Synaptic Connectivity between the Cortex and Claustrum Is Organized into Functional Modules

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INTRODUCTION

The functions of the claustrum and its connections have been postulated to include cortical integration as the primary mechanism [1], coincidence detection [1], modulation of cortical activity [2], signal amplification [3] and cortical inhibition [4]. However, few studies have examined and established the relationship between the claustrum inputs and outputs on an electrophysiological basis.

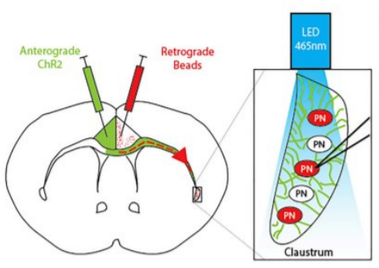
AIMS

The aim of this study (Chia et al. 2020) is to investigate the various inputs and outputs of the claustrum, specifically Anterior Cingulate Cortex projecting claustral neurons (CLA-ACC neurons), as well as the function of these connections.

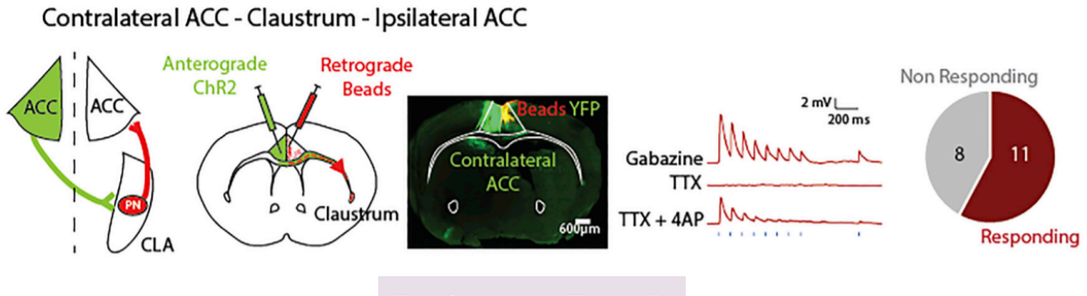
METHODS AND RESULTS

Claustral Input

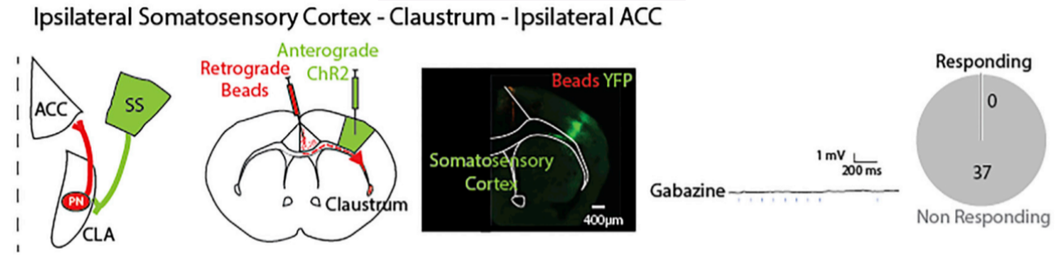
To identify the CLA-ACC neurons, red retrograde fluorescent beads were injected into the ipsilateral ACC. Anterograde AAV-mediated ChR2 virus was injected into the various cortical region. Photostimulation of ChR2 expressing neurons will produce synaptic activity in CLA-ACC neurons if the two are connected.



Explanatory Trace A

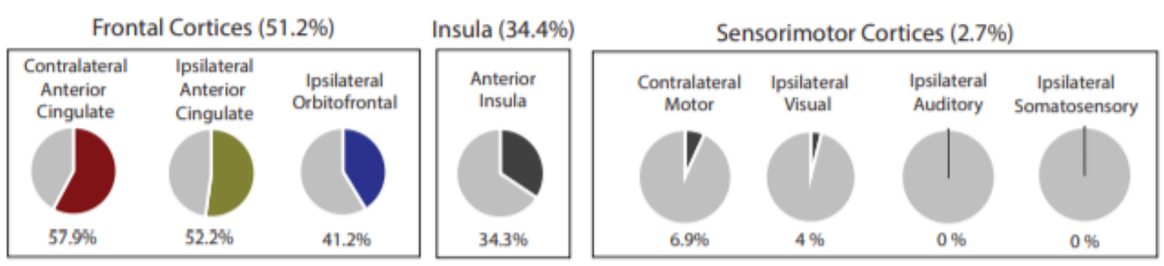


Explanatory Trace B



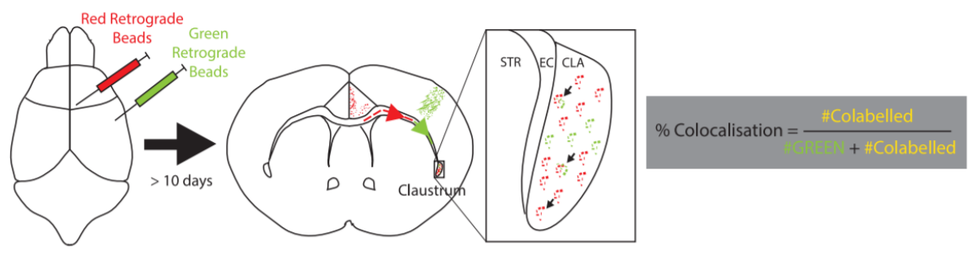
Example traces for both frontal cortices and sensorimotor areas

