Society for Claustrum Research
Third Annual Symposium
THE UNDISCOVERED CLAUSTRUM
in conjunction with
The Centenary Celebration of Francis Crick

Does the claustrum play a key role in consciousness?
“What could be more important? Why wait?” – Francis Crick

CONRAD T. PREBYS AUDITORIUM, SALK INSTITUTE
SATURDAY, NOVEMBER 12, 2016, 7AM TO 2PM

7:00-8:00 AM Welcome & Registration (continental breakfast and socialize)
8:00-8:30 AM TERRENCE SEJNOWSKI, PhD Salk Institute
Opening Remarks and Retrospective on Francis Crick
8:30-9:00 AM SHAWN OLSEN, PhD Allen Institute for Brain Science
Imaging Claustral-Cortical Projections in Transgenic Mice
9:00-9:30 AM BRIAN N. MATHUR, PhD University of Maryland School of Medicine
Illuminating the Structure-Function Relationship of the Mouse Claustrum
9:30-9:45 AM Coffee Break
9:45-10:15 AM GEORGE AUGUSTINE, PhD Nanyang Technological University, Singapore
Functional Perspective on Claustral Cells, Synapses and Circuits
10:15-10:45 AM MICHAEL HAUSSELL, PhD University College London
Multimodal Integration in Single Neurons of the Claustrum
10:45-11:00 AM Coffee Break
11:00-11:30 AM AMI CITRI, PhD The Hebrew University of Jerusalem
Attending to the Function of the Claustrum
11:30-12:00 PM JOHN D. VAN HORN, PhD USC Keck School of Medicine
Mapping White Matter Connectivity of the Human Claustrum
Using in vivo Neuroimaging
12:00-1:45 PM Lunch & Poster session
1:45-2:00 PM Concluding Remarks & Adjourn

Information and registration: www.salk.edu/crick100 or contact Mary Ellen Perry, Meeting Coordinator, meperry@salk.edu
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This Symposium is being held during the 2016 Annual Meeting of the Society for Neuroscience, November 12-15 in San Diego, CA.

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EXECUTIVE SUMMARY

Last year, the Society for Claustrum Research held its annual meeting in conjunction with The Salk Institute for Biological Studies, as part of The Salk’s celebration of the centenary of Francis Crick’s birth. Over 140 registrants took part in an exceptional program of talks and poster presentations presided over by Professor Terrence Sejnowski, the Francis Crick Chair and Head of the Computational Neurobiology Laboratory at the Salk Institute, and Professor Patricia Churchland, Presidential Chair of Philosophy at the University of California, San Diego.

Presentations at this year’s conference were organized around the theme of ‘The Undiscovered Claustrum’, with the express intent of addressing Francis Crick’s challenging final question about pursuing research on the claustrum: ‘What could be more important, so why wait?’ [1]. The invited speakers addressed the issue of the undetermined function of the mammalian claustrum, using approaches and model systems which ranged from individual cell recordings to whole-brain imaging in awake human subjects.

A key theme which has emerged from these studies is the potential role for the claustrum in selective attention and stimulus salience, as described in the summaries below.

Oral presentations

Illuminating the structure function relationship of the mouse claustrum

Dr. Brian N. Mathur
Department of Pharmacology, University of Maryland School of Medicine, USA

The meeting started off with a fascinating discussion of claustrum responses during an attention-demanding salience task in awake mice. Using GCaMP6f virally introduced into the anterior cingulate cortex (ACC) and optical fiber photometry of terminals in the claustrum, Dr. Mathur’s team detected activity in this circuit prior to cue presentation on a 5-choice, but not an attentionally unburdened 1-choice, serial reaction time task. Interestingly, when the ACC-claustrum circuit was disrupted optogenetically 0.5–1 s prior to the GO cue for a trial, the percentage of correct performance was reduced. This effect was not observed if activity in the ACC-claustrum circuit was disrupted ≥ 3 s prior to the GO signal. Crucially, the degradation of performance resulting from disruption of the ACC-claustrum circuit was more pronounced in the 5-choice task, relative to the 1-choice or control tasks.

