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The Anatomy and Physiology of Claustrum-Cortex Interactions

Jesse Jackson,[1,*] Jared B. Smith,[2,*] and Albert K. Lee[3]

[1]Department of Physiology and Neuroscience and Mental Health Institute, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada; email: jackson4@ualberta.ca

[2]Molecular Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, California 92037, USA; email: jasmith@salk.edu

[3]Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, Virginia 20147, USA; email: leea@janelia.hhmi.org

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*These authors contributed equally to this article

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Abstract

The claustrum is one of the most widely connected regions of the forebrain, yet its function has remained obscure, largely due to the experimentally challenging nature of targeting this small, thin, and elongated brain area. However, recent advances in molecular techniques have enabled the anatomy and physiology of the claustrum to be studied with the spatiotemporal and cell type–specific precision required to eventually converge on what this area does. Here we review early anatomical and electrophysiological results from cats and primates, as well as recent work in the rodent, identifying the connectivity, cell types, and physiological circuit mechanisms underlying the communication between the claustrum and the cortex. The emerging picture is one in which the rodent claustrum is closely tied to frontal/limbic regions and plays a role in processes, such as attention, that are associated with these areas.

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INTRODUCTION

The claustrum (CLA) is an often-overlooked subcortical structure that extends along much of the anteroposterior extent of the forebrain in the form of a thin sheet of tortuous shape, lying just interior to the insular cortex and lateral to the putamen. First identified by the French anatomist Felix Vicq-d'Azyr in the eighteenth century (Parent 2012, Mathur 2014), the CLA remained an obscure, underappreciated brain structure until the publication of Francis Crick's final manuscript, which catapulted the CLA to prominence and began a scientific quest for a small but dedicated group of investigators. In their article entitled "What Is the Function of the Claustrum?," Crick & Koch (2005) argued that the CLA's role was to coordinate the multitudes of neocortical areas into coherence, giving "rise to integrated conscious percepts" (p. 1271).

Crick & Koch's idea was based on the existence of reciprocal connections between the CLA and much of the cortex. However, in the decade and a half since their academic call to arms, the precise function of the CLA has remained elusive. Hypotheses about the function of the CLA range from directing attention (Mathur 2014, Goll et al. 2015, Atlan et al. 2018, White & Mathur 2018, Smith et al. 2019) to various aspects of sensorimotor processing (Hadjikhani & Roland 1998, Edelstein & Denaro 2004, Smith & Alloway 2010, Smith et al. 2012, Smythies et al. 2012) and supporting consciousness itself (Crick & Koch 2005, Koubeissi et al. 2014, Stiefel et al. 2014, Smith et al. 2017). In support of the view that the CLA has a role in higher-order cognitive processes, anatomical evidence indicates that the CLA is only present in mammals and possibly not even present in all monotremes (Ashwell et al. 2004, Butler et al. 2012, Baizer et al. 2014, Suarez et al. 2018; but for evidence of an avian homolog, see Puelles et al. 2016, and for a reptile homolog, see Norimoto et al. 2020). Furthermore, the volume of the CLA has been shown to expand in concert with the neocortex (Kowiański et al. 1999), circumstantially reinforcing the view of its importance in supporting the functional processes thought to emanate from the cerebral cortex, including conscious perceptual experience (Crick & Koch 2005).

Why has the CLA's function remained so mysterious? Research into the CLA has largely been hampered by its convoluted shape, location, and close proximity to other brain structures, which makes it difficult to target, characterize, and manipulate. Studies using traditional methods have, as a consequence, often yielded uncertain results. However, owing to the advent of viral, genetic, and other molecular approaches in the last decade, researchers have made great strides in clearly elucidating the anatomical connectivity, genetic composition, ontological origins, and physiological activity of the CLA. In this article, we review these advances, which have (*a*) clarified a role for the CLA as a limbic-motor interface, positioned to integrate information from limbic

subcortical structures (including the thalamus, amygdala, and the hippocampus) and to communicate with the cortex, particularly frontal/prefrontal areas involved in executive functions, and (*b*) greatly increased our knowledge of CLA-related physiology, such as the finding that the CLA inhibits cortex, which could explain why CLA manipulations affect attention. In various places, we suggest future directions for experiments that may help uncover the functional relevance of this once-ignored brain structure.

ANATOMY AND CONNECTIVITY OF THE CLAUSTRUM: OVERVIEW

Since the early observations of the gross anatomical features of the CLA, a great deal of work has been done to precisely define the genetic, neurochemical, and cytoarchitectural makeup of the CLA across species (recently reviewed by Smith et al. 2018). The CLA in humans, primates, and other larger species is well delineated, owing to its complete encasement in the white matter of the external and extreme capsules. However, in many smaller mammals (particularly rodents), which lack extensive white matter development, the CLA is difficult to identify, appearing seamlessly integrated with the deep layers of insula cortex (Mathur et al. 2009). Homologies in neurochemical and genetic markers for the CLA between primates and rodents have now been identified to more concretely define its anteroposterior (Dillingham et al. 2019), mediolateral, and dorsoventral extents (Smith et al. 2018), which were found to include the misnamed dorsal endopiriform nucleus in rodents. These basic anatomical studies have likewise been critical for identifying/establishing transgenic mouse lines for targeting the CLA (Wang et al. 2017, Atlan et al. 2018).

