

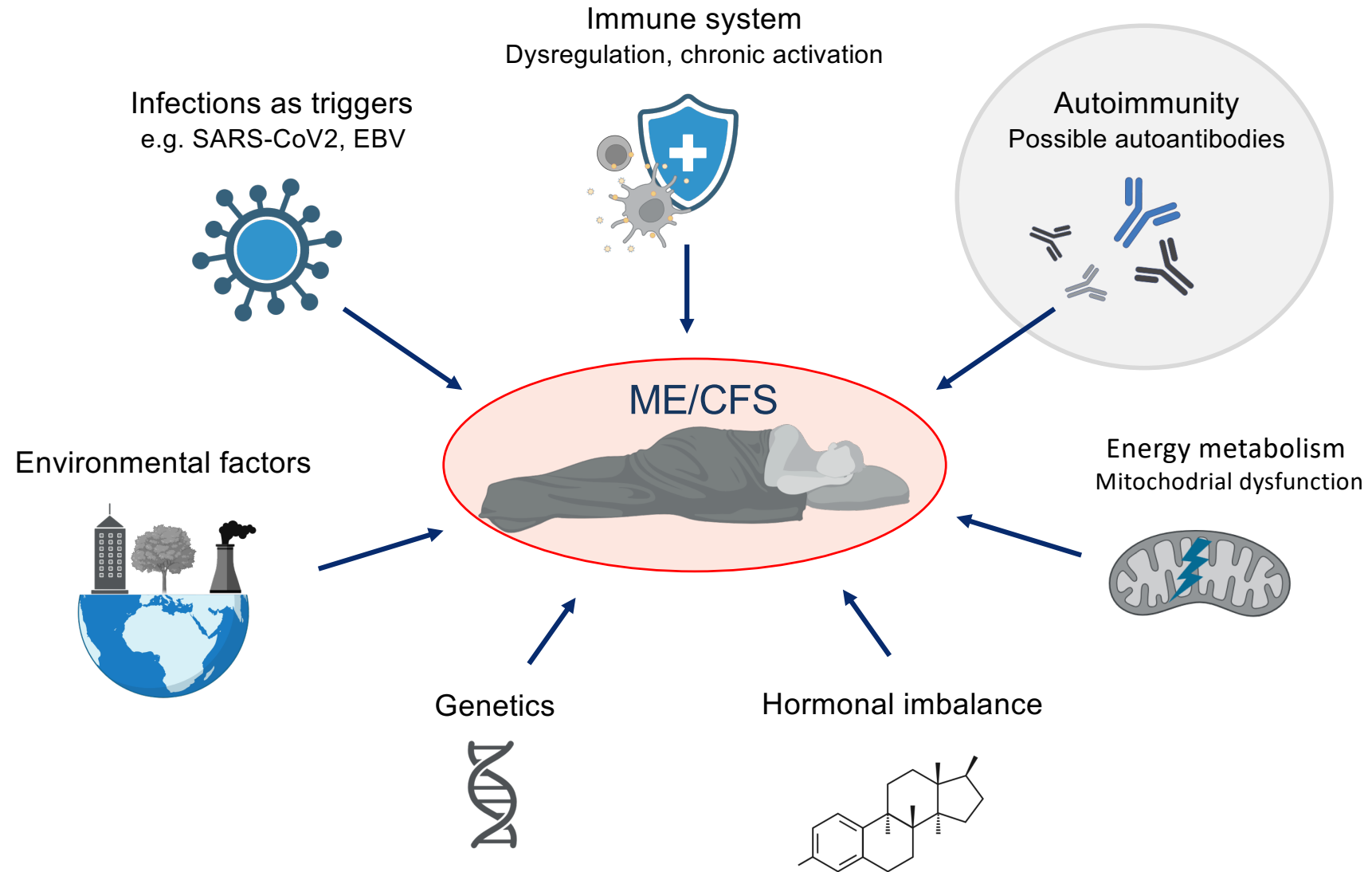
Effects of Serum Autoantibodies on Astrocyte and Microglial Activation and Neuronal Function in ME/CFS

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ME/CFS – Multifactorial Disease Causes



Autoantibodies and Neuroinflammation in ME/CFS

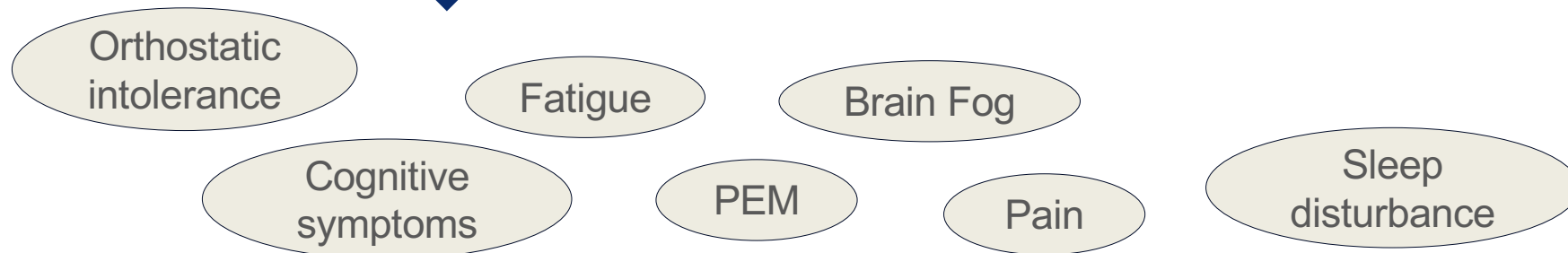
Autoantibodies



- Autoantibodies reported against adrenergic and muscarinic receptors
- Receptors belong to the GPCR family
→ altered receptor and cellular signaling ?



- autonomic dysfunction,
- impaired vascular regulation
- microcirculatory abnormalities



Autoantibodies and Neuroinflammation in ME/CFS

Autoantibodies

- Autoantibodies reported against adrenergic and muscarinic receptors
- Receptors belong to the GPCR family
→ altered receptor and cellular signaling ?



- autonomic dysfunction,
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Orthostatic intolerance