Recordings obtained from identified claustrum cells in brain slices indicated that the output of type I and II spiny projection neurons of the claustrum, which receive inputs from the ACC, is modulated by parvalbumin positive and type III claustrum interneurons. The circuit described by these experiments provides a time-delimited amplification of ACC input. Thus, strong evidence is emerging that the claustrum, in concert with the anterior cingulate region, plays a role in top-down attention in rodents.

Imaging claustral-cortical projections in transgenic mice

Dr. Shawn Olsen
Assistant Investigator, Allen Institute for Brain Science, Seattle, WA, USA

Dr. Olsen started his presentation by introducing transgenic mice used by the Allen Institute for studying the claustrum. Specifically, Gnb4-IRES2-Cre mice allow genetic targeting of the claustrum (and endopiriform nucleus) through Cre-dependent adeno-associated viruses (AAVs). Using these mice, another research group at the Allen Institute mapped the outputs of the claustrum [2]. Dr. Olsen then presented data from a new method called fMOST imaging that allows for very high spatial resolution (~1 μm) reconstructions of claustrum projection neurons in the mouse, which revealed a diverse array of projection patterns. Both ipsilaterally
and contralaterally projecting corticoclaustral cells were observed, but the spatial pattern and distribution of their axons was quite different. Moving forward, it will be crucial to understand what factors, if any, distinguish interhemispheric from intrahemispheric claustrum neurons.

Evidence for a role of the claustrum in attention/salience processing was corroborated by Dr. Olsen’s findings using single photon calcium imaging of claustro-cortical projections in mice trained on a modified virtual reality foraging task. Optical access to claustro-cortical projections was possible by Cre-dependent viral expression of GCaMP6f in Gnb4-IRE2-Cre mice, which were subsequently fitted with cranial windows to allow bilateral imaging of the entire dorsal cortical mantle. Head-fixed mice on a running ball were then trained to report when a visual stimulus changed shapes from a bird to a mushroom to receive a water reward. Visual presentation of either stimulus-type (the bird or the mushroom) evoked small increases in GCaMP activity across many cortical areas, but rewarded trials when the mouse detected a change in the stimulus resulted in a 10X increase in GCaMP activity in claustro-cortical terminals. It remains unclear to what extent this increase results from the sensory stimulus change itself, or the reward the animal received. Moving forward, this approach will likely reveal fascinating information on how the claustrum coordinates activity among multiple cortical regions during sensory detection.

**Functional perspective on claustrum synapses and circuits**

**Dr. George Augustine**
Principal Investigator, Synaptic Mechanisms and Circuits Laboratory, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Dr. Augustine’s laboratory has focused on identifying and characterizing the electrophysiological properties of the various types of claustrum neurons. Recent work has revealed at least seven cell types, based on differences in spike adaptation during in vitro electrophysiology recordings. Approximately 92% of neurons sampled so far have been projection neurons of the mildly adapting type 2 (MA2) or strongly adapting type 2, 3, or 4 (SA2, SA3, SA4) varieties. Of the claustrum interneurons sampled, approximately one-third were parvalbumin positive (Pv+), approximately one-third expressed somatostatin (Ss+), and the remainder appeared to be positive for vasoactive intestinal peptide and possibly type 3a serotonin receptors (VIP+; 5HT3A). Electrophysiological recordings indicated that the local neuron networks identified in this study have intrinsic oscillatory capability across multiple frequencies. This fundamental work will provide the foundational knowledge of the physiological properties of rodent claustrum neurons, which will aid our understanding of claustrum function and allow computer modelling of claustrum activity in the future.

**Attending to the function of the claustrum**

**Dr. Ami Citri**
The Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem, Israel

Dr. Citri has been a strong proponent of the selective attention hypothesis of claustrum function [3], first proposed by Dr. Mathur [4]. At the Salk event, he presented data from optogenetic manipulation of rat claustral neurons in an auditory circuit. First, Dr. Citri described how his group identified a mouse Cre-line to genetically access the claustrum, focusing on the gene Egr2. Using this mouse line, Dr. Citri’s group first used anterograde and retrograde tracing to map the input-output connectivity of these claustral cells, which showed similar patterns to other tracing studies though prominent subcortical inputs were identified (including amygdala, thalamus, and others).

