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Generating sleep oscillations using primary and hiPSC-derived thalamo-cortical cultures

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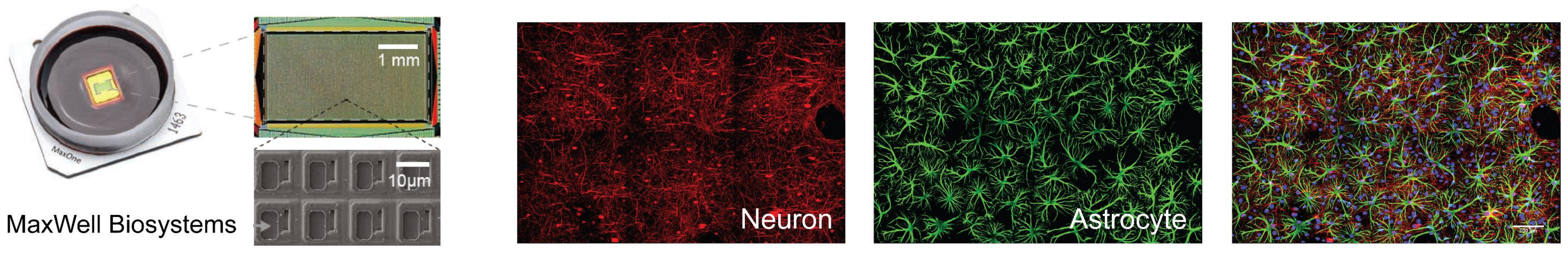
Introduction

Slow oscillations, delta waves, and spindles are the major brain oscillations during non-rapid eye movement (NREM) sleep. Whether the generation of these oscillatory patterns requires subcortical neuromodulatory inputs remain unknown.

We here show that at the level of neuronal networks, particularly those arising from isolated thalamo-cortical or cortical cells maintained in culture, oscillatory patterns of sleep represent default mode of functioning.

