

Attention: the claustrum

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The claustrum is a mysterious thin sheet of neurons lying between the insular cortex and the striatum. It is reciprocally connected with almost all cortical areas, including motor, somatosensory, visual, auditory, limbic, associative, and prefrontal cortices. In addition, it receives neuromodulatory input from subcortical structures. A decade ago, Sir Francis Crick and Christof Koch published an influential review proposing the claustrum as the ‘seat of consciousness’, spurring a revival of interest in the claustrum. We review the literature on the claustrum, emphasizing recent discoveries, and develop a detailed hypothesis describing a role for the claustrum in the segregation of attention.

Paying attention to the claustrum

The world constantly overwhelms our senses with information. Selective attention enables us to navigate this abundance by selecting the most relevant information at each moment in time. William James, in *The Principles of Psychology*, defined attention as ‘taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought...It implies withdrawal from some things in order to deal effectively with others’ [1]. This definition captures a key property of attention: enhanced processing of task-relevant information, while suppressing task-irrelevant information.

The aptly named claustrum (Latin: *claustrum*; ‘cloister’, closed place) is a fine sheet of neurons lying between the insular cortex and the striatum. Due to its delicate anatomy and enclosed location within the brain, the claustrum has been largely inaccessible to detailed functional and electrophysiological investigation and its function remains largely unknown. This year marks the decennial anniversary of the influential review by Crick and Koch [2], which proposed a function for the claustrum in binding information to create the conscious experience and reignited the passion for investigating the function of the claustrum. Here we review knowledge regarding the anatomy and physiology of the claustrum and integrate it into a detailed model ascribing a role to this structure in attention. We propose that the claustrum, due to the nature of its connectivity with the sensory modalities and its robust prefrontal and neuromodulatory input, functions to enhance the differentiation between task-relevant and task-irrelevant information,

enabling the organism to ignore irrelevant information and proceed with goal-oriented behavior.

Principles of claustrum connectivity

The vast connectivity and the unique architecture of the claustrum suggest that it could provide strong ‘gain control’ over cortical output and may be amenable to modulation by prefrontal and subcortical inputs.

The claustrum has the highest connectivity in the brain per regional volume [3], displaying extensive reciprocal connections with the visual, auditory, somatosensory, and motor cortical regions as well as allocortical and subcortical regions (Figure 1) [4–17]. The inputs to the claustrum display anterior–posterior and dorsal–ventral organization, with reciprocal connectivity back to the cortex from within the same region in the claustrum [8–10,12,18–28] (Figure 1). The broad and unique cortical connections of the claustrum suggest it might serve as a central network hub, coordinating activity of the cortical circuitry (Box 1) [29].

Several allocortical regions receive inputs from the claustrum, including the piriform cortex, subiculum, and entorhinal cortex, as well as the ventral zones of the prefrontal cortex [30,31]. Thus, the claustrum is strongly tied to areas processing sensory information as well as regions processing information regarding the location of the organism and its physical and emotional state.

The sensory claustrum

The sensory input to the claustrum is largely segregated by modalities. Furthermore, the claustrum displays a significant preference for peripheral sensory information. In this section we review the literature regarding the interaction of the claustrum with the cortical representation of sensory information, which provides support for a role of the claustrum in segregating attention between modalities.

The visual claustrum of the cat receives convergent input from several visual cortical areas and projects back to these same areas. These claustrum-cortical loops are organized retinotopically, such that the claustral regions receiving visual input deal with the same region in the visual space as the cortical region with which it interacts [8]. The visual claustrum contains a single, orderly, and unified map of the contralateral visual hemifield and of a small part of the ipsilateral field. The representation of the peripheral visual field is expanded and the fraction of cells that project to the claustrum from cortical parts devoted to the peripheral visual field is overly represented [7], forming a ‘reversed’ topography compared with the primary visual cortex. Most claustral neurons are binocular and

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Keywords: claustrum; cortex; sensory modalities; attention; top down; bottom up.