The anatomical connectivity of the CLA has been its most well-studied aspect (reviewed by Edelstein & Denaro 2004, Mathur 2014, Goll et al. 2015, Smith et al. 2018) and our knowledge of it has greatly benefited from the recent advent of new viral tracing technologies and transgenic mice (Atlan et al. 2017, 2018; Wang et al. 2017; Zingg et al. 2018) as well as noninvasive imaging methodologies such as diffusion tensor imaging for mapping CLA connections in humans (Fernandez-Miranda et al. 2008, Milardi et al. 2013, Torgerson et al. 2015). The CLA is most noted for its extensive connectivity with the neocortex, as shown in **Figure 1*a***. The traditional view of claustral connectivity with the cortex depicts these connections as being reciprocal and topographically organized into modality-specific CLA regions, with a uniform connection strength across each modality. However, results from the last decade of neuroanatomical tracing in rodents have significantly shifted this view. As illustrated in **Figure 1*b***, quantitative anatomical studies have shown that the bulk of the corticoclaustral inputs originate from areas of the frontal cortex, including orbitofrontal, prelimbic, cingulate, and secondary motor cortices, whereas regions of sensory cortex (somatosensory, auditory, visual, etc.) provide little or no inputs to the CLA (Smith & Alloway 2010, 2014; Smith et al. 2012; Wang et al. 2017; Zingg et al. 2018). The same seems to be true of claustrocortical projections, with the bulk of the CLA output targeting frontal cortex, especially areas of the medial prefrontal cortex (mPFC), including the secondary motor cortex, cingulate, and prelimbic cortices (Smith & Alloway 2010, 2014; Zingg et al. 2014, White et al. 2017). It should be noted that there may be differences in this overall picture across species (described below; e.g., the visual cortex has a strong input to the CLA in cats).

Beyond its connectivity with the cortex, the CLA is now known to receive inputs from a number of subcortical limbic structures as well, particularly the mediodorsal (MD) thalamus, basolateral amygdala (BLA), and hippocampus (**Figure 1*b***). Connections with the hippocampus appear to be unidirectional, with CLA neurons receiving input from the ventral hippocampus (Zingg et al. 2018), whereas outputs of the CLA target the parasubiculum but not CA1 (Atlan et al. 2018, Jackson et al. 2018). The connectivity pattern with the thalamus appears to be unidirectional as well, with the MD thalamus sending projections to the CLA, but the surrounding insular cortex,

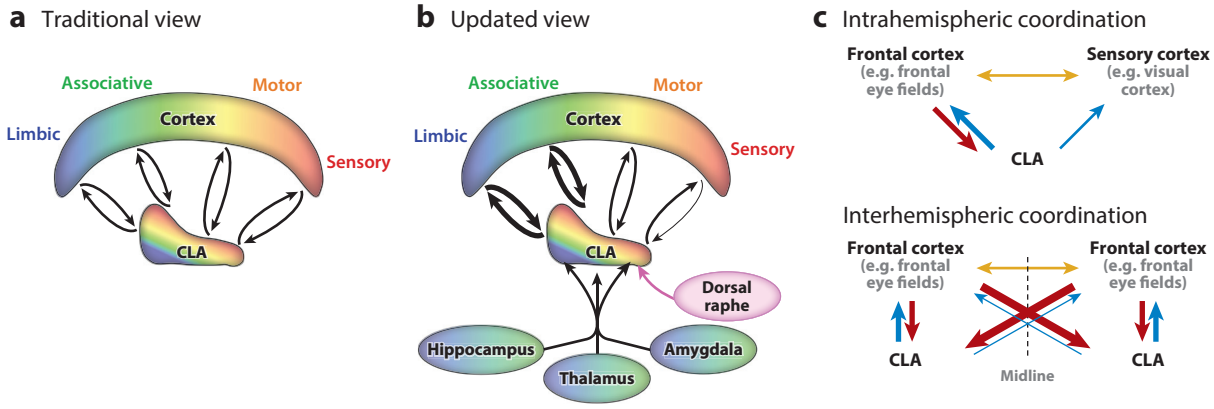

Figure 1

Circuit diagrams summarizing main theories of anatomical connectivity of the claustrum (CLA). (*a*) Early theories of CLA connectivity suggested equal, topographically segregated, reciprocal connectivity with the entire cerebral cortex. Colors illustrate corresponding regions of cortex and CLA. Note that the CLA is drawn such that top-bottom approximately corresponds to the dorsoventral axis and left-right to the rostrocaudal axis. (*b*) Results from the last decade of neuroanatomical tracing studies of the CLA in the rodent indicate a more complex connectome. Whereas the CLA does seem to have a topographically organized projection to the entire cortical mantle, the bulk of these projections target frontal cortices. Importantly, the primary input to the CLA originates from limbic, associative, and motor areas of frontal cortex, with fewer inputs from sensory regions in parietal, temporal, or occipital cortex. Additionally, subcortical regions, including the thalamus, basolateral amygdala, and hippocampus, provide one-way inputs to CLA, as well as dense neuromodulatory innervation by serotonergic neurons of the dorsal raphe nucleus. These results may differ across species. (*c*) The CLA has been shown to support modality-related corticocortical connectivity. Top panel illustrates intrahemispheric connections, where inputs from the frontal eye field (FEF) innervate CLA neurons that project to both FEF and visual cortex, supporting the direct connections between these cortical areas. Similarly, the bottom panel depicts interhemispheric CLA circuits that support callosal communication between homotopic, frontal cortical areas in each hemisphere. Corticoclaustral (*red*), claustrocortical (*blue*), and corticocortical (*yellow*) connections are shown.

rather than the CLA, providing inputs to the thalamus (Mathur et al. 2009; Smith et al. 2017, 2019). Lastly, the connections between the BLA and CLA appear to be reciprocal, though the feedback from CLA to BLA is much weaker (Majak et al. 2002, Atlan et al. 2018, Zingg et al. 2018, Smith et al. 2019). Interestingly, projections from BLA to CLA are bilateral, whereby axons from the BLA bifurcate, sending one collateral to the ipsilateral CLA, while the other branch traverses the anterior commissure to target the CLA in the contralateral hemisphere (Smith et al. 2019). Together, the verification of these subcortical limbic inputs to the CLA and its predominant output to frontal cortex suggests a role for the CLA as a limbic-motor interface, allowing information about emotional valence and spatial navigation to direct action.