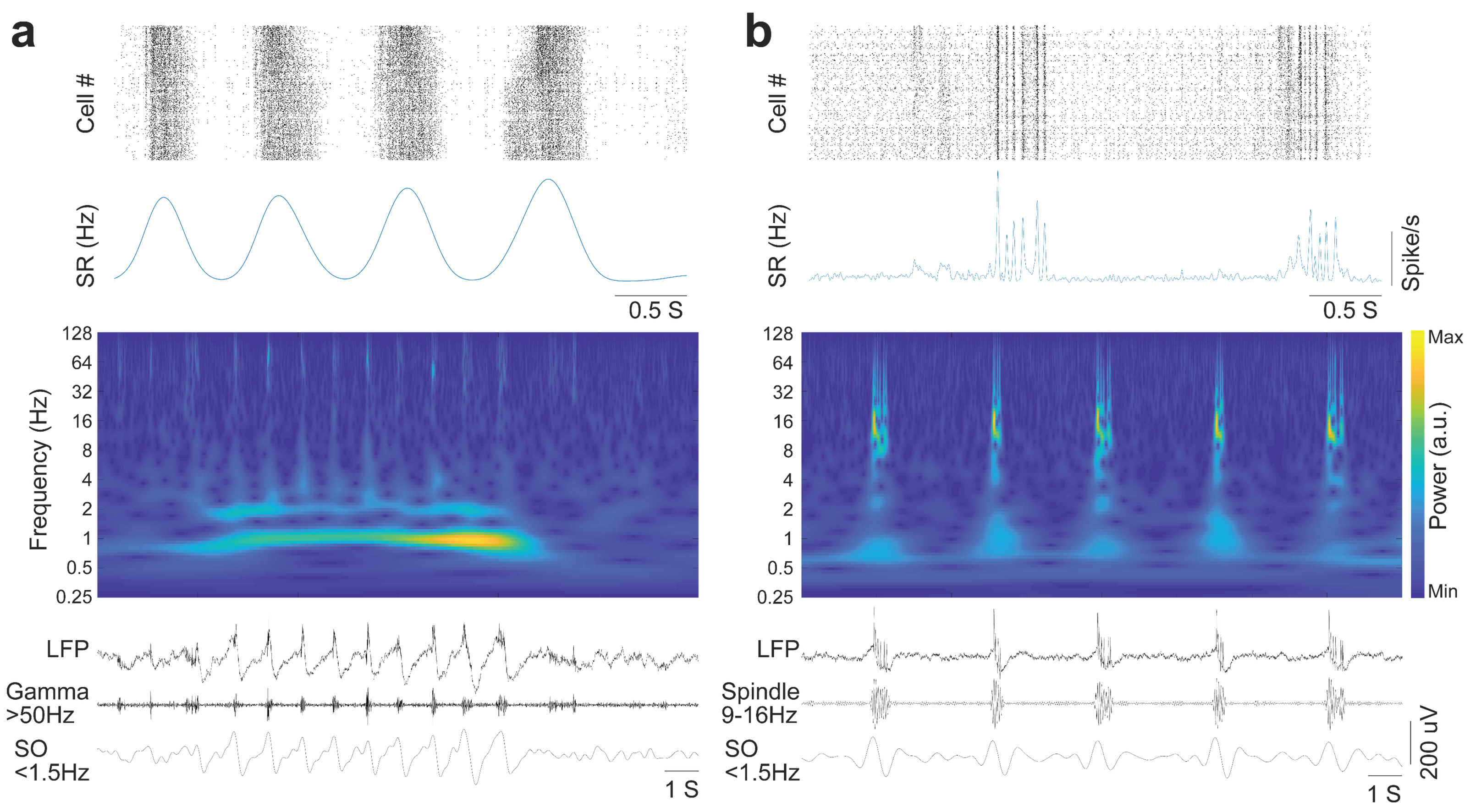
Methods

Using a high-density microelectrode array with 26400 electrodes, we recorded both single-unit activity and local field potential (LFP) of primary and hiPSC-derived cortical, thalamic, and thalamo-cortical co-cultures, and assessed their spontaneous oscillatory patterns.



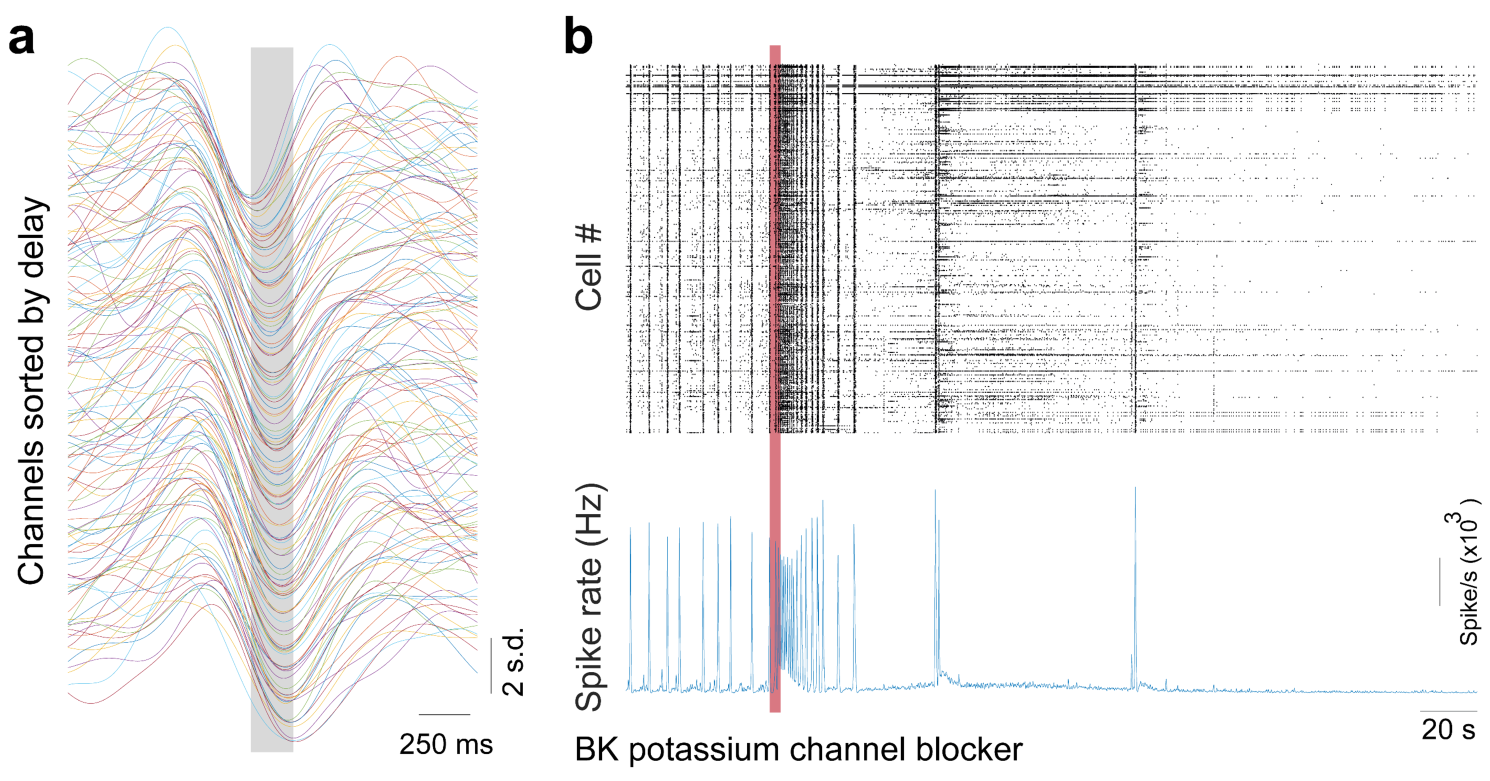
2. Slow waves and spindles in cortical and thalamo-cortical co-cultures