Fatigue

Cognitive symptoms

PEM

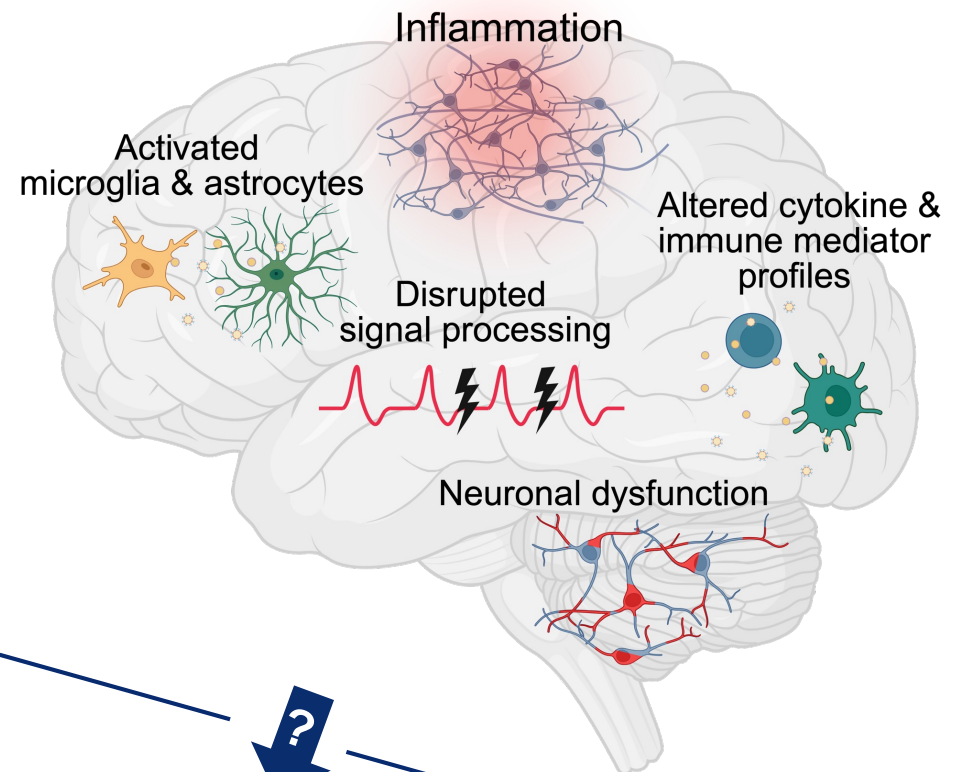
Brain Fog

Pain

Sleep disturbance

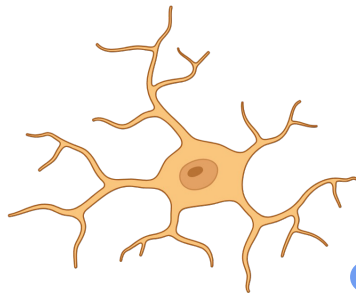
Neuroinflammation

Possible processes



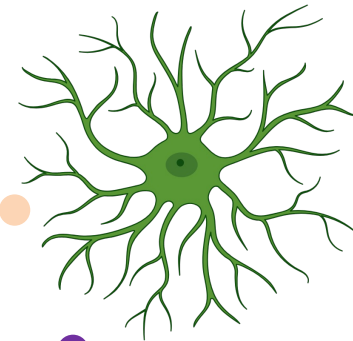
Function of Glia Cells and Neurons in the Brain

Microglia



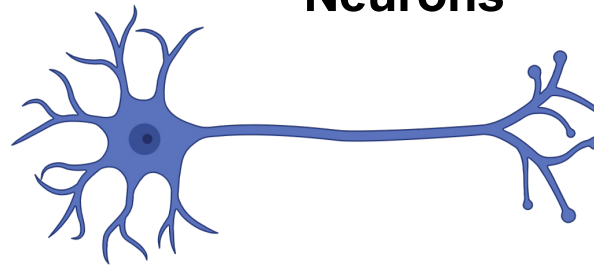
- Immune cells of the brain
- phagocytosis
- synapse remodeling
- OPC and myelin homeostasis
- hippocampal neurogenesis
- learning and memory
- CNS vasculature and BBB integrity

Astrocytes



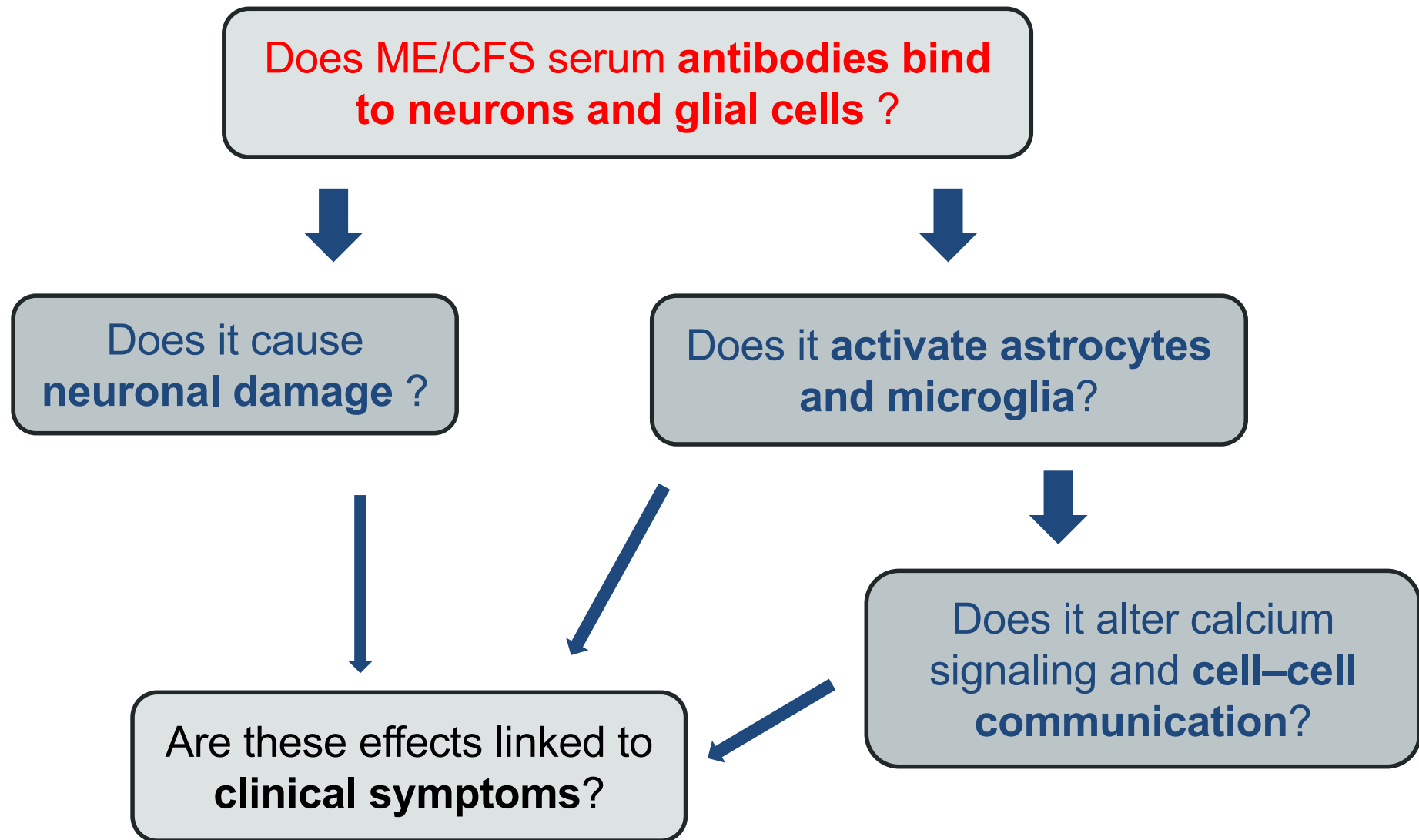
- Support neuronal function
- Regulate metabolism and ion balance
- Maintain the blood–brain barrier
- glutamate synthesis, uptake & recycling
- excitatory and inhibitory synaptogenesis
- Synaptic pruning
- Hippocampal neurogenesis