Another principle of CLA anatomy has emerged, indicating a motif in which the CLA complements corticocortical communication. This view suggests that any two cortical areas that share direct corticocortical connections will be supplemented by projections from the same CLA subregion, including a small percentage of CLA neurons that collateralize to innervate both cortical areas (Pearson et al. 1982, Minciacchi et al. 1985, Smith et al. 2012, Smith & Alloway 2014). As demonstrated in the top panel of **Figure 1*c***, this organizational theme has been anatomically demonstrated for modality-related regions of sensory and motor cortex [e.g., visual cortex and frontal eye field (FEF)] within the same hemisphere. In this example, the visuomotor region of CLA receives inputs from FEF and in turn innervates both FEF and visual cortex. This circuit organization could be ideal for top-down control of the CLA to subsequently coordinate activity in FEF and visual cortex (e.g., by synchronizing them) to enhance visual processing during target-directed visual search (i.e., visual attention). In addition to this intrahemispheric

circuitry, the CLA is also involved in unique interhemispheric connectivity between regions of frontal cortex (e.g., FEF) that share direct corticocortical connections via the corpus callosum. As diagrammed in the bottom panel of **Figure 1*c***, FEF sends bilateral projections to the CLA (though stronger to the contralateral CLA), which in turn sends bilateral projections back to FEF (though favoring the ipsilateral hemisphere) (Smith & Alloway 2010, 2014). Together, these two circuit motifs suggest that the CLA is specifically connected to facilitate long-range corticocortical communication, both within and across hemispheres.

Although less well characterized than the connectivity with the cortex, the CLA has extensive intrinsic connections across its anteroposterior axis. These connections, first proposed by Crick & Koch (2005), have been subsequently confirmed by anatomical tracing, indicating an all-to-all pattern whereby (*a*) central regions of the CLA project both rostrally and caudally, (*b*) anterior regions of CLA project to the most posterior extent of the structure, and (*c*) neurons in the posterior part of the CLA project all the way to the anterior limit of the CLA (Behan & Haberly 1999, Smith & Alloway 2010, Watson et al. 2017). Though there appears to be extensive connectivity in the rostrocaudal dimension, there do not appear to be any dorsoventral interconnections, indicating the modality-related topographical regions of the CLA (which are arranged more dorsoventrally) are segregated into distinct processing streams (Smith et al. 2018). These longitudinal connections could facilitate long-range synchronization of activity within each modality in the CLA, in support of the coordinating/synchronizing effect that the CLA may provide to modality-related regions of cortex, as discussed above.

In support of these neuroanatomical tracing results, resting-state functional MRI (rsfMRI) measurements of brain-wide correlations in the BOLD signal have been used to study the CLA (Smith et al. 2017, 2019; Krimmel et al. 2019a,b), functionally confirming the connections above and revealing the CLA's involvement in the rodent homolog of the salience network, a network that includes limbic brain areas and processes the emotional relevance of stimuli (Sforazzini et al. 2014, Gozzi & Schwarz 2016). The salience network (**Figure 2*a***) is traditionally viewed as strong functional connectivity between the cingulate and insular cortex as well as other subcortical structures, including MD thalamus (Seeley et al. 2007, Menon 2011). However, disambiguating the insula from CLA in rsfMRI is extremely challenging. To address this issue, we recently employed higher-strength magnetic fields in awake rats in conjunction with conventional neuroanatomical tracing (Smith et al. 2019) (**Figure 2**). We first compared seed region analyses of the CLA and insula. The CLA showed robust resting-state correlations with areas of mPFC and MD thalamus, whereas the insula seed showed extremely weak functional connectivity with these regions. Subsequent analysis of a seed region in the mPFC showed strong functional connections with both CLA and MD thalamus. Likewise, analyses of an MD thalamus seed found strong correlations with mPFC and CLA. These functional connections were independently confirmed using conventional neuroanatomical tracing, as shown in **Figure 2*c***. Together, these data reveal a core network involving the CLA that appears to represent the rodent homolog of the salience network. Interestingly, these functional connections, as measured by rsfMRI, were lost following isoflurane-induced loss of consciousness (Smith et al. 2017, 2019), providing support, albeit insufficient, for the role of the CLA in supporting a conscious, vigilant state.

One final anatomical finding of note is the role of neuromodulatory inputs to the CLA. The strongest evidence for neuromodulation of the CLA points to serotonin and endogenous opioids. In the case of opioids, it is specifically the kappa opioid receptor that is richly expressed in the CLA (Mansour et al. 1994), and evidence suggests these opioid receptors may play a role in the hallucinatory aspects of some drugs, such as *Salvia divinorum* (Stiefel et al. 2014). Similarly, serotonergic innervation of the CLA is extremely dense (Baizer 2001, Sitte et al. 2017), with an abundant expression of the 5-HT2a receptor, which has demonstrated extraordinary binding in the CLA for

