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# Opto-fMRI of the Locus Coeruleus

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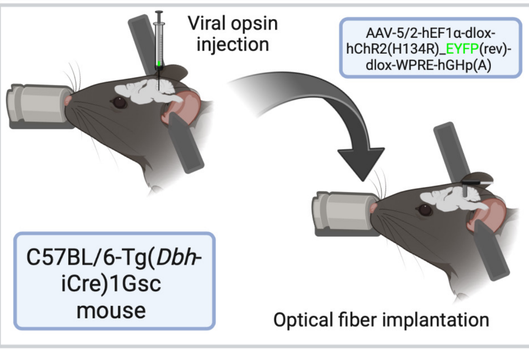
## BACKGROUND

Noradrenaline (NA) release from the brainstem nucleus locus coeruleus (LC) changes activity and connectivity in neuronal networks across the brain, thus modulating multiple behavioural states. NA release is mediated by both tonic and burst-like neuronal LC activity. However, it remains unknown whether the functional changes in downstream projection areas depend on these firing patterns. Using optogenetics, pupillometry, photometry, and functional MRI in mice, we show that tonic and burst LC firing patterns elicit brain responses that are specific to the activation frequency and temporal pattern. Tonic activation of the LC evokes nonlinear responses in prefrontal, limbic, and cerebellar regions, in line with the proposed inverted-U relationship between LC activity and behaviour. We further demonstrate that LC activity enhances network integration and acts as a facilitator of brain state transitions, hence increasing brain flexibility. Together, these findings reveal how the LC-NA system achieves a nuanced regulation of global circuit operations.