Neurons

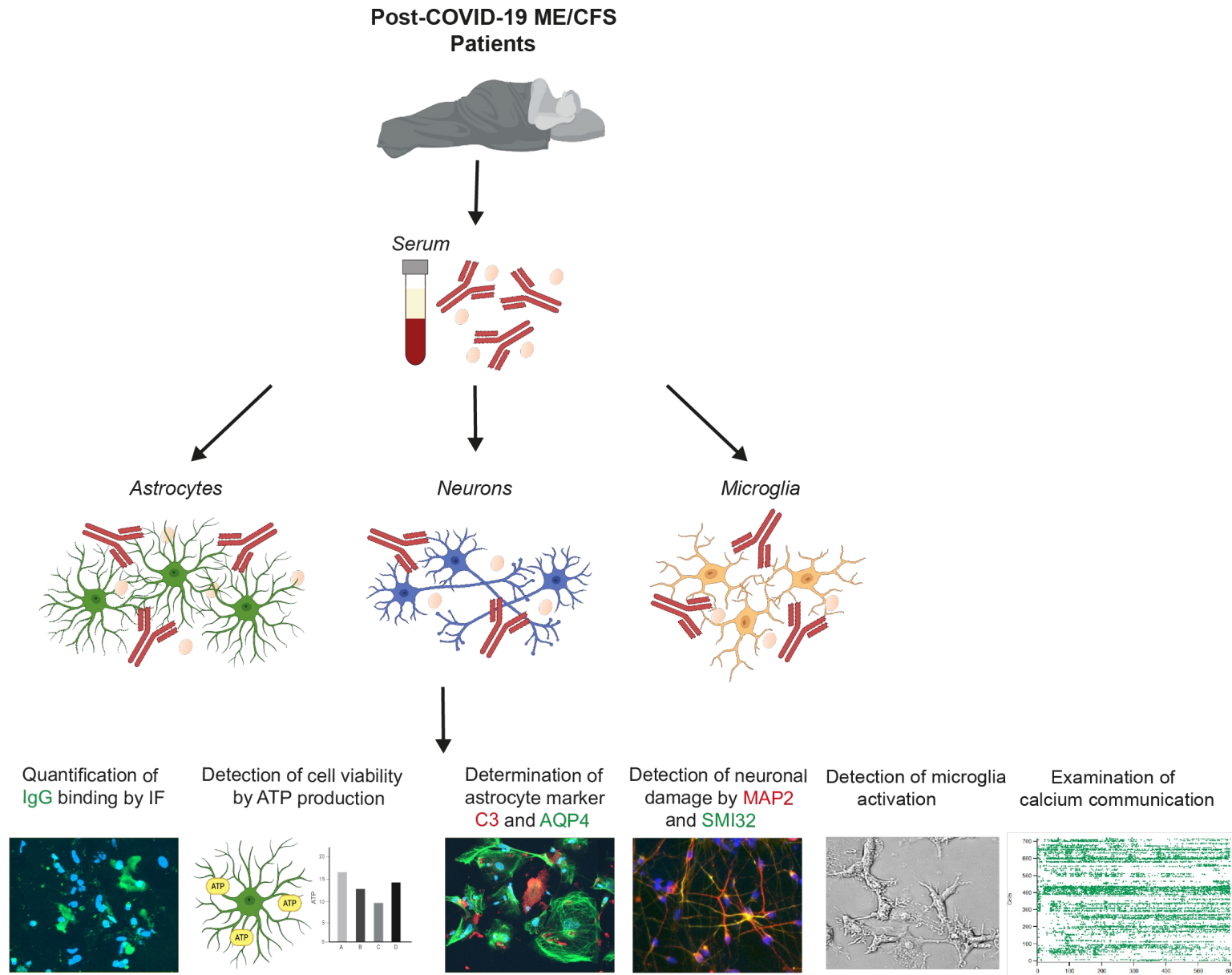


- Transmit and process electrical signals
- Essential for normal cognition
- Involved in neural plasticity
- Support long-term memory formation