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0166-2236/

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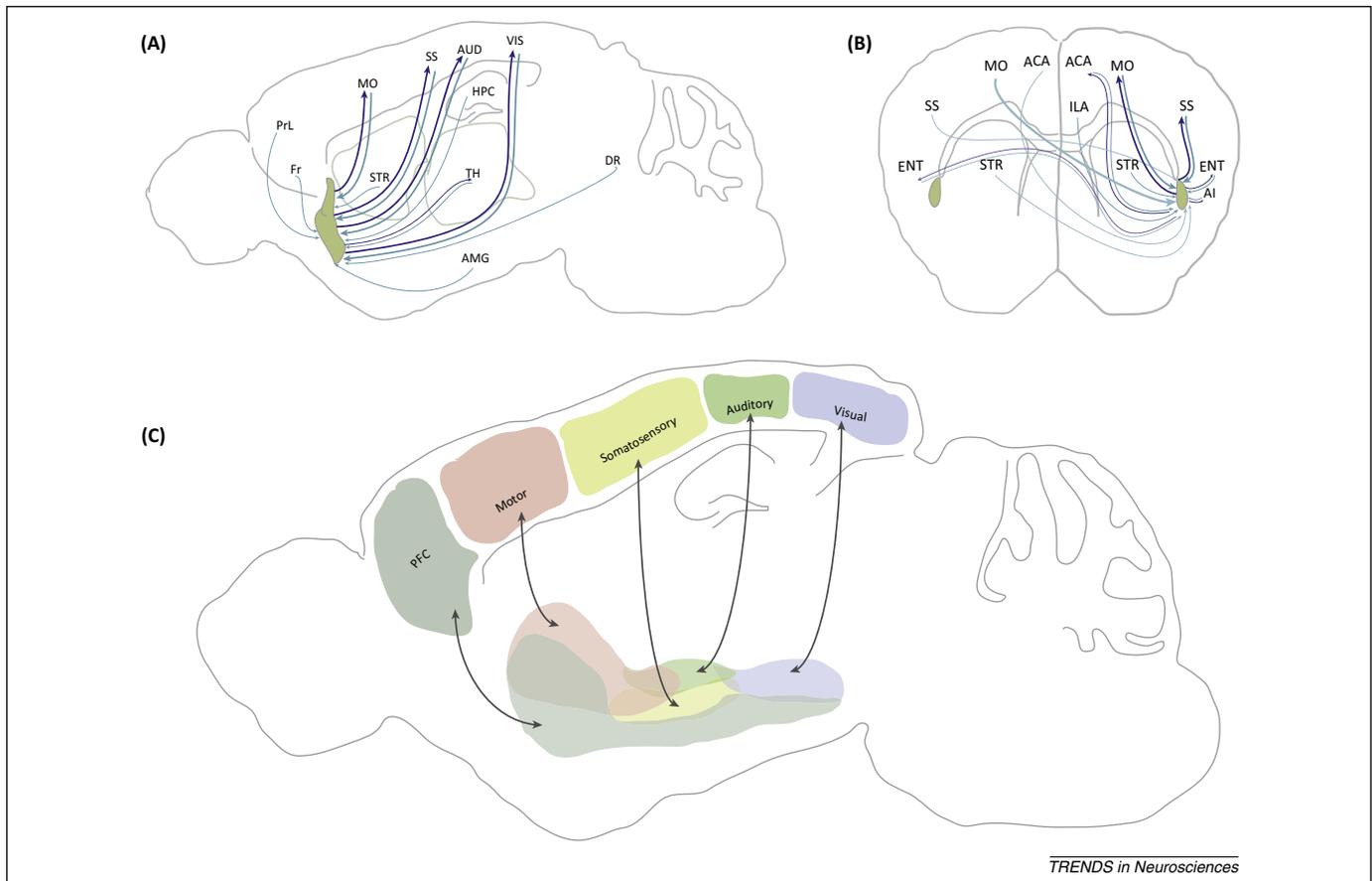


Figure 1. Input–output connectivity of the claustrum. The architecture of the input–output connectivity of the claustrum is charted in (A) sagittal and (B) coronal sections of the rodent brain. The primary inputs to the claustrum are from the cortical modalities, which display symmetrical reciprocal connections. Additional inputs come from the prefrontal cortex as well as subcortical inputs from the striatum, thalamus, amygdala, and dorsal raphe. Abbreviations: PrL, prelimbic cortex; ACA, anterior cingulate area; ILA, infralimbic area; MO, motor cortex; SS, somatosensory cortex; ENT, entorhinal area; AI, agranular insular area; PIR, piriform area; PrL, prelimbic area; Fr, frontal cortex; AUD, auditory cortex; VIS, visual cortex; STR, striatum; TH, thalamus; AMG, amygdala; HPC, hippocampus; DR, dorsal raphe. (C) Cartoon model demonstrating the spatial mapping of the connectivity from the cortex to the claustrum. Several studies have produced different results within and across species. Phylogenetic differences in the organization of the sensory system of different species mean that homologous areas are not always found. Therefore, the map depicted should be taken as a general outline, consistent with the majority of the data, and is most highly similar to the data presented in [26].