## METHODS

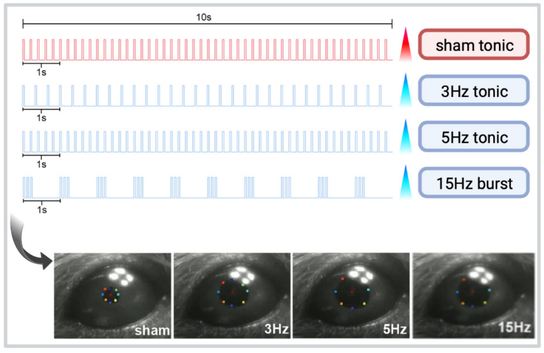
### Step 1

*Opto-tagging of LC NA neurons*



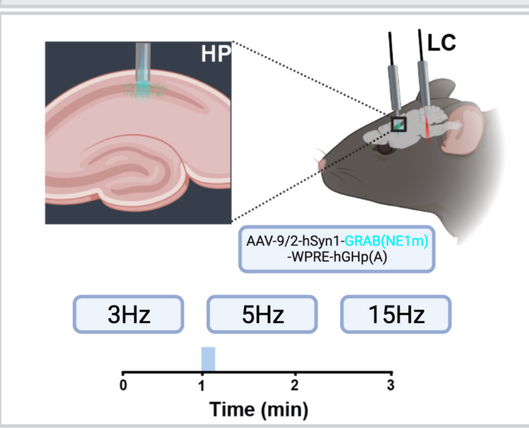

### Step 2

*LC Pupillometry*



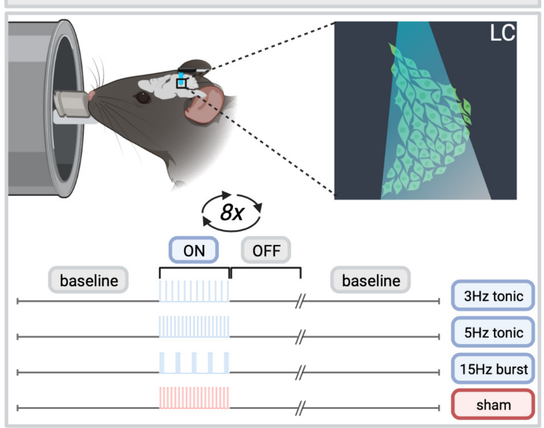

### Step 3

*NA fibre photometry*



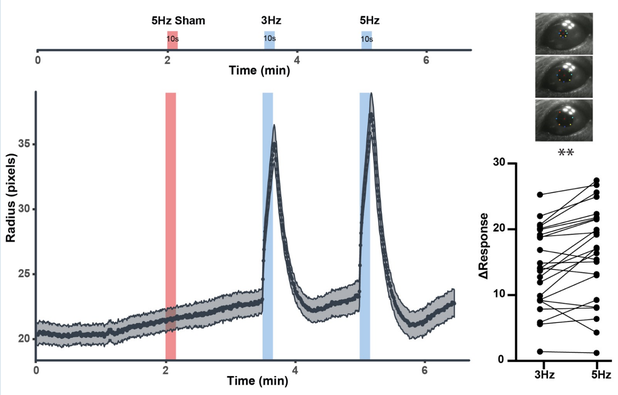

### Step 4

*LC Opto-fMRI*

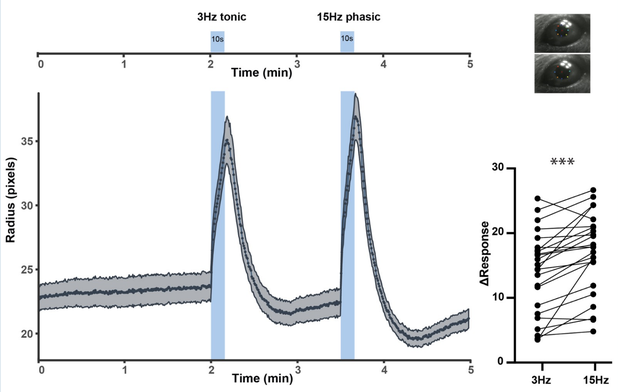



## RESULTS (1) - Pupillometry

### Tonic: 3Hz vs 5Hz

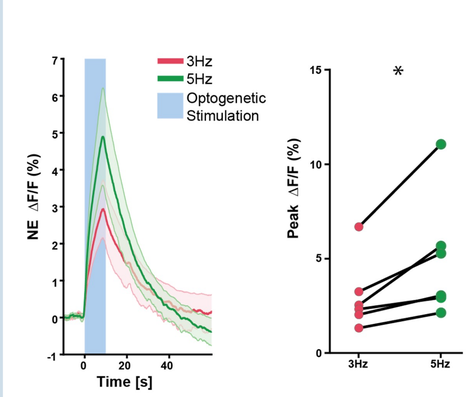



### Tonic vs burst: 3Hz vs 15Hz

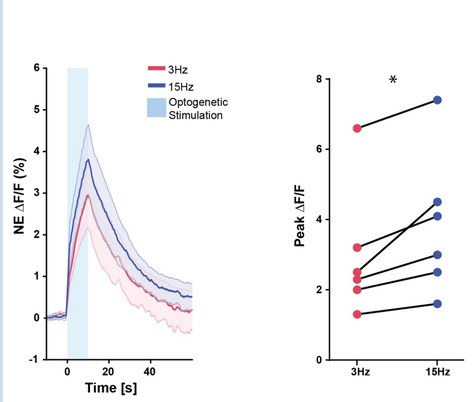



## RESULTS (2) - Photometry

### Tonic: 3Hz vs 5Hz

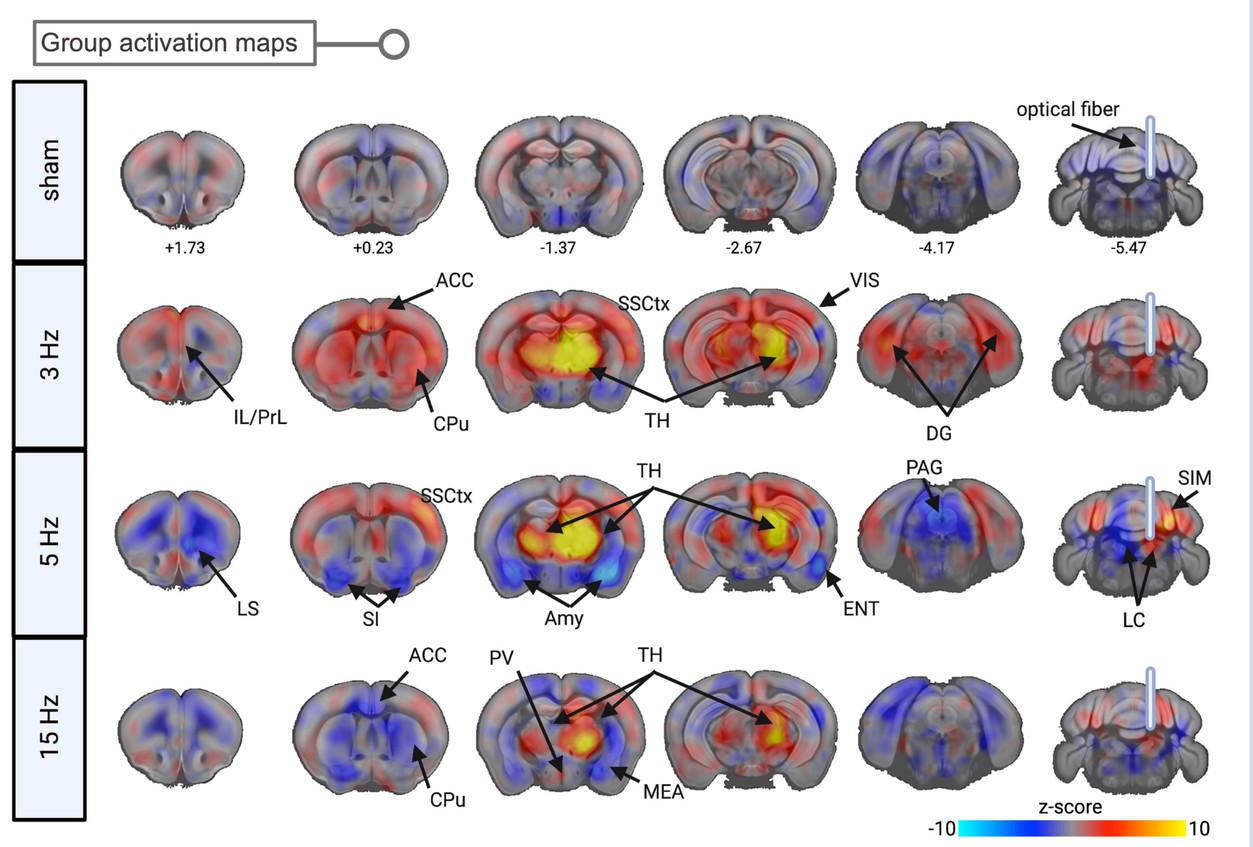



### Tonic vs burst: 3Hz vs 15Hz

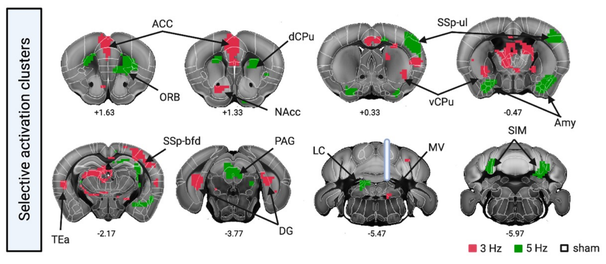



## RESULTS (3) – LC Opto-fMRI

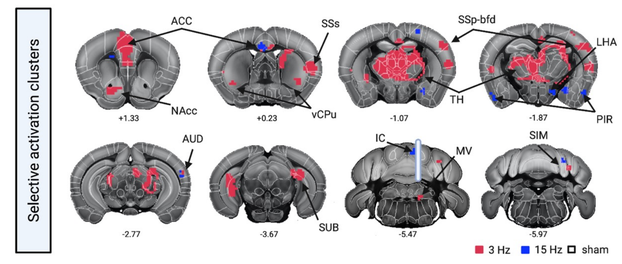