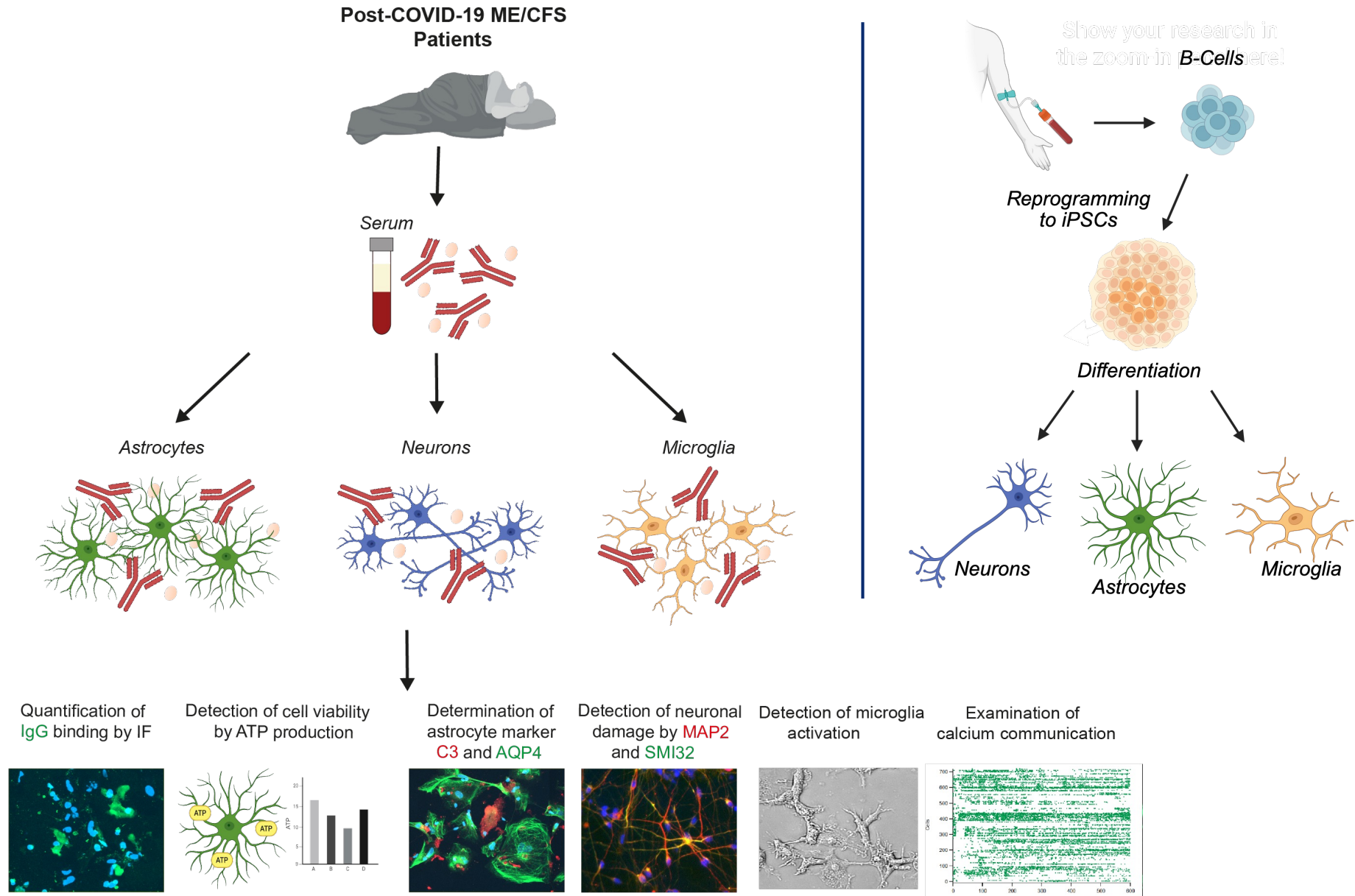
Research Questions



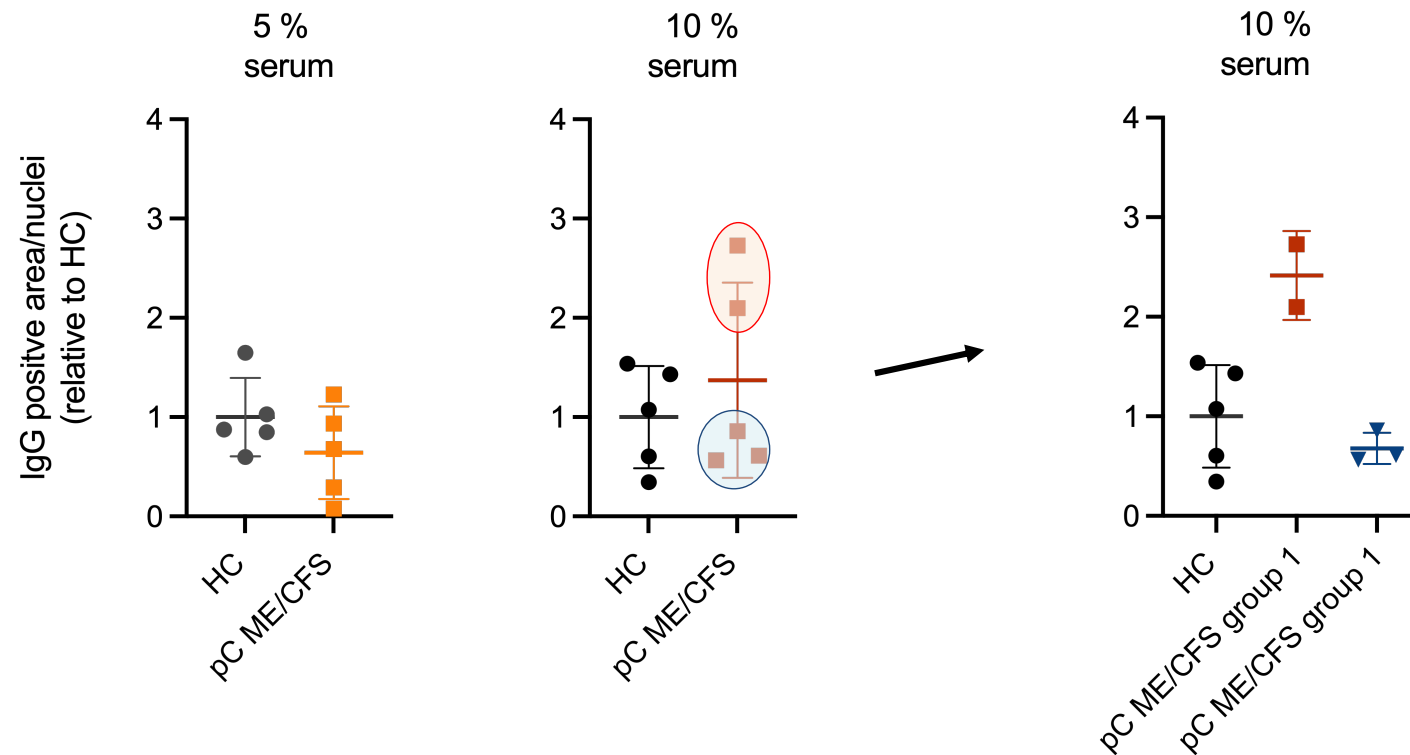
Design of Experiments



Design of Experiments

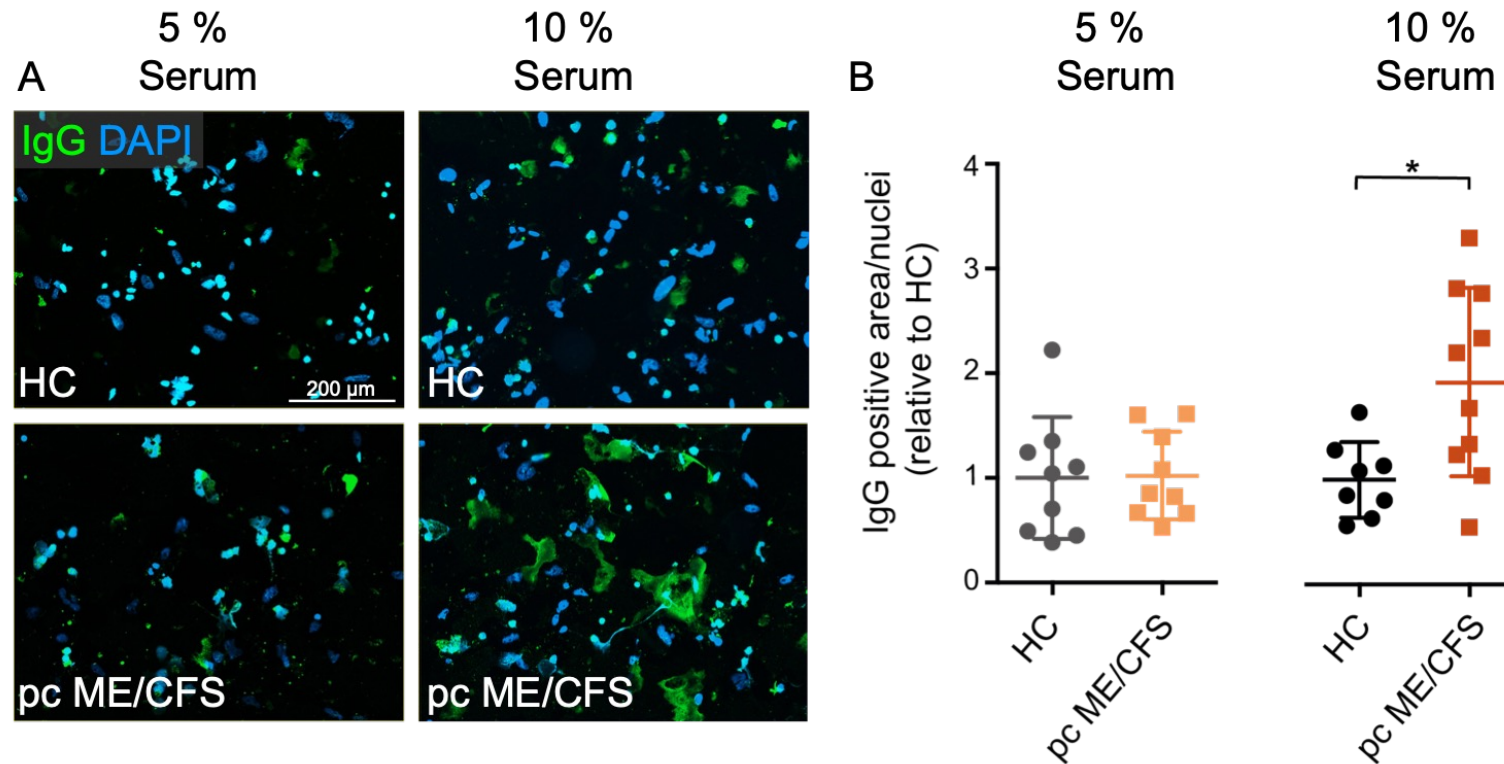


Antibodies in Serum of ME/CFS Patients Bind to Neurons



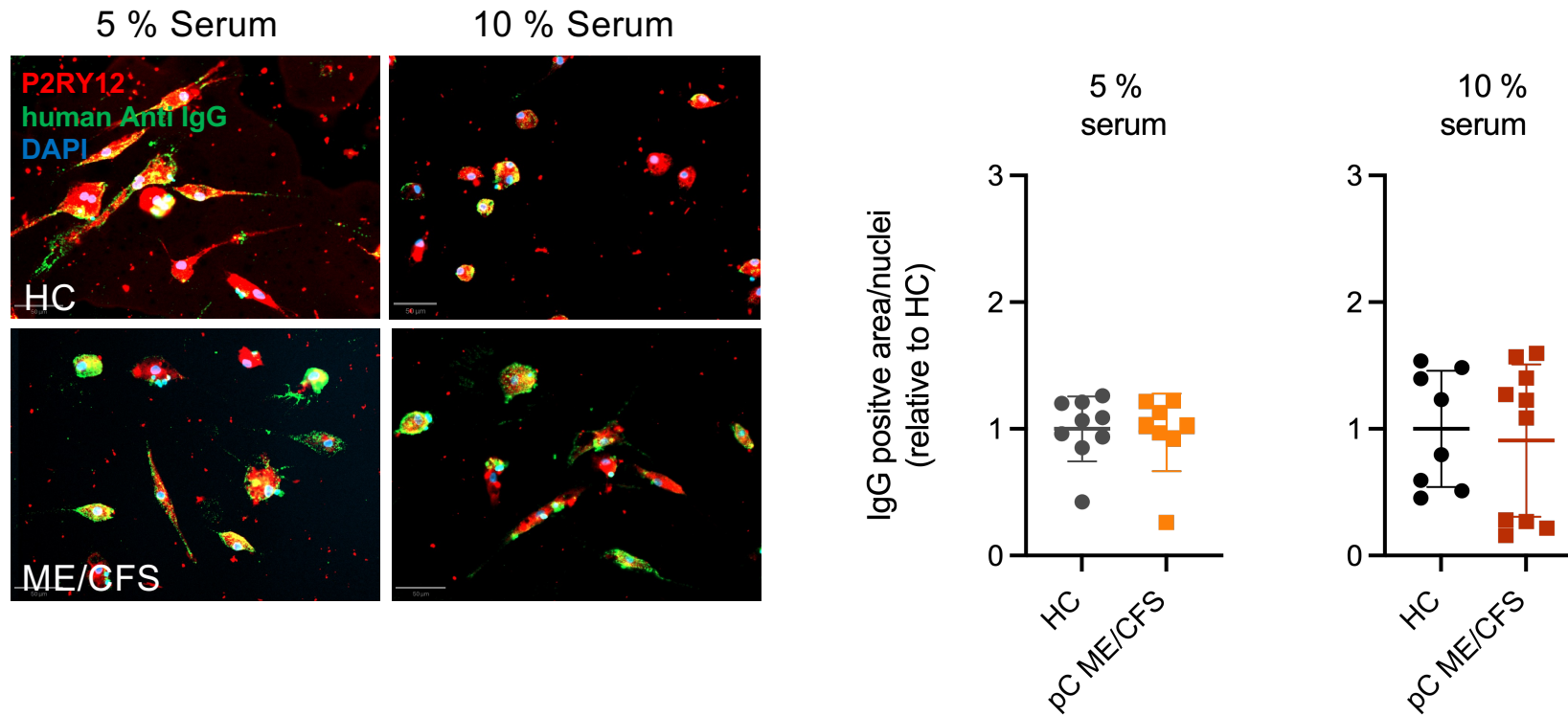
Binding of IgG to neurons after 1-hour exposure to 5% and 10% serum from pc ME/CFS patients and HC (n=5).