prefer elongated moving stimuli while being tolerant of direction, velocity, width, and contrast, in contrast to their cortical input, which is direction selective and largely monocular [11,32]. The output from the visual cortex to the claustrum and the lateral geniculate nucleus (LGN) project from within the same layer (layer VI) and the same regions of cortex but originate from neurons with different morphologies and connectivities [33]. Furthermore, while spatially defined visual information arrives at the LGN, the claustrum receives information preferably pertaining to motion in the periphery of the visual field [5,11,34].

Displaying similar architecture and organizational logic as the visual claustrum, the auditory claustrum of the cat is organized topographically and is aligned with the position of the auditory cortex [19,35]. The auditory responsive cells prefer long latency stimuli (from either ear) and have broad tuning that extends over several octaves as well as a strong preference for noisy stimuli over pure tones [9,19]. These properties obviously contrast with those of neurons in the tonotopic auditory field [36] and, together with the information regarding the visual claustrum, suggest that the claustrum registers the onset of surprising stimuli rather than being occupied with the detailed information carried by the sensory input.

Somatosensation is an active sense, requiring motor activity such as whisker movement or palpation for detection of features of an object. Thus, it may be useful to consider the motor and somatosensory cortices and their connections with the claustrum as a single sensory–motor system. Similar to the observations in visual and auditory cortices, the somatomotor claustrum of the cat displays an inverse topography compared with that observed in the somatosensory cortex, with the largest somatosensory zone in the cat claustrum being occupied by the foreleg [9,37] while the facial area is smaller. Rats and other nocturnal animals build a representation of their surrounding world primarily through whisker-mediated somatosensation. Accordingly, a significant projection to the claustrum is observed from the primary motor whisker region [15,16,18]. The whisker primary somatosensory cortex has not been found to project directly to the claustrum, but claustral neurons in the region that receives whisker motor innervations project back to the whisker motor cortex and the whisker somatosensory cortex. This cortical–claustral–cortical circuit has been suggested to play a role in sensorimotor coordination of whisker movements necessary for orientation and object palpation [15,16,38].

Box 1. Input–output connectivity of the claustrum

Experiments in cats and monkeys using retrograde tracers have demonstrated that the claustrum primarily receives glutamatergic input from cortical layer VI. The claustral neurons that receive input from the cortex are thought to be excitatory projection neurons [49,50] providing reciprocal input back to the cortex, terminating mainly in layer IV [5–7,21,30,35,82]. Such corticoclaustrocortical circuits are established throughout the claustrum. While this organization appears to account for the bulk of the connectivity of the claustrum with the cortex, excitatory input onto interneurons in the claustrum has also been reported [4,8,83,84] and afferents from the claustrum have been reported to project to layers VI and I/II [34]. The claustral afferents to layer VI and I/II predominantly contact spines, probably on cortical pyramidal neurons. By contrast, claustral afferents to layer IV contact spine and smooth dendritic shafts about equally and thus appear to convey a major input to inhibitory interneurons [6,13] (Figure 1). This type of connectivity could, in principle, generate feedforward inhibition on cortical function [56] and dramatically affect cortical processing and output.

The output from the claustrum to cortex is almost exclusively ipsilateral. While inputs from frontal cortical regions appear to be bilateral, inputs from the cortical modalities appear to have an ipsilateral preference and inputs from the motor cortex show a contralateral preference [14–16,18,26,29,44,85–87]. Outputs from the claustrum have been reported to bifurcate and project to more than one cortical modality, suggesting that the reciprocity of the connections is not fully symmetrical, but this is unlikely to be a major feature of claustric connectivity [14–16,22,26,41,85,88].

The endopiriform nucleus, located ventrally to the claustrum, is occasionally treated as a ventral claustral nucleus. While it shares some traits with the claustrum and connects bidirectionally with allocortical and subcortical nuclei [89] as well as olfactory areas, it is now generally believed that the endopiriform nucleus is distinct from the claustrum (reviewed in [44]). Due to its olfactory connectivity and larger proportion in rodents, it may be speculated that the endopiriform nucleus functions as an olfactory region, performing functions analogous to those performed by the claustrum for other sensory

inputs. While potentially worthy of experimental investigation, this is hypothetical [8,23,39,46,90].