Cell assemblies of cortical cultures and thalamo-cortical co-cultures show the slow oscillation (<1Hz) and spindles (9-16 Hz), respectively, similar to NREM sleep. Interestingly, spindles of thalamo-cortical co-cultures show strong coupling to the slow oscillation as in vivo.



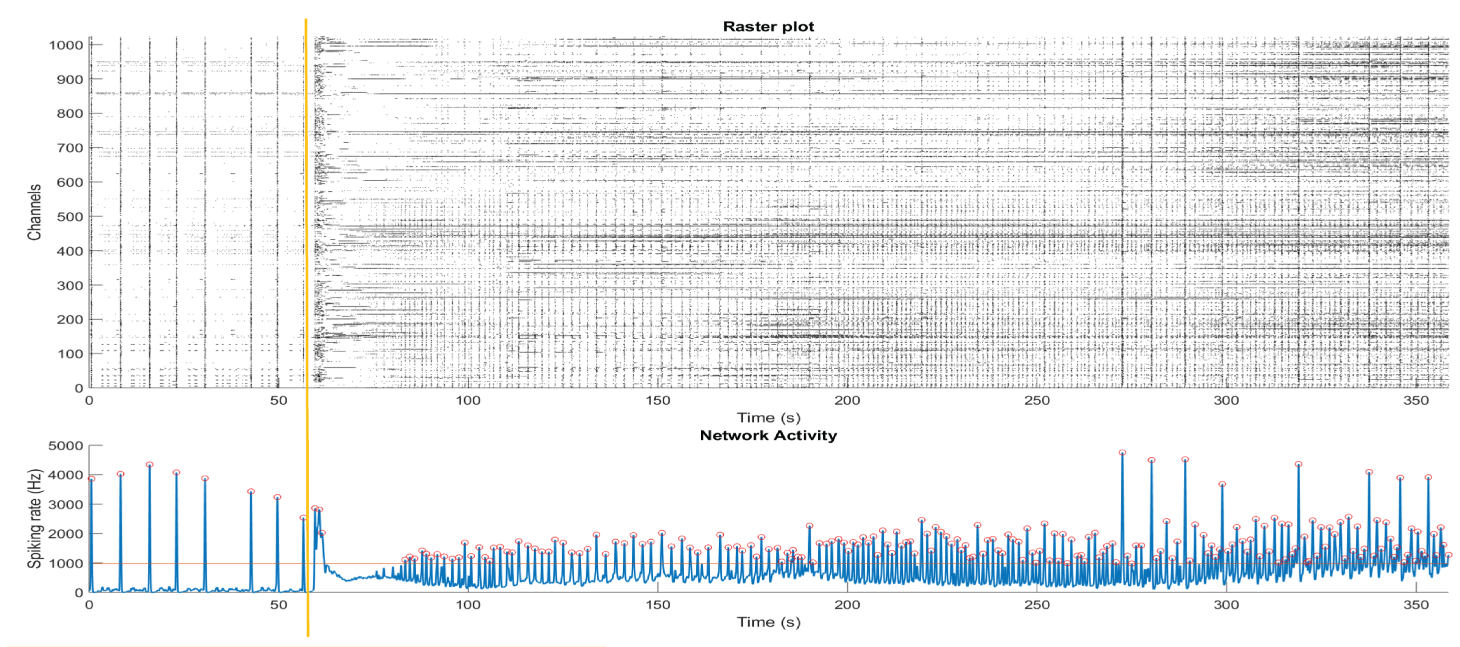
4. The slow oscillation travels in cortical cultures

The slow oscillation travels across the cortical cultures. Addition to cortical cultures of an antagonist of calcium-activated potassium channels suppressed the slow oscillation, suggesting a subcellular pathway for travelling of this oscillation.