Serum Antibodies of ME/CFS Patients bind to Astrocytes



Binding of IgG to astrocytes after 1-hour exposure to 5% and 10% serum from pc ME/CFS patients and HC. (A) Representative images showing IgG binding to astrocytes. (B) Astrocytes incubated with 10% patient serum exhibit a significant increase in IgG binding compared to HC serum ($n=8-10$). Statistical analysis was performed using the Mann-Whitney U test; $*p < 0.05$.

No increased antibody binding to microglia in ME/CFS



Binding of IgG to microglia after 1-hour exposure to 5% and 10% serum from pc ME/CFS patients and HC (n=9-10)

Research Questions

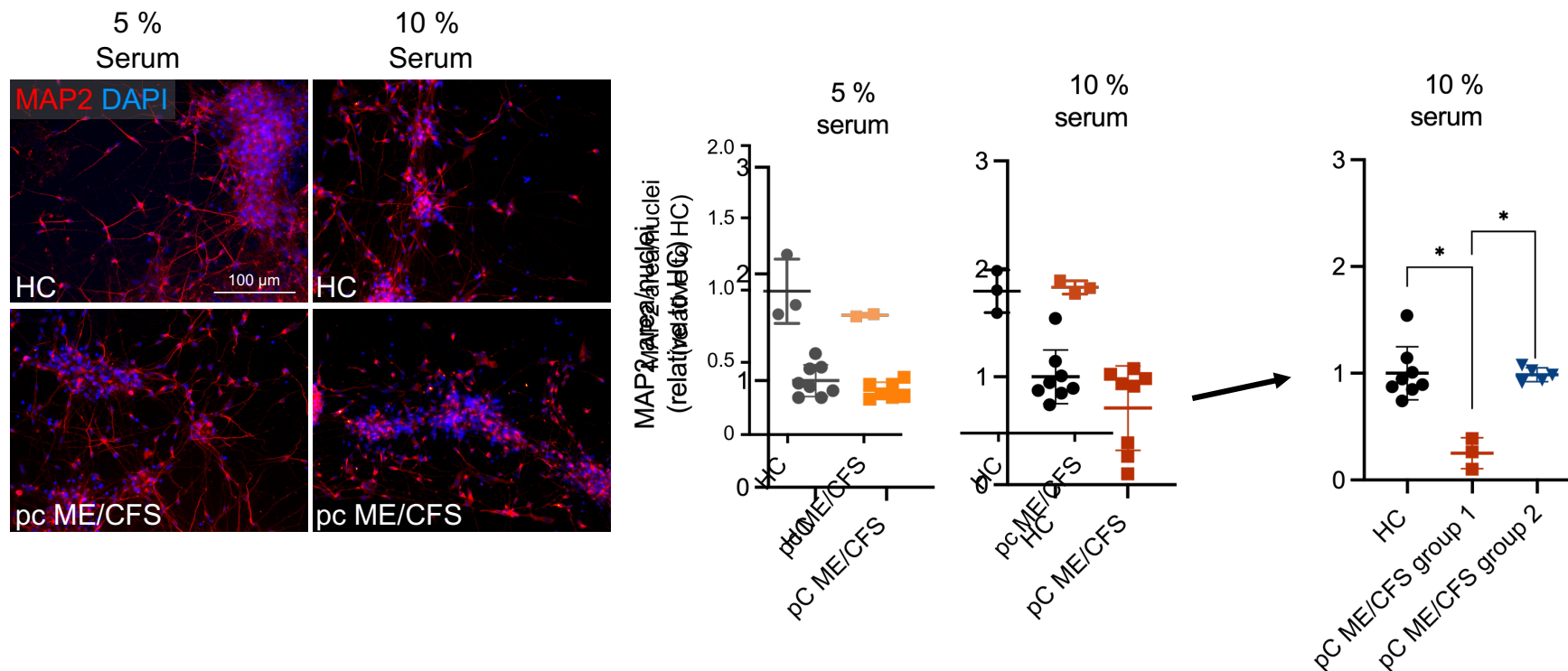
Does ME/CFS serum **antibodies bind to neurons and glial cells** ?

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graph TD; A[Does ME/CFS serum antibodies bind to neurons and glial cells ?] --> B[Does it cause neuronal damage ?]; A --> C[Does it activate astrocytes and microglia?];
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Does it cause **neuronal damage** ?

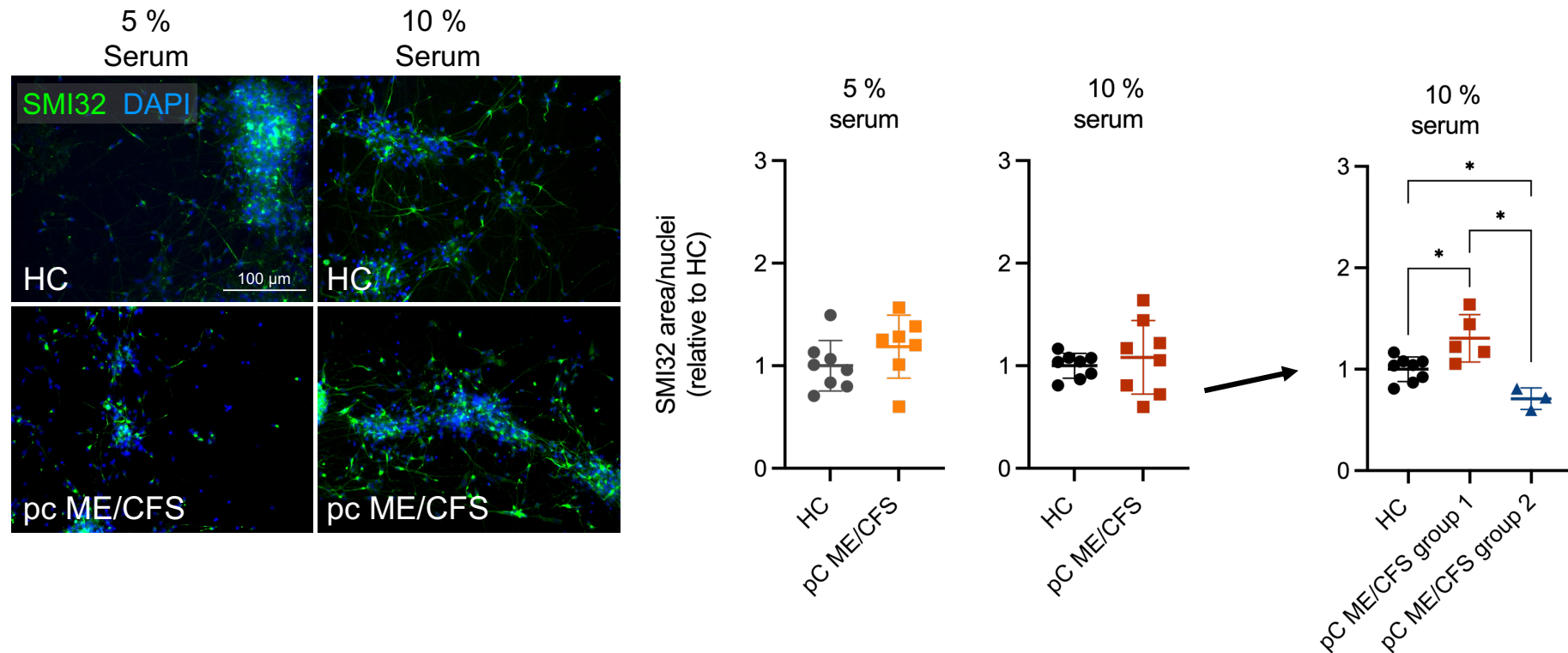
Does it **activate astrocytes and microglia**?