To explore the physiology of these connections, Dr. Citri’s group expressed channel-rhodopsin in the claustrum and then used loose-patch recordings in auditory cortex. Activating claustrum afferents prior to playing an auditory tone results in a flattening of tuning curves in auditory cortex neurons, meaning a decrease in the response amplitude to that neuron’s preferred auditory frequency.

Dr. Citri went on to present data showing that claustrum inhibition (using DREADDS and Kir2.1 channel expression) during a visual discrimination task makes mice highly sensitive to auditory distracter stimuli. A second component of Dr. Citri’s work surrounds the behavioral paradigm of maternal pup retrieval. Pup retrieval was disrupted in response to auditory stimuli when claustrum function was disrupted by constitutive expression of a potassium channel. Dr. Citri concluded by pointing that this data supports a role for the claustrum in gain control of sensory processing that enables selective attention.

**Mapping white matter connectivity of the claustrum using in vivo neuroimaging**

**Dr. John (Jack) Van Horn**
Laboratory of Neural Imaging, USC Keck School of Medicine, Los Angeles CA, USA

Dr. Van Horn is one of the few researchers using human neuroimaging who focus on the claustrum using magnetic resonance imaging (MRI), particularly employing diffusion tensor imaging (DTI). Dr. Van Horn provided a comprehensive overview of modern imaging...
approaches, with an emphasis on understanding the data analysis and visualization methods underpinning diffusion imaging. His team has recently identified the claustrum as a key member of the brain’s ‘rich club’ of highly connected areas, based on imaging studies of over 100 patients. A key point raised by Dr. Van Horn surrounds the difficulty of isolating the claustrum, even in gross anatomical studies, due to its deep location and thin profile. This message was reinforced with the meeting’s only major visual aid, a preserved and sectioned human brain with the claustrum exposed, which was made available for examination by conference participants. In closing, Dr. Van Horn issued a challenge to the imaging community, by pointing out that none of the currently available automated parcellation programs used in allocating functional activity to anatomical areas includes a separate mask for the claustrum, which is likely to be a major source of bias in the claustrum literature. To date, his team have generated ROI seed areas by hand, which has been a fruitful approach, but which is clearly inadequate to the task of generating and sharing data for future studies.

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Poster abstracts
The claustrum activates the cortex during paradoxical (REM) sleep
Pierre-Hervé Luppi
Sleep team, UMR 5292 CNRS/U1028 INSERM, University of Lyon, France
Recent studies strongly support a role of the paradoxical sleep (PS) in learning and memory consolidation [1]. However, the mechanisms underlying the beneficial effect of PS on learning and memory have not yet been identified. To this aim, we recently identified at cellular level the populations of cortical neurons activated and displaying plasticity during PS hypersomnia by means of functional neuroanatomy [2]. Our mapping clearly shows for the first time that only a small number of limbic structures are activated during PS in contrast to waking. These structures are the cortical amygdaloid nucleus, the anterior cingulate, retrosplenial and medial entorhinal cortices, the claustrum, and the dentate gyrus (DG) [2]. Further, combining retrograde tracing, neurotoxic lesion and FOS immunostaining, we showed that neurons of the claustrum and from the lateral part of the supramammillary nucleus (SuML) are responsible for the activation of the cortical structures and the DG during PS [2]. These surprising results pointed out for the first time that the claustrum and the SuML activate a subset of limbic cortical neurons specifically during PS. We propose that such activation might play a key role in the previously reported beneficial effect of PS on learning and memory. Indeed, many studies clearly indicate that PS is instrumental for memory consolidation [3]. Further, it has recently been shown that PS deprivation in rats impairs consolidation of contextual fear conditioning [4]. Our results also point out a key role of claustrum neurons in cortical activation taking place during PS. In summary, original new converging data strongly suggest that the claustrum is activated during PS and plays a key role in activating neurons located in selected cortical limbic structures.