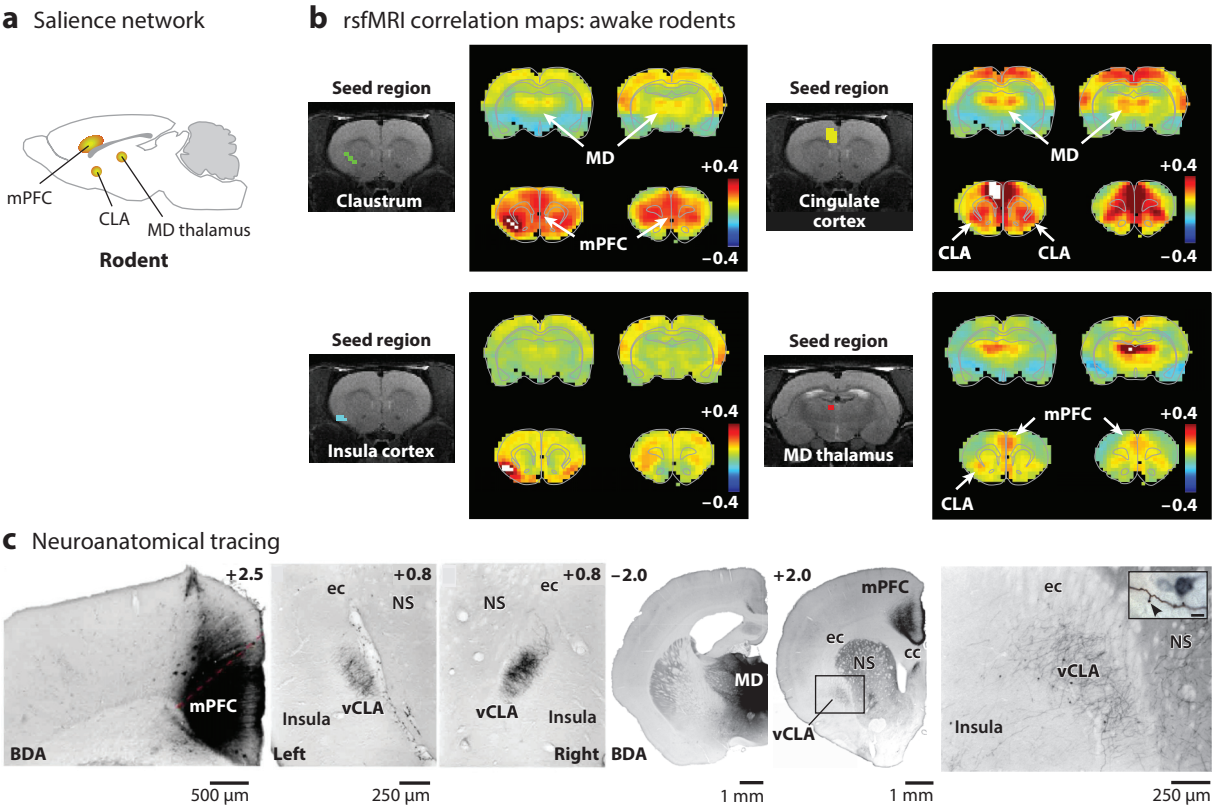

Figure 2

Resting-state functional MRI (rsfMRI) studies of the claustrum (CLA) indicate its role in the salience network. (*a*) Diagram of the rodent homolog of the salience network, including nodes in the medial prefrontal cortex (mPFC) [specifically cingulate (Cg) cortex], mediodorsal (MD) thalamus, and CLA. (*b*) rsfMRI in awake, head-fixed rats with seed regions in CLA, insula cortex, Cg cortex, and MD thalamus. These data demonstrate the strong functional connections between mPFC, MD thalamus, and CLA, but importantly not insula cortex. (*c*) Conventional neuroanatomical tracing with biotinylated dextran amine (BDA) reveals the structural connectivity supporting the functional connections shown in the rsfMRI. The left three panels show an injection into the mPFC (Cg cortex), with dense bilateral labeling in CLA. The right three panels show an injection into the MD thalamus, revealing projections to mPFC (Cg cortex) and CLA. Inset reveals morphology of thalamoclaustral synaptic bouton. Figure adapted from Smith et al. (2019) under the Creative Commons Attribution (CC BY 4.0) International license.

another hallucinatory drug, lysergic acid (Yagaloff & Hartig 1985). The role of neuromodulators on the CLA will no doubt be critical for understanding its function, and the prominent roles of opioids and serotonin support views of the involvement of the CLA in mechanisms of salience and novelty (Remedios et al. 2014, Kitanishi & Matsuo 2017, Smith et al. 2019).

PHYSIOLOGY OF THE CLAUSTRUM

Although knowledge of CLA anatomy is quite extensive, very few studies have explored its physiology. Only recently have the first in vitro studies been conducted, identifying the intrinsic properties of different CLA neuron subtypes (Shibuya & Yamamoto 1998, Kim et al. 2016, Chia et al. 2017, White & Mathur 2018, White et al. 2018). Across all of the recent slice recording studies, spike-frequency adaptation has emerged as a hallmark neurophysiological feature of CLA

excitatory neurons. CLA neurons exhibit either rapidly adapting or mildly adapting firing rate phenotypes in response to both current injection and optogenetic activation of excitatory synaptic inputs. In addition, these different CLA subtypes appear to be differentially distributed across the rostrocaudal axis and project to dissociable neocortical targets (Chia et al. 2017, White & Mathur 2018, White et al. 2018). Future work using molecular approaches to identify the different subtypes of CLA projection neurons (and interneurons) and using retrograde tracing from the various downstream regions that CLA neurons project to will be invaluable for identifying the extent of heterogeneity in the cells composing the CLA.

Most physiological studies of CLA neural firing in vivo have been performed using extracellular recordings in cats and primates, primarily evaluating responses to sensory stimuli. A common theme appears to be that the modality-specific subregions of CLA respond to stimuli of that modality, but with less specificity than the corresponding cortical areas. Early work in cats established the presence of visual and somatosensory maps in the CLA of cats (Olson & Graybiel 1980; LeVay & Sherk 1981a,b,c,d; Sherk & LeVay 1983), indicating both retinotopic and somatopic maps in their respective spatial domains within the CLA. In the case of visual responses, CLA neurons were found to have unique response properties compared to visual cortex. For instance, while CLA neurons do exhibit orientation tuning, they display a preference for long stimuli (LeVay & Sherk 1981c). Subsequent studies found that the only consequence of ablating the CLA was a reduction in the number of end-stopped cells (hypercomplex cells) in the ipsilateral primary visual cortex (V1). This was suggested to result from the loss of CLA cells that respond to long stimuli, which, according to this hypothesis, would normally provide surround inhibition for end-stopped cells (Sherk & LeVay 1983).