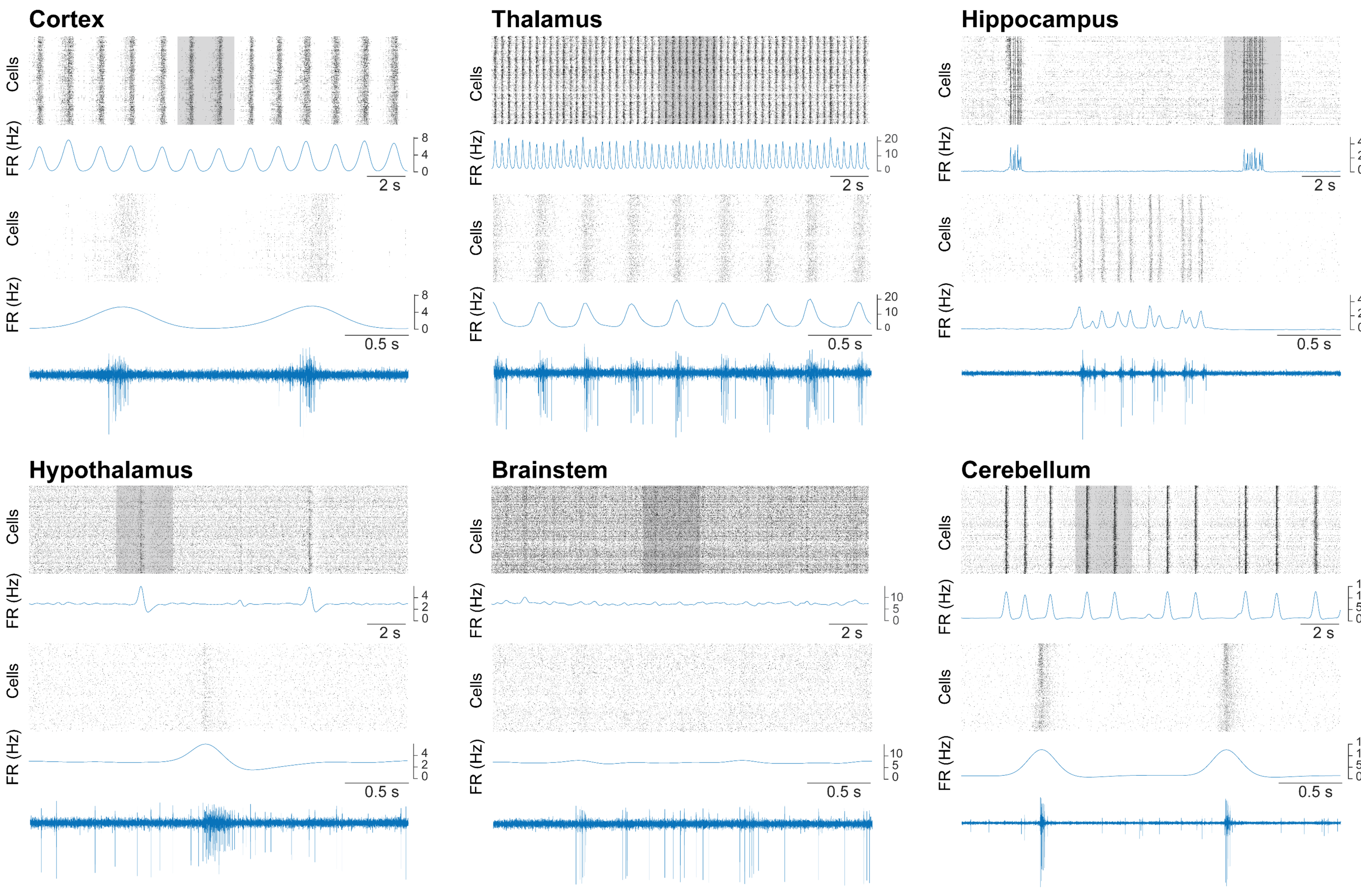
6. Desynchronizing (waking up) the cultures

Stimulation of these networks using wake-promoting neuromodulators induced desynchronized wake-like states in cultures, characterized by low-amplitude fast oscillations.