Expression of the cytoskeleton-associated protein and dendritic marker MAP2 is partly affected by serum from ME/CFS patients



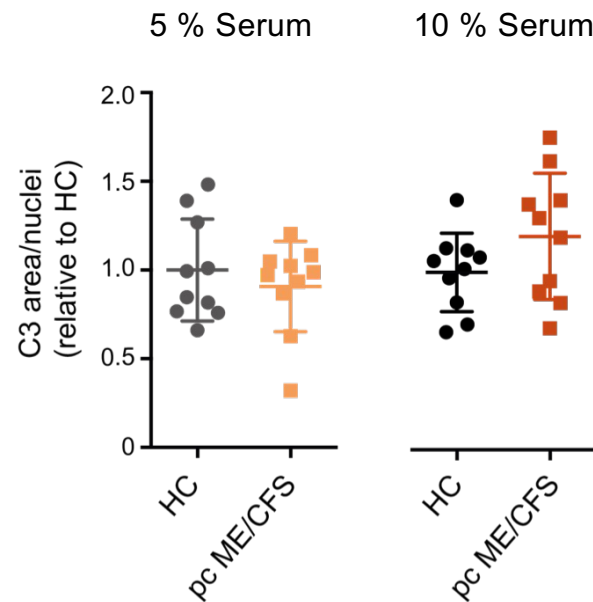
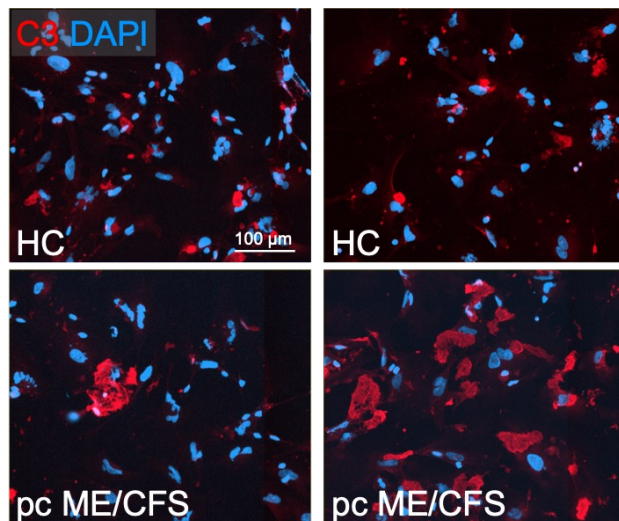
Expression of MAP2 after exposure to 5% and 10% serum from pc ME/CFS patients and HC for 24 h. Statistical analysis was performed using the Mann-Whitney U test, * $p < 0.05$, (n=8)

Expression of SMI32 is elevated following incubation with serum from ME/CFS patients, suggesting potential neuronal damage



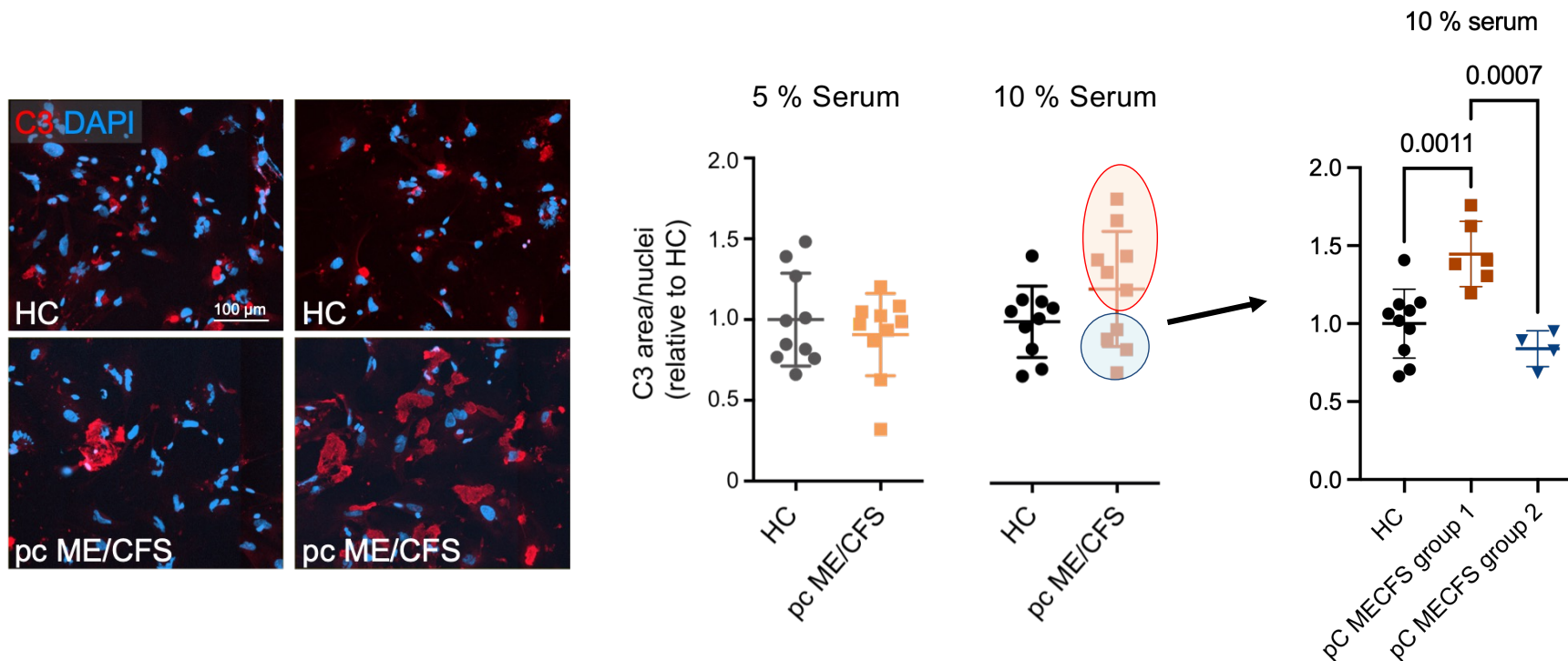
Expression of SMI32 after exposure to 5% and 10% serum from pc ME/CFS patients and HC for 24 h. Statistical analysis was performed using the Mann-Whitney U test, * $p < 0.05$, (n=8)

Serum from ME/CFS patients partially increases C3 expression in astrocytes, indicating astrocyte activation