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Secondary Autism Spectrum Disorder following a bilateral lesion of the claustrum: a case report
Maria Cristina Patrua, Sven Hallerb,de, Markus Kosela, Joel Plussb
Presenter: Maria Cristina Patru
aDepartment of Mental Health and Psychiatry, University Hospital, Geneva, Switzerland;
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Despite a growing interest in the role of the claustrum, its function in normal neurological and
psychological processes remains largely enigmatic. Nevertheless, there is recent evidence that suggests the claustrum is structurally and functionally compromised in disorders such as epilepsy, autism, schizophrenia, and Alzheimer’s disease [1,2]. We present the case of a 5-year-old boy diagnosed with febrile infection-related epilepsy syndrome (FIRES). Approximately three weeks after the onset of this illness, characterized by daily refractory multiple focal seizures, isolated bilateral claustral lesions were observed on a repeated brain MRI. The T2 hypersignal was not visible during the acute phase (i.e., Day 2 and Day 4) and was no longer evident at 3 months after onset. On clinical follow-up, this boy, with previous normal psychological development, progressively developed autistic symptoms that persist to this day. He is now 11 years old and exhibits in addition drug-resistant epilepsy. Brain MRI coupled with PET scan at age 7 revealed respectively cortical atrophy and hypometabolism of the frontal, parietal, and temporal cortical association areas. Our observation is one of the very few describing isolated acquired lesion of the claustrum [3,4]. Typically, lesions of the claustrum are associated with concurrent and overt subcortical and cortical damage, thus complicating efforts to establish specific and reproducible relationships between damage to the claustrum and psychiatric or neurological diseases. To the best of our knowledge, this is the first case describing a secondary acquired autistic features in the setting of bilateral lesion of the claustrum. The late onset of autistic symptoms is intriguing and, as suggested by the latest MRI, could be related to damage to corticoclaustral connections, which play a critical role in sensory integration (See supplemental file 1).

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Functional connectivity of the claustrum in humans and rats at 7T MRI

David Seminowicz, Samuel L. Krimmel, Austin P. Ramsey, Natalie Hesselgrave, Michael G. White, Matthew Panicker, David H. Reser, Brian N. Mathur

Presenter: David Seminowicz

University of Maryland School of Medicine, Baltimore, MD, USA;

Department of Physiology, Monash University, Clayton, VIC, Australia

The claustrum has reciprocal connectivity with multiple cortical networks and potentially has an important role in orchestrating activity across these function networks. However, the claustrum’s sheet-like shape and close apposition to medially lying putamen and laterally lying insular cortex have hindered such assessments with functional MRI. To surpass the confounds associated with imaging of claustrum, in both rats and humans, we used 7-Tesla fMRI datasets to examine the whole-brain resting state connectivity of the claustrum compared to its neighboring regions, the insula and striatum. Adult female Sprague–Dawley rats (200–250 g) were scanned on a Bruker BioSpec 70/30USR Avance III 7-Tesla scanner (Bruker Biospin MRI GmbH, Germany) including a high resolution T1-weighted scan (RARE, TR = 2000 ms, TE = 14 ms, 256 × 256, in plane resolution = 100 μm, 24 axial slices, 1 mm slice thickness) and resting state scans (TR = 1500 ms, TE = 35.0966 ms, 75 × 75, in plane resolution = 0.4 × 0.4 × 1 mm, 24 axial slices). We also analyzed a publicly shared dataset of 17 human subjects [1] scanned on a 7T MR scanner (MAGNETOM 7T, Siemens Healthcare, Erlangen, Germany) that included a structural 3D MP2RAGE with resolution of 0.7 mm isotropic voxels and a resting state functional EPI scan with resolution of 1.5 mm isotropic voxels. Preprocessing of both datasets included slice timing correction, realignment, normalization, smoothing, physiological and scanner noise reduction, and band-pass filtering. We performed seed-based connectivity analyses by delineating the striatum (putamen in humans, caudate-putamen in rats), insula, and claustrum for each subject individually. A cluster-forming threshold of p < .001 was used for all analyses and significant clusters based on family-wise error correction are reported. In both rats and humans, our preliminary findings suggest that the claustrum is functionally connected to widespread cortical and subcortical brain areas. In rats, the connectivity of the claustrum with multiple cortical regions was significantly greater than insula or striatum. Furthermore,
there were no regions in the brain that had greater connectivity to the insula or striatum than to the claustrum. In humans, insula connectivity to widespread cortical areas was greater than claustrum, while claustrum had greater connectivity than striatum to sensorimotor and visual cortices. Our results suggest that while it is possible to examine claustrum connectivity in rodents and humans at high-field MRI, determining specific connectivity of the human claustrum is highly confounded by its three-dimensional structure. Our ongoing studies in rats use optogenetic drive of known corticoclaustral pathways to disambiguate claustrum-specific activation signals from neighboring structures.