In primates, auditory and visual responses have been measured in distinct central and ventral regions of the CLA, respectively (Remedios et al. 2010). This dorsoventral response mapping aligns with anatomical inputs from auditory and visual cortices (Pearson et al. 1982). Auditory responses in the CLA were found to have similar magnitudes across different categories of sounds (environmental sounds, vocalizations, etc.). Sensory responses in CLA neurons showed rapid bursting at greater than 30 Hz within ~60 ms of the presentation of a stimulus, with this activity arising from a quiescent prestimulus baseline then quickly dropping (Remedios et al. 2014). Combined with the anatomical identification of reciprocal loops between the CLA and cortex, these physiological results suggest a fast mechanism for feedback to the relevant neocortical area providing the sensory information. Based on the feedforward inhibition that the CLA provides to cortex (discussed below), sensory responses in CLA may help focus attention, not by enhancing the signal but by reducing the noise in the sensory cortex that originally provides the sensory information to the CLA.

With respect to the motor system, primate CLA activity related to basic arm movements has been reported (Shima et al. 1996). In support of the topographic organization of the CLA discussed above, these responses were obtained from the most dorsal aspect of the CLA, which is known to connect to somatosensory and motor cortex (Pearson et al. 1982). Unlike motor cortical neurons, which often responded selectively to one type of arm movement (push, pull, or turn), most CLA neurons responded to multiple arm movements, though not to other movements. CLA movement-related activity preceded the onset of the movement, similar to motor cortex, indicating that motor cortex is the likely driver of this motor-related activity in CLA. These early findings suggest that the CLA receives motor planning information from frontal motor cortex, which could in turn prime regions of sensory cortex, decreasing background noise in these areas to sharpen attention for expected sensory events based on the planned motor action. For example, the FEF may provide motor planning information about an upcoming saccade, which is in turn used by the CLA to prime activity in visual cortex to focus attention toward the expected visual

target. This motif suggests a pathway for CLA-mediated, top-down control of neural activity in posterior (sensory) cortical regions, in addition to the direct corticocortical connection between FEF and visual cortex.

Beyond sensory and motor processing, recordings from the anterior regions of the CLA in rats also demonstrated place cell firing in a small population (3%) of neurons (Jankowski & O'Mara 2015). Such higher-order processing in the CLA could originate from ventral hippocampus or cortical inputs related to hippocampal output such as entorhinal or retrosplenial cortex. Considering the full anatomical connectivity of the CLA (**Figure 1*b***), it is possible that the CLA is engaged in numerous higher-order processes, from spatial navigation to cognition and beyond.

INTRACLAUSTRAL CONNECTIVITY: INTEGRATION OR SEGREGATION?

The postulated communication between excitatory CLA neurons was an integral part of Crick & Koch's (2005) hypothesis relating the CLA to consciousness. Under the original CLA-consciousness framework, communication between different CLA nodes could serve to integrate inputs from multiple sensory and motor cortical areas, then relay an integrated, cohesive signal back to the neocortex regarding context. Potential mechanisms for this excitatory communication between CLA subregions included direct excitatory connections between glutamatergic projection neurons, gap junction coupling, dendrodendritic communication, and synchronization through inhibitory interneurons.

Experimentally, there is mixed evidence for communication between excitatory cells within the CLA. One recent study used patch clamp recordings and showed that only ~2% of CLA projection neurons were connected (Kim et al. 2016). This is a lower connection probability than reported during similar experiments in the cortex, which ranged from ~5% to 25% (Holmgren et al. 2003, Brown & Hestrin 2009, Ko et al. 2013). However, when brain slices were made in the horizontal plane (better preserving rostrocaudal CLA connections), spontaneous synchronized activity was observed across large spatial distances within CLA subnetworks (Orman et al. 2015). Therefore, the slice orientation may be an important factor when determining connectivity rates between cells in the CLA in vitro. Additionally, more recent tracing studies have indicated that the longitudinal connections are specific, with segregated channels that extend rostrocaudally and correspond to the dorsoventrally ordered, modality-based topography of the CLA (Smith & Alloway 2010, Watson et al. 2017, Smith et al. 2018). Future work investigating intraclaustral communication should take this anatomical finding into account and directly test the hypothesis that the connection rate between excitatory neurons varies as a function of the dorsoventral, mediolateral, and anteroposterior axes of the CLA.

In addition to coupling between excitatory CLA neurons, there is ample evidence that interneurons in the CLA can provide synchronous inhibition to large populations of excitatory CLA neurons. Fast-spiking parvalbumin (PV) interneurons connect to excitatory cells with a high connection probability of ~29%, and inputs from the cortex activate these interneurons, leading to inhibitory postsynaptic potentials in CLA excitatory cells (Kim et al. 2016). Given these robust inhibitory connections, CLA excitatory neurons could be synchronized through local inhibitory inputs and the common recovery from inhibition. Within other neural networks such as CA1 of the hippocampus, local connectivity rates between excitatory cells are very low (Deuchars & Thomson 1996), yet these neurons undergo synchronized firing, in part due to local inhibitory synchronization (Stark et al. 2014). To date, the study of interneuron physiology in the CLA has been centered primarily on fast-spiking PV cells, although other interneurons containing somatostatin and neuropeptide Y (NPY) are also present within the CLA (Eiden et al. 1990, Guirado et al. 2003, Baizer et al. 2014). The local connectivity profile and function of these other interneurons

await discovery. Future studies using single-cell tracing (Wang et al. 2019, Winnubst et al. 2019) should map the extents of axonal projections for both CLA projection neurons and CLA interneurons, as it is possible that CLA interneurons have widespread axons and participate in intraclaustral synchrony.