- During whole cell clamp recordings, Gabazine did not inhibit electrical activity while NBQX and APV did, indicating connections were excitatory and not inhibitory.
- Next, Tetrodotoxin (TTX) was added, followed by 4-aminopyridine (4-AP). This allows only CLA-ACC neurons that receive direct excitatory input from neurons transfected with ChR2 viruses (under UV light) to be reactivated. Restoration of electrical activity (seen in TTX + 4AP trace) indicates that these connections are monosynaptic.
- Explanatory Trace A shows strong connections between the CLA-ACC neurons with the contralateral ACC as red beads can be seen in fluorescent green areas under UV light. 57.9% of brain slices show these positive traces.
- Explanatory Trace B shows no connection between the ipsilateral somatosensory cortex and the CLA-ACC neurons, as the fluorescent green areas do not interact with areas containing red beads (CLA-ACC neurons).



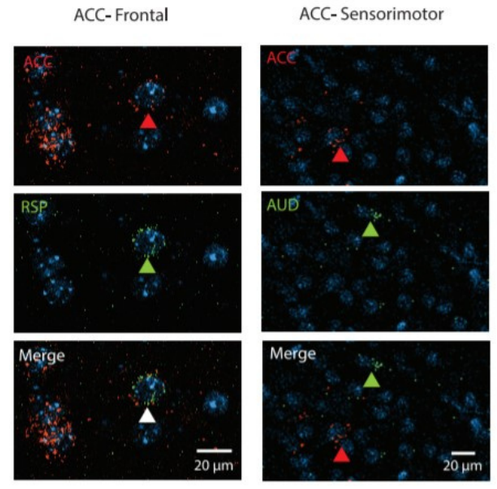
These charts show the percentage of response rates for various inputs to CLA-ACC neurons. CLA-ACC neurons preferentially receive input from frontal and limbic cortices rather than sensorimotor cortical input .

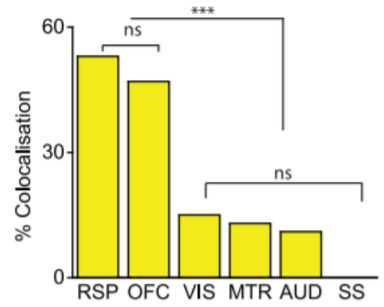
Claustral Output



To identify cortical projections of the CLA-ACC neurons, green retrograde beads were injected into various probable cortical regions, while red retrograde beads were injected into the ipsilateral ACC to identify CLA-ACC neurons.

- (ACC-Frontal) Coloured beads show localisation of different neurons in the same CLA-ACC neuron and overlap in the final Merge image show colocalisation, that claustral neurons that project to the ipsilateral ACC also projects to the frontal cortex.
- (ACC-Sensorimotor) The last merged image of the ACC-sensorimotor trace shows the 2 beads at different locations with no colocalization, which indicate that CLA-ACC neurons do not also project to the sensorimotor cortex.

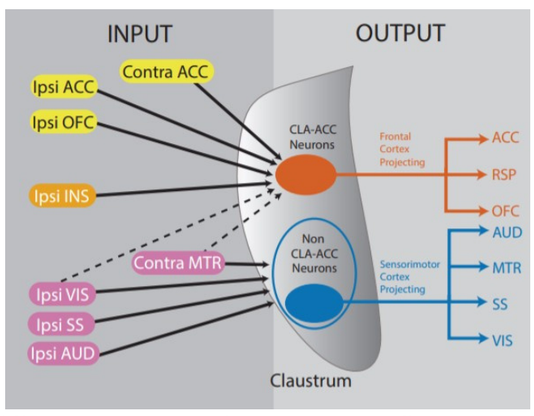




The chart summarizes the rate of colocalisation of CLA-ACC neurons and other cortical targets. CLA-ACC neurons interact strongly with frontal and limbic cortical areas (Orbitofrontal cortex and Retrosplenial cortex), but have minimal interactions with sensorimotor cortices.

Summary of Modular Organization of Cortico-claustral Interconnectivity

In summary, CLA-ACC neurons receive monosynaptic, excitatory inputs from various cortical areas shown in yellow (above), while projecting to some of these same areas (OFC and ACC) or other frontal cortical areas (RSP).



OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; RSP, retrosplenial cortex; INS, insula; MTR, contralateral motor cortex; SS, somatosensory cortex; VIS, visual cortex; AUD, auditory cortex

DISCUSSION AND CONCLUSION

- Claustrum projection neurons are organized into at least two distinct targeting systems, with CLA-ACC neurons mainly interacting with frontal cortical areas, and non CLA-ACC neurons interacting with sensorimotor cortical areas.
- This suggest a possible general organizational principle for the claustrum, where CLA-ACC neurons are interconnected with selected cortical regions to form functional modules
- A follow up experiment could be to find the role of the claustra in the neural circuits of the Salience Network

References

Paper: Chia Z, Augustine GJ, Silberberg G. Synaptic Connectivity between the Cortex and Claustrum Is Organized into Functional Modules. Curr Biol. 2020;30(14):2777-2790.e4.

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