Reference

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On similarity of claustral and cortical neurons

Akiya Watakabe
Lab for Higher Brain Function, RIKEN Brain Science Institute, Japan

Gene expression is a window through which we can take a glimpse of the nature of the cells of interest. It reflects cell types, some functional properties, as well as developmental and evolutionary background. During the course of my study to find universal marker genes for cortical projection neuron subtypes, I noticed that a set of genes that are enriched in the rodent claustrum (latexin, nur1, cxu2, and netrinG2) are co-expressed in a select population of deep cortical neurons in the lateral cortex. This observation raised the possibility for common developmental and evolutionary origins for claustral and cortical neurons. To gain more insight to this problem, I performed comparative analyses of these and other genes in macaque monkeys and marmosets and found the following: (1) claustral gene expression appears to be overall conserved across rodents and monkeys; (2) cortical expression of these genes can differ across species. For example, latexin was not expressed in the cortical neurons in macaques or marmosets. Tmem163 gene was expressed in layer 3 and not in deep layers; (3) a subpopulation of layer 6 neurons, which likely project to other cortical neurons, co-express nur1 and netrinG2. The neuronal subtype characterized by these genes exists only in the lateral cortex in the rodents, but seem to scatter across entire cortical areas in macaques and marmosets. Based on these data and nur1 expression in embryonic monkeys, we propose common origin of claustral and cortical neurons which migrate and acquire differential properties in the adult monkey brain (See supplemental file 2).

Micro- and macrocircuit components of a putative attention filter

Michael G. White, Matthew Panicker, Ashley M. Carter, Bradley M. Roberts, Poorna A. Dharmasri, and Brian N. Mathur
Presenter: Michael G. White
Department of Pharmacology, University of Maryland, School of Medicine, Baltimore, MD, USA

The claustrum has broad cortical interconnectivity and transiently responds to salient stimuli. This enigmatic forebrain structure is therefore proposed to enable the intercortical communication necessary for attentional allocation 2014 [1]. Using neuronal tract tracers we explore the connectivity profile of the mouse claustrum with cortical areas implicated in attention. We find that the claustrum displays dense interconnectivity with the ACC in particular, which is functionally implicated in attentional control in rodents. To examine the responsivity of claustrum neurons to ACC input, we use whole-cell patch clamp electrophysiology and optogenetics in acute mouse brain slices. We find that claustral spiny projection neurons faithfully fire in response to ACC afferent stimulation and that inhibitory claustral microcircuits provide feedforward and feedback inhibition, thus sculpting the ACC-mediated drive of claustrum projection neurons. Our results suggest that the claustrum is organized to filter and propagate incoming frontal cortical signals (See supplemental file 3).

Reference

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The claustrum related to the formation of the temporal lobe

John I. Johnson, T. T. Sheridan
Presenter: J. I. Johnson
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The claustrum was originally conceived as a layer of gray matter enclosed between fibrous laminae of the external and extreme capsules [1]. It has for too long been reputed to be a dependency of overlying insular cerebral cortex. Rather than any functional or anatomical connections, study has now shown [2] that the inferior edge of the claustrum is simply juxtaposed to:
(1) the inferior edge of the insula (the limen insulae),
(2) the posterior-most reach of the medial surface of the frontal lobe, and
(3) the proximal-most portion of the temporal lobe.

Together these regions make up the piriform cortex, the central terminal region of the lateral olfactory tract, giving rise to its designation as ‘primary olfactory cortex’.

Depending on one’s criteria of primarihood, this folded region could as well be thought of as a secondary olfactory cortex, receiving input connections from the true primary olfactory cortex located in the glomerular layer of the peripheral olfactory bulb, where the olfactory receptor cells make their first contact with the cortical layers that have been shaped into layers of dendrites of mitral and tufted cells of the olfactory bulb.