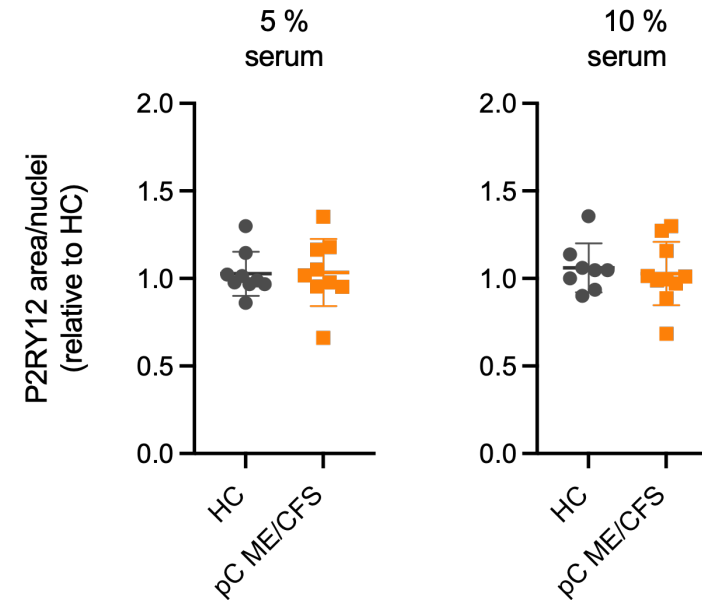
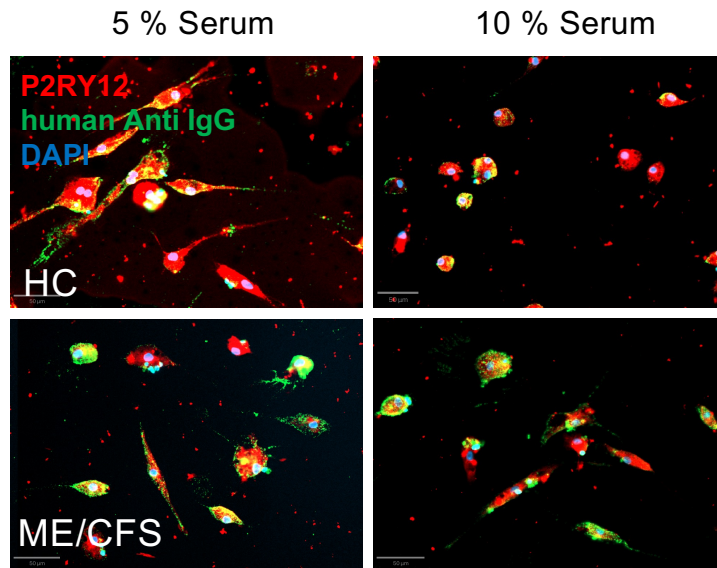
Expression of C3 after exposure to 5% and 10% serum from pc ME/CFS patients and HC for 24 h. Statistical analysis was performed using the Mann-Whitney U test, * $p < 0.05$, ($n=10$)

Serum from ME/CFS patients partially increases C3 expression in astrocytes, indicating astrocyte activation

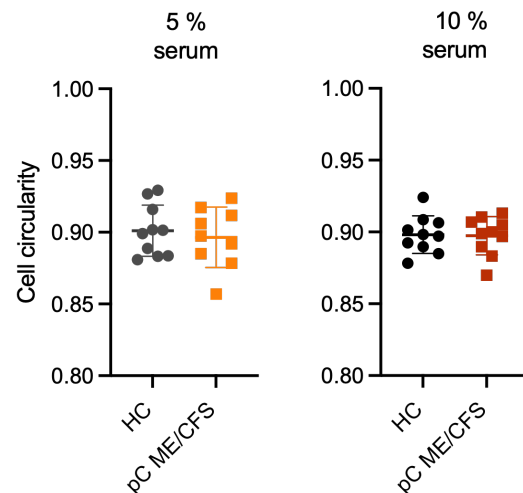


Expression of C3 after exposure to 5% and 10% serum from pc ME/CFS patients and HC for 24 h. Statistical analysis was performed using the Mann-Whitney U test, * $p < 0.05$, ($n=10$)

Serum from ME/CFS patients do not alter the expression of microglia resting marker

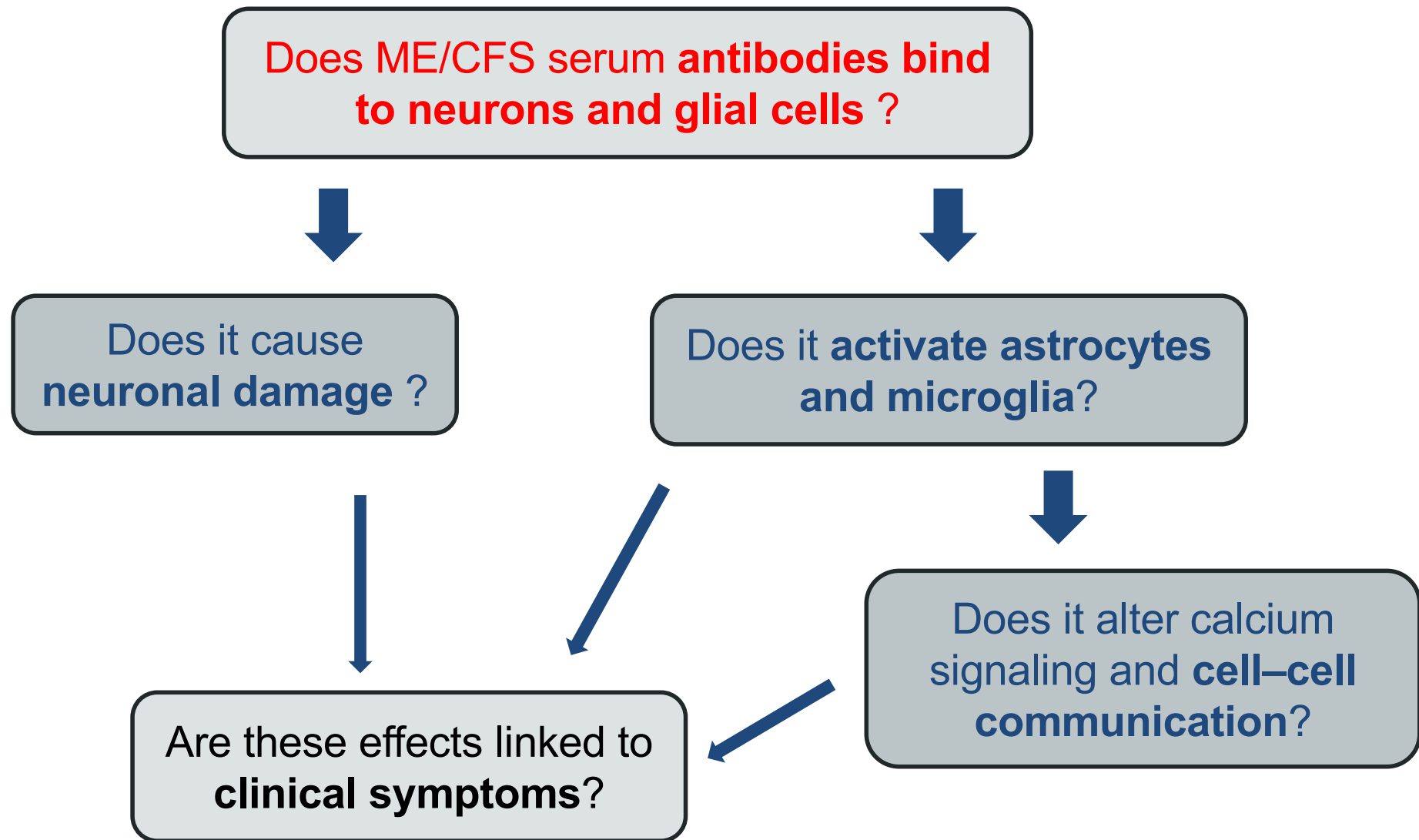


Expression of P2RY12 after exposure to serum from pc ME/CFS patients and HC for 24 h

