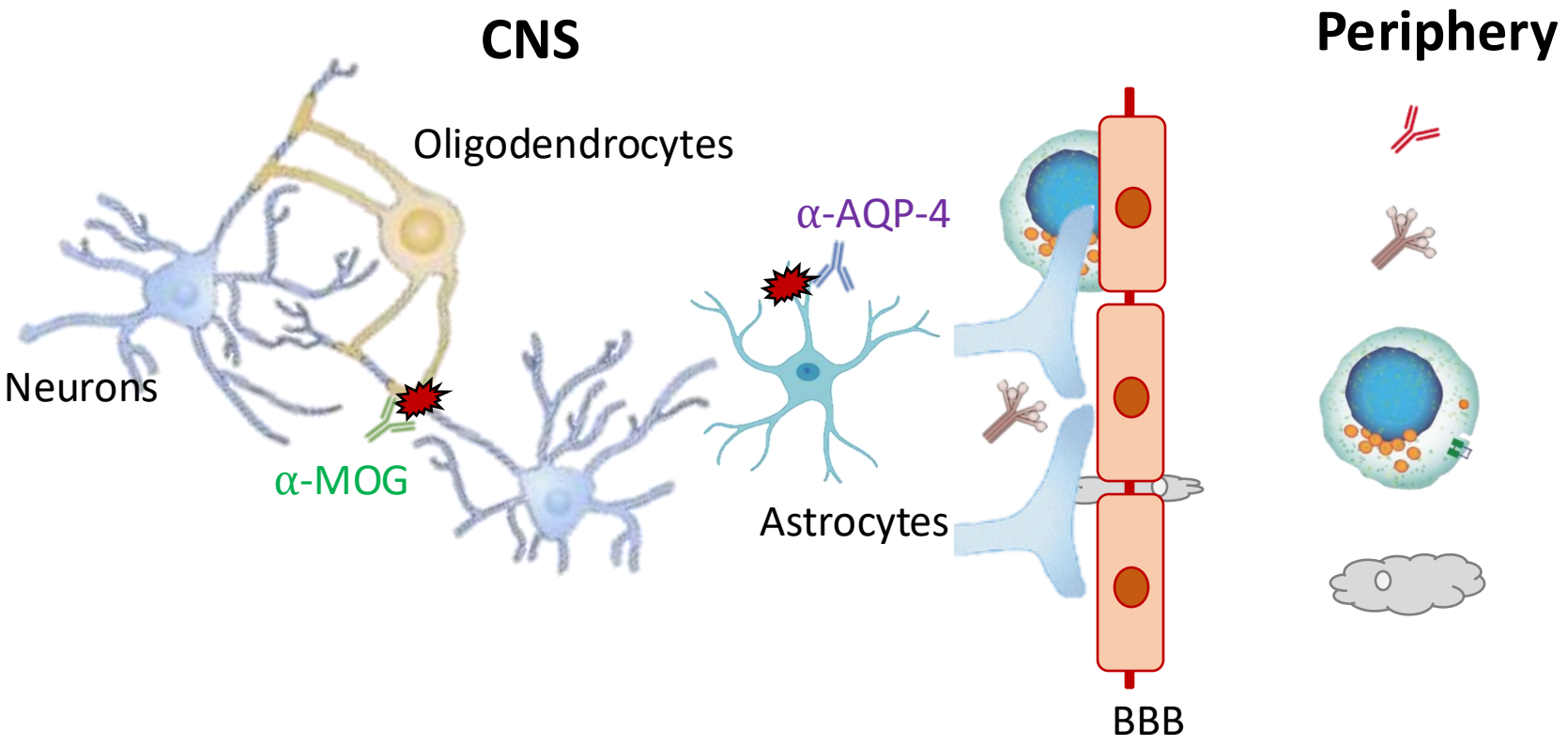


Evaluate synapses

Structure
- Similar synapse number
- Increased size of synapses

Function
- Increased firing frequency
- Increased network activity
- Neurons shift toward higher activity state at the single neuron level

Ongoing work & future directions



- Understand the role of oligodendrocytes in neuronal signaling and how this is disrupted by MOG Abs
- Understand the role of astrocytes in neuronal signaling and how this is disrupted by AQP4 Abs
- Elucidate the role of other inflammatory elements in disease pathogenesis

Thanks!

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- Susana Dominguez-Peñuela
- David Acero-Garces

Bergles Lab
- Dwight Bergles
- Yevgeniya Mironova
- Jaime Eugenin Von Bernhardi

Habela Lab
Morris Lab
Gerber Lab
Calabresi Lab
Sotirchos Group

SRNA Through the years connect. care. cure. | Siegel Rare Neuroimmune Association

NIH National Institute of Neurological Disorders and Stroke

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