### Group activation maps




### Tonic: 3Hz vs 5Hz

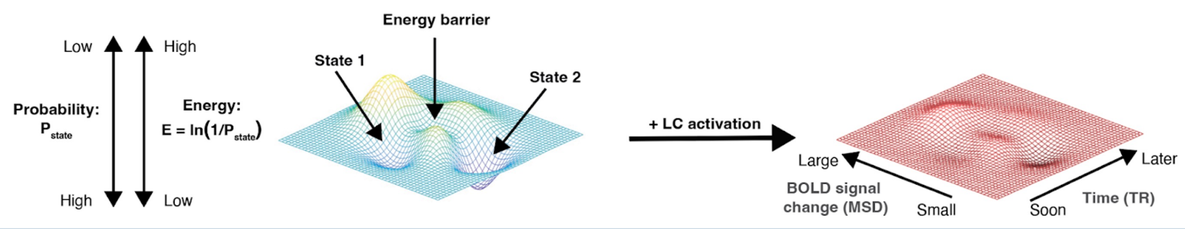



### Tonic vs burst: 3Hz vs 15Hz

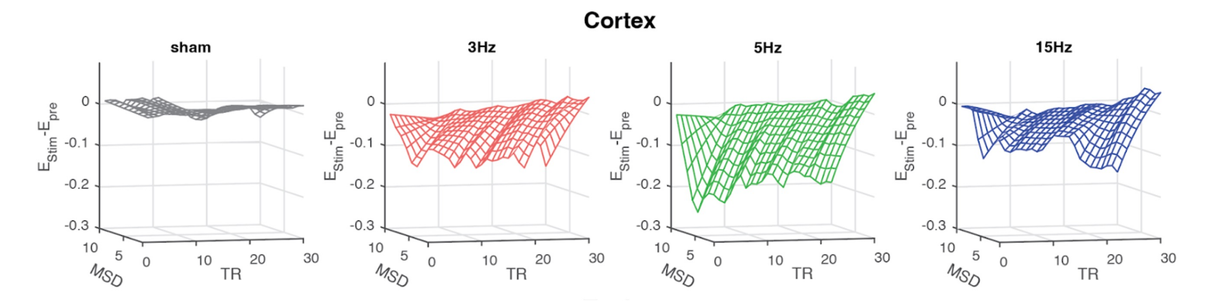



## RESULTS (4) – Energy landscapes

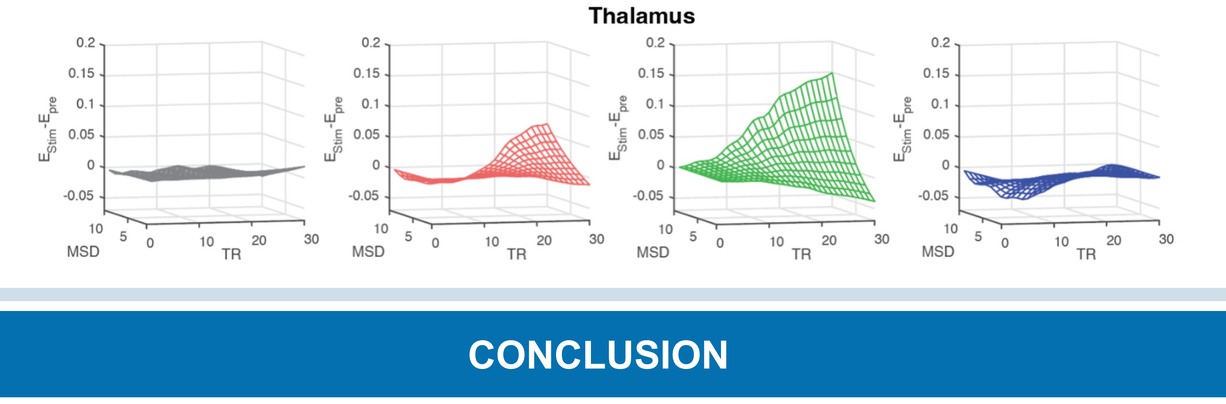
### LC NA activity effects on energy landscape




### Cortical energy landscape during LC stimulation




### Thalamic energy landscape after LC stimulation




## CONCLUSION

- *Different LC-NA firing patterns and frequencies evoke **different physiological responses***
- *LC-NA activity influences **brain activity** depending on firing patterns and frequency*
- *LC-NA activity changes **brain dynamics** and facilitates **brain state changes***

## REFERENCES

Zerbi, V., Floriou-Servou, A., Markicevic, M., Vermeiren, Y., Sturman, O., Privitera, M., von Ziegler, L., Ferrari, K.D., Weber, B., De Deyn, P.P., et al. (2019). Rapid Reconfiguration of the Functional Connectome after Chemogenetic Locus Coeruleus Activation. Neuron 103, 702-718.e705. 10.1016/j.neuron.2019.05.034.
Munn, B., Müller, E., Wainstein, G., and Shine, J. (2021). The ascending arousal system shapes neural dynamics to mediate awareness of cognitive states. Nature communications *12*. 10.1038/s41467-021-26268-x.
Privitera, M., Ferrari, K.D., Von Ziegler, L.M., Sturman, O., Duss, S.N., Floriou-Servou, A., Germain, P.-L., Vermeiren, Y., Wyss, M.T., De Deyn, P.P., et al. (2020). A complete pupillometry toolbox for real-time monitoring of locus coeruleus activity in rodents. Nature Protocols 15, 2301-2320. 10.1038/s41596-020-0324-6.

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