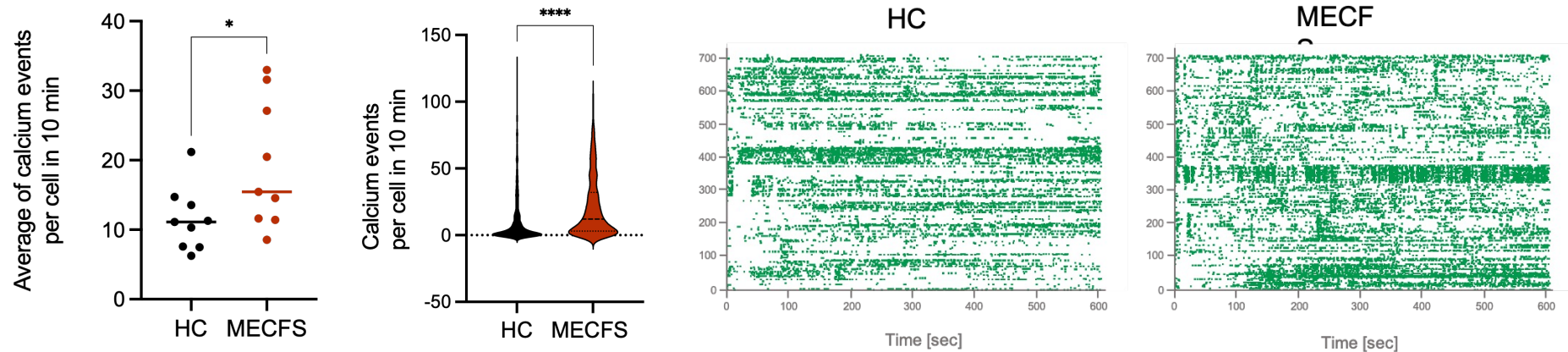


No changes in cell morphology

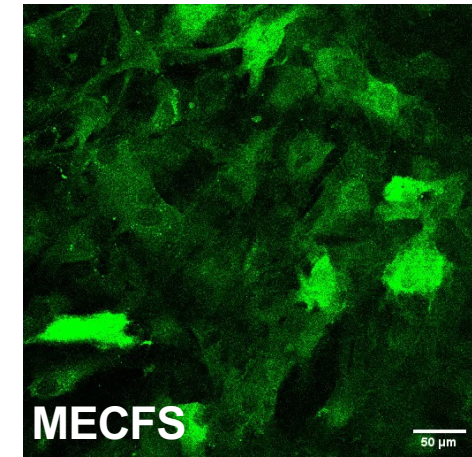
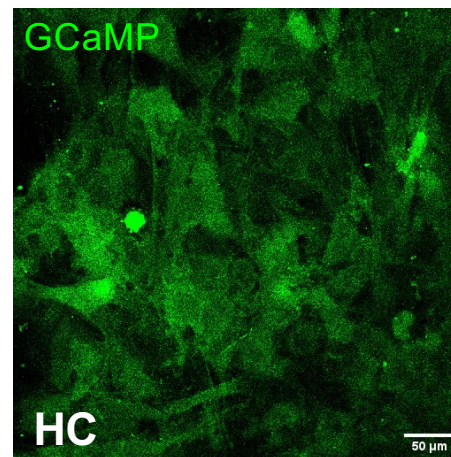
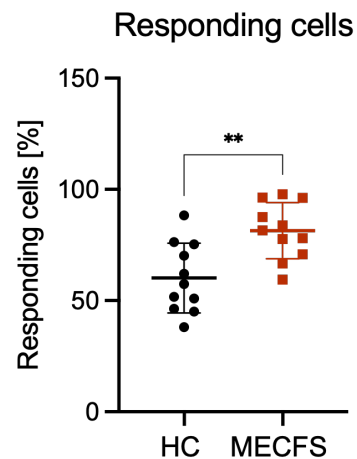
Research Questions



Calcium Communication in Astrocytes after Serum Incubation

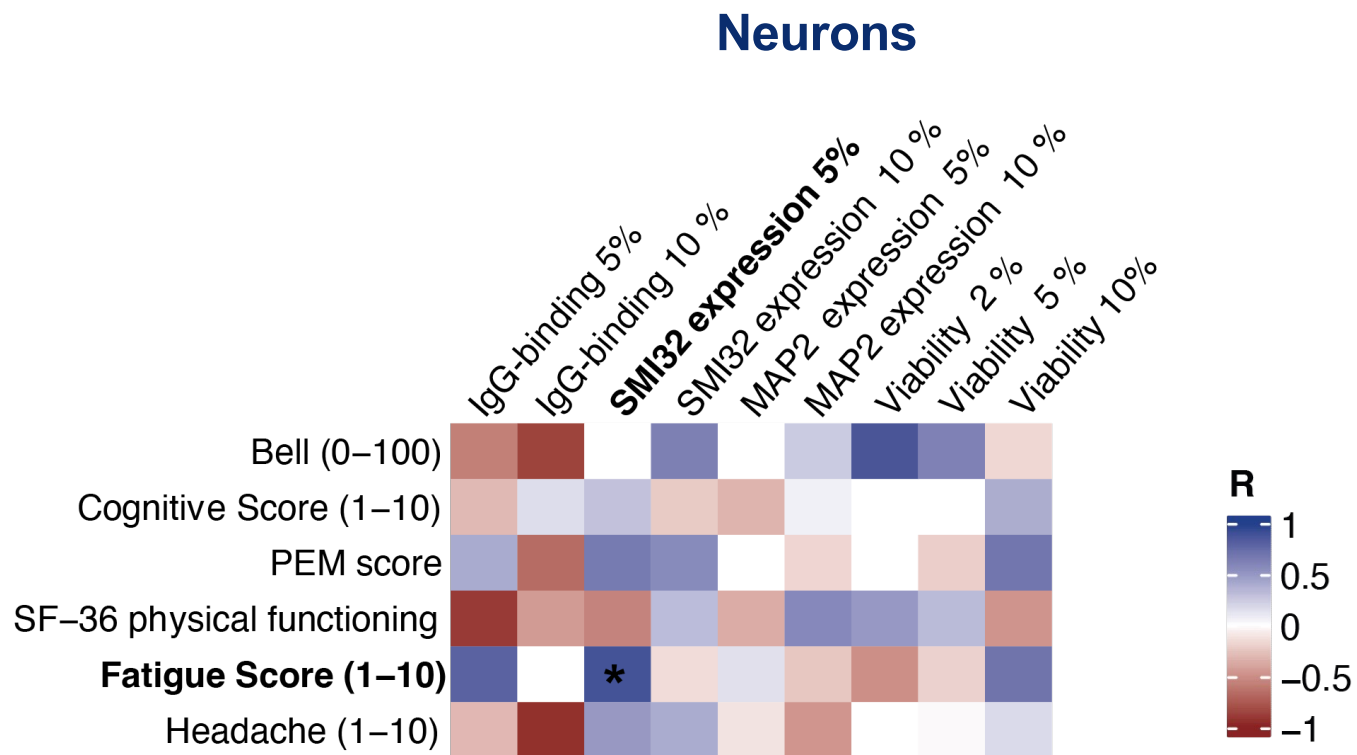


Detection of calcium events after exposure to 10% serum from pc ME/CFS patients and HC for 24 h. Mann-Whitney U test, * $p < 0.05$, (n=11)



Detection of responding cells after exposure to 10% serum from pc ME/CFS patients and HC for 24 h. Mann-Whitney U test, * $p < 0.05$, (n=11)

Correlation Between Neuronal Effects and Clinical Symptoms



Spearman correlation, *p < 0.05



Summary

Does ME/CFS serum **antibodies bind to neurons and glial cells** ?

- **Neurons**: Antibody binding may be present in a subset (small sample size!)
- **Astrocytes**: Significantly increased antibody binding
- **Microglia**: No significant antibody binding

Summary

Does serum cause **neuronal damage** ?

→ Reduced MAP2 and increased SMI32 expression after incubation with serum from some (not all) patients indicate neuronal damage

Does serum **activate astrocytes and microglia**?

→ Microglia: no activation
→ Astrocytes: partially increased C3 expression indicating activation

Does serum **alter calcium signaling in astrocytes**?

→ Increased calcium events and responding cells indicate enhanced astrocytic intercellular communication

Summary

Are detected effects linked to **clinical symptoms**?

→ Significant correlations were found between IgG binding, neuronal damage, astrocytic calcium activity and clinical scores

Next steps?

- Complete the experiments using serum from 20 ME/CFS patients
- Perform experiments with isolated IgG from the sera of ME/CFS patients
- Analyze pro-inflammatory mediators in the supernatants of activated astrocytes and microglia
- Conduct RNA-seq analysis of glial cells and neurons

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