Besides the integrity of the lateral olfactory tract, another tie that keeps these diverse regions together is their common substantial connection with the amygdala. A popular ontogenetic possibility, the claustrum-amygdalar hypothesis, suggests that claustrum and amygdala both derive from common, or at least closely neighboring, lateral pallial primordiums [3,4].

For years the claustrum was considered to have dorsal and ventral parts, the dorsal underlying insular meso- and neo-cortex, then after a narrowing, spreading out into a ventral part underlying the piriform olfactory paleocortex. The notion that the ventral portion is actually a distinct cellular region, named the endopiriform, is supported by its proteomic profile different from that of the dorsal portion [5].

However, the claustrum and endopiriform, often and perhaps always, maintain continuity with one another that we call the root of the claustrum. Whatever it is that claustrum does for all reaches of meso- and neo-cortex, then the endopiriform might perform a similar function for the paleocortical piriform cortex. The boundary between claustrum and endopiriform is directly internal to the fundus of the rhinal sulcus that separates paleo- from meso- and neo-cortex.

In the evolution of several large mammalian brains, the rhinal sulcus deepens and expands, separating the temporal and frontal lobes. The temporal lobe expands laterally rather than in some other direction, and then folds to fit inside the skull. The crease of the fold holds the piriform laterally and includes the cortical amygdalar nuclei always located near the temporal pole. Internal to this is the root of the claustrum, with the paleocortical endopiriform disto-laterally and the ‘true claustrum’ proximo-superiorly internal to the meso- and neo-cortical regions of the insula. The temporal expansion can be ascribed to additions of cascades of connections that form the information pathways, to and from the bulk of neocortex and the processing factories of amygdala and hippocampus, used by all neocortical regions (See supplemental file 4).

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Characterization and functional analysis of claustral VIP interneurons

**Martin Graf**<sup>a,b</sup>, **George Augustine**<sup>a,b</sup>

**Presenter: Martin Graf**

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The claustrum is a little-understood structure that is embedded within the deep layers of the insular cortex. As in all other brain regions, it is likely that interneurons play important roles in information processing within the claustrum. We have defined the morphology, intrinsic electrical properties, and functional connectivity of one type of claustral interneuron: VIP expressing interneurons (VIP+ INs). The electrical properties of these interneurons were determined via patch clamp recordings in acute brain slices. VIP+ INs from transgenic mice expressing Channelrhodopsin-2 exclusively in VIP neurons could be identified by photostimulation when exposed to blue light. VIP+ INs differed from other claustral INs in their somatic shape, which were either multipolar or elongated/bipolar. Their neurites projected mainly to the shell or edge of the claustrum core, which contrasts from the enrichment of processes from PV INs within the core. VIP+ INs had the highest input resistance, broadest AP half-width, the shallowest AHP, and lowest maximum firing rate of any claustral INs. High-speed optogenetic circuit mapping [1] revealed that VIP+ INs are connected to projection
neurons as well as to other IN populations. Remarkably, this inhibitory input was much stronger and more efficient for INs than for projection neurons. Thus, it appears that claustral VIP+ INs specifically target other local IN populations and might relieve projection neurons from local inhibition imposed by PV+ and SST+ interneurons. In general, VIP+ INs are strategically situated to increase signaling of claustral projection neurons via disinhibition, well-positioning these INs to regulate information flow through the claustrum during attention allocation [2], consciousness [3], or other functions proposed for this highly interconnected brain region.

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Computer models of claustrum subnetworks

William Lytton*a, Jing Xuan Limb,c, Salvador Dura-Bernalb, George J. Augustineb,c