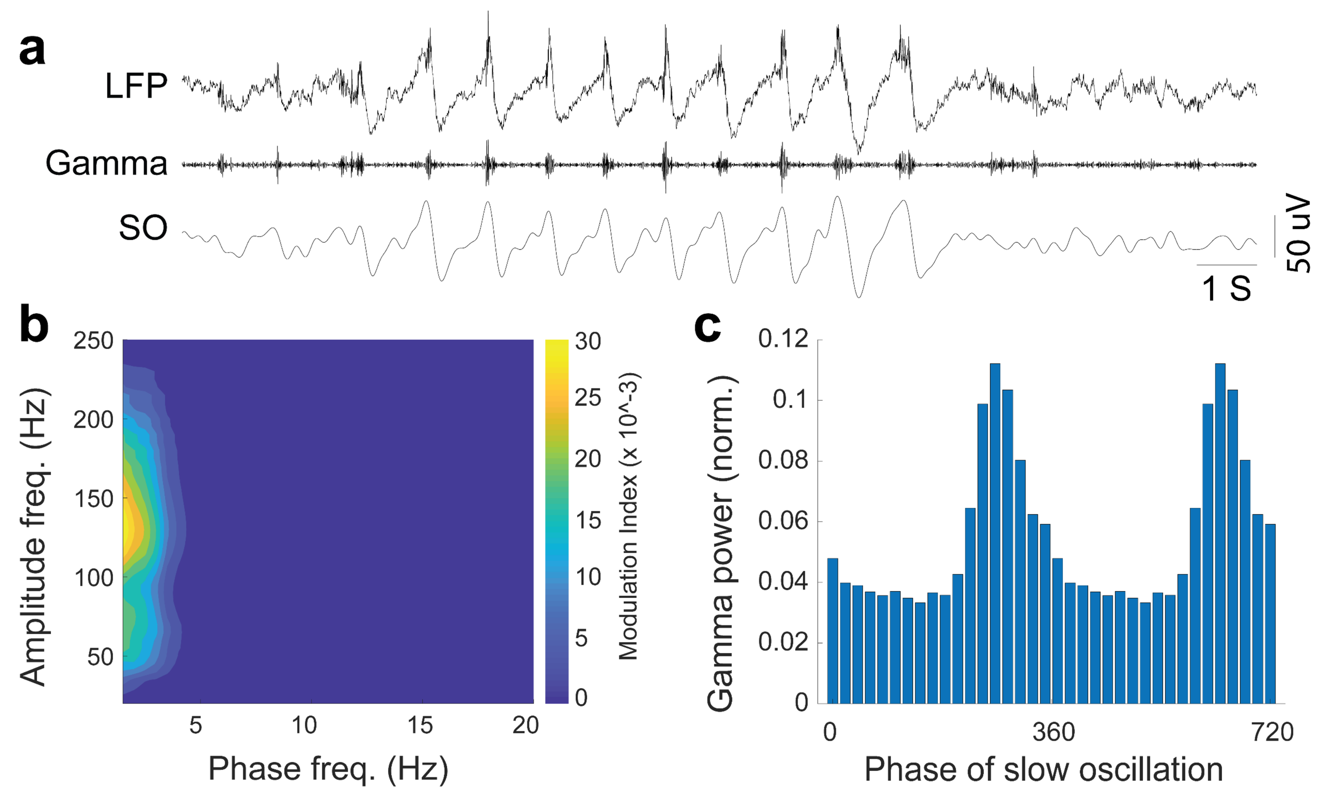
Wake-promoting cocktail		
Carbacol	Serotonine	NMDA
Orexin A	Histamine	AMPA
Norepinephrine	Dopamine	Kainate