CLAUSTROCORTICAL OUTPUTS: INHIBITION OF CORTEX

The cellular and synaptic mechanisms by which CLA neurons communicate with the cortex have been studied since at least the 1980s. Electron microscopy work showed that CLA axons primarily innervate dendritic spines of excitatory neurons across all layers of cortex but with the greatest density in layers II/III and VI (LeVay & Sherk 1981a,b,c,d; LeVay 1986; da Costa et al. 2010). Inputs to smooth dendrites (presumed to be inhibitory neurons) were also noted in these studies.

Early work with electrical stimulation in cats found that activation of the CLA causes powerful modulation of neuronal firing throughout the prefrontal, motor, and visual cortices (Ptito & Lassonde 1981; Tsumoto & Suda 1982; Salerno et al. 1984, 1989; Crescimanno et al. 1989, 1990; Cortimiglia et al. 1991). CLA stimulation generates one of two response profiles: (*a*) activation followed by suppression or (*b*) long-lasting suppression (Ptito & Lassonde 1981, Salerno et al. 1989, Cortimiglia et al. 1991). In vivo intracellular recordings from putative excitatory cells in the visual cortex showed prominent inhibitory postsynaptic potentials following CLA activation and inhibition of spiking occurring at longer latencies than excitation, implying the recruitment of feedforward or feedback inhibition in the cortex following CLA activation (Tsumoto & Suda 1982). The aforementioned works all discussed the possibility that inhibitory interneurons were directly activated by the CLA. However, at the time, very little was known about interneuron physiology and function in the cortex.

Following the rationale of these earlier physiological studies, we were interested in determining the neural circuitry underlying claustrocortical communication. The advent of new molecular tools has enabled the manipulation of specific pathways in the brain, without the known caveats of electrical stimulation. Employing a dual virus approach, we specifically activated the population of CLA neurons projecting to the mPFC. This involved using a Cre-dependent channelrhodopsin-2 (ChR2) (Boyden et al. 2005) virus in conjunction with a highly efficient retrograde AAV expressing Cre (Tervo et al. 2016). This technique reduces the probability of off-target activation of neighboring brain regions, while enabling direct control of CLA neural activity. We found that brief optogenetic activation of these CLA neurons was sufficient to silence neural firing in the mPFC (Jackson et al. 2018). Electrophysiological recordings both in vivo and in vitro showed that activation of the CLA depolarized interneurons more strongly than excitatory PFC cells (**Figure 3**). As PV interneurons have been extensively implicated in feedforward inhibition (Delevich et al. 2015), we initially predicted that CLA-mediated cortical inhibition arose from PV cells. Although PV interneurons were activated by the CLA, their chemogenetic suppression (reviewed in Sternson & Roth 2014) did not completely block the CLA-mediated cortical inhibition. However, the suppression of NPY interneurons did prevent feedforward inhibition. These data suggest that both PV and NPY cells sense CLA inputs and that NPY cells may be an especially critical cell type controlling how the CLA influences cortical networks. Two other recent studies have also provided evidence for claustrocortical feedforward inhibition in CLA projections to the auditory cortex (Atlan et al. 2018) and orbitofrontal cortex (Narikiyo et al. 2018), suggesting that this circuit mechanism may generalize across different claustrocortical pathways. Corroborating these physiological findings, rabies tracing has shown that the CLA provides projections to several classes of PFC interneurons, including PV, somatostatin, and vasoactive intestinal polypeptide cells (Ährlund-Richter et al. 2019).