Presenter: William Lytton

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*bInstitute of Molecular and Cell Biology, A*STAR, Singapore
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The dynamical properties of a brain area are determined by its connectivity and by the activation properties of its cells. We utilized data obtained from electrophysiological characterization of newly identified cell types in the claustrum to create a model with four classes of excitatory (E) and three classes of inhibitory (I) neurons. E cells were classified by degree of adaptation in response to current clamp spike patterns: strongly adapting (SA); mildly adapting (MA). I cells were classified by adaptation and by peptide markers: somatostatin (SST) and parvalbumin (PV). Network circuitry between classes was estimated based on functional mapping experiments using optogenetic stimulus to identify locations and, in some cases, cell-type identity of neurons synapsing on a recorded postsynaptic neuron. A simplified spiking neuron model was used to allow running of many thousands of network simulations efficiently. Simulations were run in NEURON on the San Diego Supercomputer via the Neuroscience Gateway. Driving the model with continuous subthreshold background white noise input induced a persistent excitatory state. In the setting of low background drive, single activation of any one of the 4 E-neuron types would also lead to persistent activation. Stimulation of the MA2 subpopulation gave immediate network activation. Network activation was slightly delayed with stimulation of SA3 or SA4, and delayed >1 s with stimulation of the SA2 population. These delays represented the time required to secondarily activate the MA2 population. The initial activity transient was generally followed by a sustained oscillation whose frequency and amplitude varied depending on precise connection strength parameters. Ongoing activity depended on strong reciprocal connectivity within the MA2 population, which sustained low-level activity in the network during periods between the recurring phases of widespread network activation. Increasing the MA2-MA2 connection strength generally increased oscillatory frequency. Our results suggest that the MA2 neuronal population’s strong reciprocal connections would make this a critical population for controlling activation of the claustrum. This suggests this cell population as a possible entry point for claustrum activation which would provide the most rapid activation.

Bilateral claustro-cingulate connections in the origin of the corpus callosum

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The claustrum is a region of the pallial subplate highly interconnected with several cortical regions. It is present in all mammalian lineages, located deeply at the temporal boundary of the allocortex and isocortex. A remarkable feature of claustral circuits is their wide range of connections both within and between hemispheres. Interestingly, while interhemispheric connections course through both the corpus callosum and the anterior commissure in placental mammals, they only use the anterior commissure in monotremes and marsupials. Here I highlight the interhemispheric circuitry between the claustrum and cingulate cortices across mammals to understand the origin of the corpus callosum. I will argue that claustro-cingulate bilateral circuits arose in early mammals possibly related to multimodal integration, and that functional conservation of developmental circuits was critical for axon rerouting and the evolution of the corpus callosum in placental ancestors.
Synaptic organization of the neuronal circuits of the claustrum

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The claustrum is a poorly understood subcortical structure located bilaterally in mammals that forms widespread connections with almost all cortical areas. However, the cellular organization of claustral circuits remains largely unknown. Based primarily on anatomical data, it has been proposed that the claustrum plays a role in multimodal sensory integration. However, the extent to which the synaptic organization of claustral circuits supports integration from cortical areas is unclear. Here, we used whole-cell recordings of unitary synaptic connections and optogenetic activation of corticoclaustral axons to determine the cellular organization of the claustrum in the mouse. Recordings in mouse brain slices showed that unitary synaptic connections among claustrocortical neurons were rare. In contrast, we found that parvalbumin (PV) positive inhibitory interneurons were highly interconnected with both chemical and electrical synapses. In addition, we found that claustrocortical neurons and PV interneurons formed frequent chemical synaptic connections. Using optogenetic approaches, we found that corticoclaustral afferents formed monosynaptic connections onto both claustrocortical neurons and PV interneurons, consistent with data from anatomical studies. By comparing the cortical input to these two cell types, we found that cortical responses were comparatively stronger in PV interneurons relative to claustrocortical cells. Consistent with the overall circuit organization that we elucidated, activation of corticoclaustral afferents generated monosynaptic excitatory responses as well as disynaptic inhibitory responses in claustrocortical neurons. Taken together, these data indicate that recurrent excitatory circuits within the claustrum alone are unlikely to integrate across sensory modalities. Rather, the cellular organization of the claustrum is typical of circuits sensitive to correlated inputs. Although single claustrocortical neurons may integrate corticoclaustral input from different cortical regions, our results are consistent with more recent proposals implicating the claustrum in detecting sensory novelty or in amplifying correlated cortical inputs to coordinate the activity of functionally related cortical regions. More details of this work can be found in: Kim J, Matney CJ, Roth RH, Brown SP. Synaptic organization of the neuronal circuits of the claustrum. Journal of Neuroscience. 36:773–784.