1. Neural firing patterns of cultured brain regions



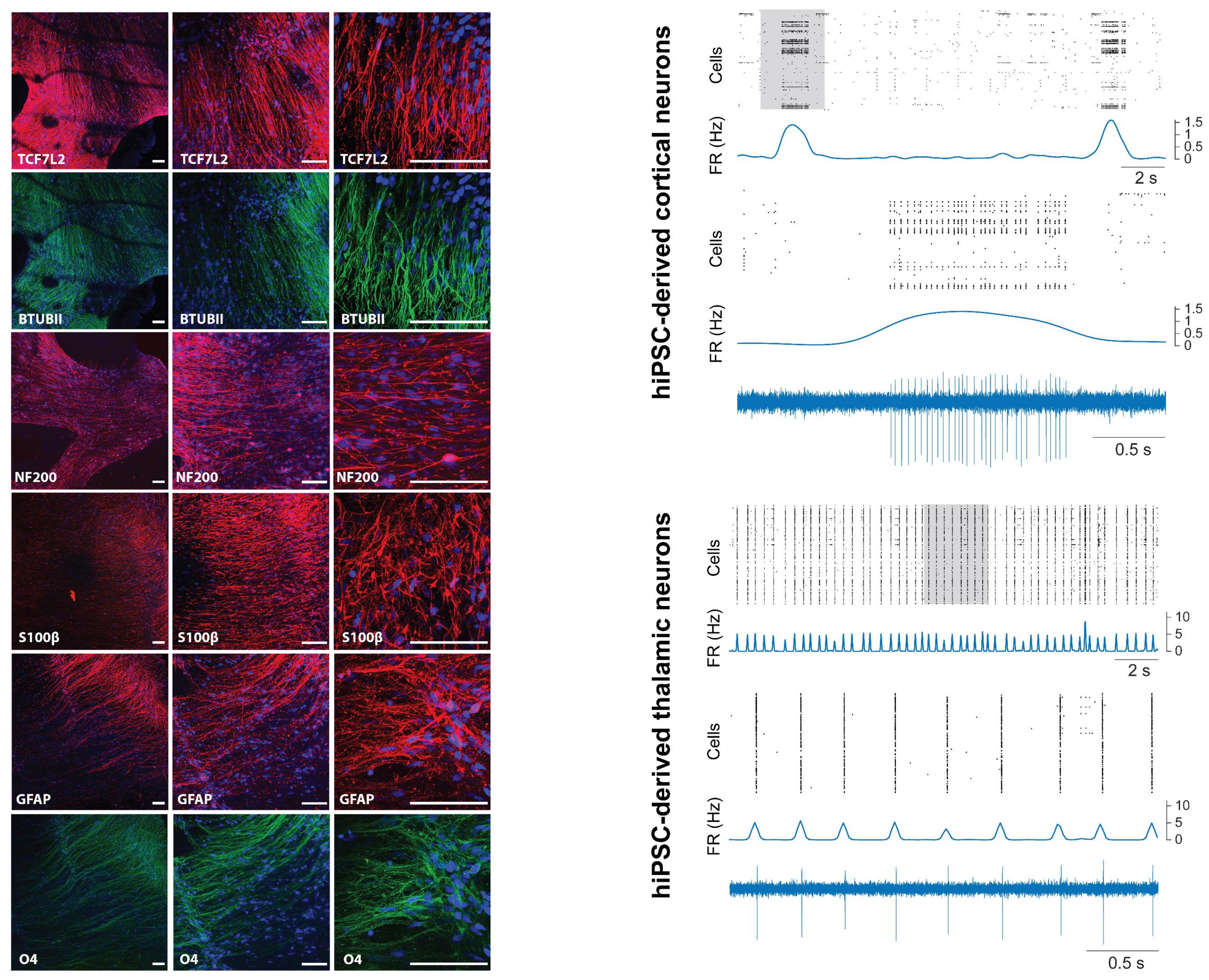
3. Phase-amplitude cross-frequency coupling in cortical cultures

The slow oscillation in cortical culture is accompanied with phase-locked gamma oscillations.



5. Mimicking sleep oscillations using hiPSC-derived aggregates

We generated hiPSC-derived cortical and thalamic aggregates and measured their neuronal activity using the HD-MEAs. Cortical cultures showed burst firing patterns (UP/Down states) and thalamic cultures fired in the delta range (3-4 Hz).



Conclusions

- Our results demonstrate that NREM sleep with its oscillatory characteristics is the default state of the cortical and thalamo-cortical networks.
- Mimicked oscillations using cultured cells show similar properties as in vivo brain oscillations during NREM sleep.
- Our sleep-in-a-dish model provides a powefull tool to investigate basic mechanisms of sleep oscillations and to discover their molecular and cellular underlying pathways.

References

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