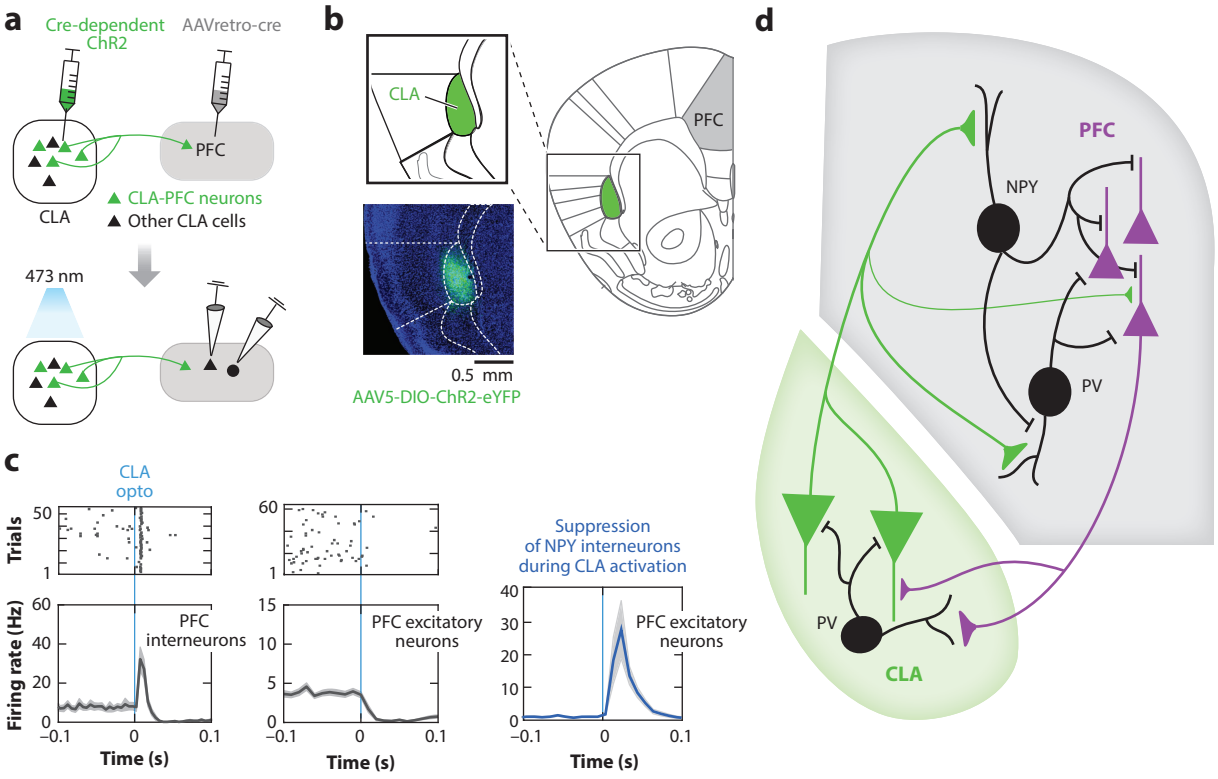

Figure 3

Claustrum (CLA) input to cortex primarily drives interneurons, thereby suppressing pyramidal neurons. (*a*) Strategy to optogenetically control CLA neurons projecting to prefrontal cortex (PFC) using AAVretro-Cre virus. (*b*) Histological verification of channelrhodopsin-2 (ChR2) expression in CLA. (*c*) In vivo electrophysiological recordings from putative interneurons (*left*) and pyramidal neurons (*center*) in PFC with optogenetic activation of the CLA (*blue bar*). Data revealed that CLA activation strongly drives interneurons, causing a prolonged inhibition of cortical pyramidal cells (for ~150 ms), which was often followed by rebound excitation. Suppression of NPY interneurons (*right*) prevents the CLA-mediated feedforward inhibition and unmasks the excitatory input from CLA neurons onto PFC pyramidal neurons. (*d*) Circuit diagram summarizing the findings from two recent papers indicating that both corticoclaustral and claustrocortical projections involve feedforward inhibition (Kim et al. 2016, Jackson et al. 2018). Panels *a–c* adapted from Jackson et al. (2018) under the Creative Commons Attribution (CC BY 4.0) International license.

These results have important implications for how CLA neurons communicate with the cortex. Feedforward inhibition is an efficient way to limit excess firing in neural networks and to synchronize spike timing (Pouille & Scanziani 2001, Higley & Contreras 2006). Many (if not all) long-range excitatory pathways into the PFC generate feedforward inhibition. The excitatory inputs from the BLA, MD thalamus, and hippocampus all activate PV cells in the PFC (Dilgen et al. 2013, Delevich et al. 2015, McGarry & Carter 2016, Marek et al. 2018). However, these inputs generally first drive transient excitation, not the blanket network suppression observed with the stimulation of CLA (with the exception of the BLA, which has been shown to exert both inhibition and excitation of the PFC) (Floresco & Tse 2007, Dilgen et al. 2013). Therefore, the CLA may perform a unique gating role among PFC inputs, functioning to balance stronger excitatory inputs from these other regions. Collectively, the findings that CLA axons bifurcate across layers and cortical regions (Wang et al. 2019) and provide activation of interneurons suggest that the CLA is in a position to control spike timing and interareal brain communication.

CORTICOCLAUSTRAL INPUTS

The recent comprehensive tracing of mouse corticoclaustral projections has highlighted that most cortical areas do provide some degree of input to the CLA but that these projections arise preferentially from the frontal midline cortex (including secondary motor, anterior cingulate, and prelimbic cortices), the insular cortex, and the temporal cortex (including the entorhinal, ectorhinal, and perirhinal regions) (Oh et al. 2014, Atlan et al. 2017, Wang et al. 2017, Zingg et al. 2018).

It should be noted that corticoclaustral inputs appear to vary considerably between the rodent, cat, and primate brain. This difference is perhaps most obvious when comparing projections from V1 to the CLA in the cat, primate, and rodent. In the cat, dense inputs from V1 to CLA are present (LeVay & Sherk 1981a), whereas in the rodent and primate, these inputs are weak (Sherk 1986, Smith & Alloway 2014). Functionally, CLA neurons in the primate and cat respond robustly to visual information and exhibit orientation tuning (Remedios et al. 2010). In the mouse, the activation of V1 inputs, using ChR2 circuit mapping, only weakly depolarizes a subset of CLA neurons (White et al. 2018). These physiological data nicely align with anterograde mapping showing that visual inputs to the CLA are relatively weak in the rodent (Smith & Alloway 2014, Wang et al. 2017). These data are suggestive of species-specific organizational principles, at least at the level of CLA inputs, and may relate to species differences in the relative importance of vision in primates and cats versus rodents.

In the mouse, cortical inputs to the CLA arise predominantly from layers II–V in frontal cortex and layer VI in sensory cortex (for a review, see Smith et al. 2018). Sensory-related corticoclaustral neurons compose a subtype of layer VI neuron separate from corticothalamic projection cells (LeVay & Sherk 1981a). In the frontal cortex, corticoclaustral cells were found to arise from both layer II/III corticocortical cells and layer V intratelencephalic neurons, but not from layer V pyramidal tract neurons (Smith et al. 2016). Functionally, this suggests that the CLA receives information more related to motor planning instead of actual motor output (Shepherd 2013). A curious feature of inputs to the CLA is that dense inputs arise from the premotor region of the contralateral hemisphere (Smith & Alloway 2010, 2014; Zingg et al. 2018), suggesting a strong functional importance. As mentioned above, in addition to the cortex, several subcortical brain regions, including the BLA, ventral hippocampus, and MD thalamus, all provide an input to CLA neurons (Smith et al. 2017, 2019; Atlan et al. 2018; Narikiyo et al. 2018; Zingg et al. 2018). Based on these inputs, the CLA, as described above, appears most intimately linked with the limbic system—neural circuits responsible for emotional processing, memory, and attention.

POSSIBLE FUNCTIONS OF THE CLAUSTRUM

Identifying the cognitive and behavioral function of the CLA is a major goal of ongoing research efforts, as the exact function of the CLA is still unknown. The list of proposed functions of the CLA is long; therefore, we focus here on experimental studies where CLA activity has been explicitly measured or manipulated. For the most part, early CLA work was performed on cats and primates. These studies, as previously discussed, found evidence that CLA neurons respond to sensory stimuli (visual, auditory, somatosensory) and produced data showing neural activity preceding arm movements. Importantly, these responses were observed in distinct dorsoventral regions, matching the topography of corticoclaustral inputs. As highlighted above, the anatomical connectivity of the CLA differs between species, suggesting differences in function. Moving forward, the wider range of available techniques likely means the rodent will provide key mechanistic insights into the details of CLA function. The first wave of these rodent studies employing molecular techniques found a role for the CLA in regulating attention to sensory stimuli, particularly during situations of high cognitive load, apparently facilitating attention by suppressing

distractions. Evidence from rsfMRI indicates that the cingulate cortex and CLA constitute the core of the rodent homolog of the salience network, which is aligned with the view that the CLA facilitates attention toward behaviorally relevant sensory events.

One leading hypothesis of CLA function posits a role in attention. Supporting this hypothesis, a recent behavioral study interfered with anterior cingulate inputs to the CLA during an attention task (White et al. 2018). The authors used a five-choice serial reaction time task, which required the mouse to detect the presence of a visual cue on one of five ports, then, following a delay, select the cued port to receive a reward. This task required attentional mechanisms to detect the location of the sensory stimulus and form the corresponding motor plan to approach the correct location. Optogenetic perturbation (both excitation and inhibition) of the anterior cingulate inputs in the CLA impaired the accuracy of mice performing this task. Importantly, when the task was made simpler by using only a single port, no effect of CLA input perturbation was detected. Using a similar task that required maintaining visual attention, Atlan et al. (2018) showed that suppressing a subset of CLA neurons (genetically identified and suppressed with potassium channel overexpression or chemogenetic means) also led to a deficit in task performance, but only in the presence of an auditory distractor. Together, these studies suggest that top-down inputs to the CLA provide a signal that activates the CLA to ensure sustained attention to the task at hand, specifically via suppressing activation of the cortex by irrelevant sensory cues (Atlan et al. 2018). Common to both of these studies was the general finding that CLA suppression caused impairments specifically during more cognitively challenging versions of the same task, suggesting that the importance of the CLA scales with cognitive load.

Another leading hypothesis outlines a role for the CLA in sleep-dependent brain activity. For instance, a parallel set of experiments proposed that the CLA may be preferentially active during sleep (Hong et al. 2009, Renouard et al. 2015, Narikiyo et al. 2018). Functional imaging in humans (Hong et al. 2009) and immediate early gene labeling in rodents (Renouard et al. 2015) have described an upregulation of CLA activity during rapid eye movement (REM) sleep. A recent report performed electrical recordings from optogenetically tagged CLA neurons and demonstrated increased CLA activity during slow-wave sleep relative to wake (Narikiyo et al. 2018), although the data for REM activity was not reported. Sleep contributes to consolidating memories (Marshall et al. 2006; reviewed in Diekelmann & Born 2010), and some evidence of a role for the CLA in memory consolidation is provided by recent work employing a fear-memory retrieval paradigm. Mice undergoing manipulation of CLA networks during the encoding of fearful experiences exhibited less context-dependent freezing behavior the day following the experience, suggesting impairment of some aspect of the consolidation or retrieval process (Kitanishi & Matsuo 2017). Interestingly, the CLA is densely connected with the amygdala, prefrontal cortex, and medial entorhinal cortex—three structures important for the systems-level consolidation of episodic memory (Kitamura et al. 2017). Neurons active during the encoding of episodic memory are replayed during sleep (Wilson & McNaughton 1994, Louie & Wilson 2001, Lee & Wilson 2002, Ji & Wilson 2007), a process that could support systems-level consolidation. Indeed, CLA neurons are active (as measured by c-fos) following the encoding of novel spatial environments (Kitanishi & Matsuo 2017), and an earlier c-fos approach showed elevated CLA activity during both wake and sleep (Pompeiano et al. 1994). Recently, a CLA homolog was described in reptiles and found to be critically involved in the production of sharp-wave ripples during slow-wave sleep (Norimoto et al. 2020), and these ripples represent a prime candidate mechanism for replay-based consolidation in mammals. Future work should monitor (using electrophysiology or calcium imaging) identified CLA neurons during the encoding and consolidation of episodic memories as well as manipulate the CLA neurons during candidate periods for consolidation.

CONCLUSIONS

Overall, the recent anatomical data show that the CLA communicates most densely with medial regions of frontal cortex (e.g., cingulate cortex) and ventrolateral areas of the temporal lobe (e.g., entorhinal cortex), while receiving prominent inputs from brain regions processing limbic information such as the amygdala, hippocampus, and MD thalamus. These anatomical findings indicate that the function of the CLA will most likely reside under the umbrella of limbic-related functions such as attention, memory, valence processing, anxiety, and vigilance, subsequently directing such limbic information to multiple regions of the cortex to modify perception and actions. Notably, the CLA appears to exert feedforward inhibitory control over the cortex to achieve these functions. However, the precise ways in which such inhibition participates in shaping task-related neural activity remains an open question. With new molecular techniques to specifically control and measure different CLA neuron subtypes, the next decade of research should converge on answers to how neural activity in the CLA participates in guiding behavior.

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