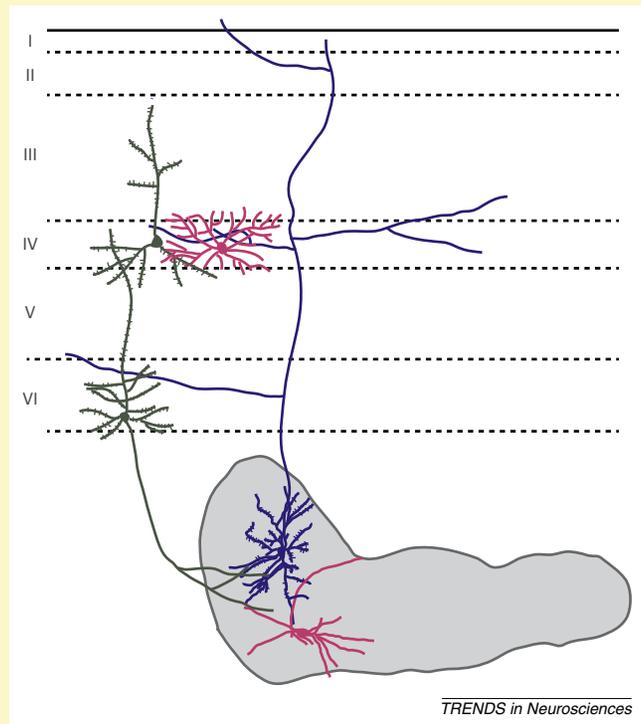


Figure 1. Diagram of the reciprocal connectivity of the claustrum with cortex, demonstrating a layer VI cortical projection neuron sending an axon to the claustrum that synapses on a claustral projection neuron as well as a local inhibitory interneuron. The claustral projection neuron primarily innervates a layer IV pyramidal neuron and a local interneuron, but also sends collaterals to layers I and II.

The visual, auditory, and somatomotor regions of the claustrum share consistent characteristics. The properties of the sensory claustrum contrast with the properties of associated cortical areas. The visual claustrum seems to be concerned with the peripheral visual field, comprising binocular cells that have elongated receptive fields and no orientation selectivity. Similarly, cells in the auditory claustrum are not tightly tuned, have broad receptive fields, and show preference for noise coming from either ear. Finally, claustral neurons associated with somatomotor information appear to represent a limited repertoire of somatosensory stimuli and may coordinate active sensation, such as active whisking and voluntary eye movement, through output to the frontal eye fields [15,16].

While in this section we integrate literature regarding the function of the claustrum in different model species (primarily primates, cats, and rodents), the phylogenetic differences in the sensory organization of these model species are not trivial. For example, the organization of the visual system differs significantly among species with relation to their dependence on the modality, visual acuity, and color vision. Furthermore, while we do not elaborate on this point, the topographical arrangement of the claustrum appears to differ between rats, cats, and primates [6,10,20–22,26,27,39–42]. Also of importance for further study is the fact that the anatomical definition of the boundaries of the claustrum remains not universally accepted (e.g., [43–45]).

Unambiguously defining the anatomy and boundaries of the claustrum is crucial to enable the field to move forward, as well as to promote noninvasive imaging of the claustrum. Obviously, more work is necessary in this field, but we propose that the organizational principles we outline here are common across phyla, albeit fine-tuned to the specific needs and modality dependencies of the organism studied.

Claustral physiology

Excitation of the various sensory modalities elicits responses in claustral neurons, which are typically quiet [9,12,46,47]. While some studies found multimodal responses in the claustrum [36,46,48], other studies [9,12,47] failed to find multimodal cells in the claustrum but rather found clear-cut regional specialization. In Box 2 we discuss the internal structure of the claustrum, a topic closely associated with the issue of modality integration in the claustrum. Obviously, the issue of whether claustral neurons are uni- or multimodal is important for understanding the function of the claustrum and should be a priority of future research.

Claustrocortical connectivity is mediated by the action of claustral glutamatergic projection neurons, which project primarily to layer IV, as well as layers I&II and VI. The projections to layer IV have been reported to synapse onto dendritic spines of pyramidal neurons as well as on shafts

Box 2. The internal structure of the claustrum

The claustrum has simple internal architecture with no lamination, and few cell types [91–93]. The most common cell type in the claustrum (90% of claustral neurons [4]) is glutamatergic [50,64,94] with large cell bodies, heavily spiny dendritic arborization [8,24,92,95], and an axon projecting out of the claustrum, primarily to the cortex [24,31,95]. Other neurons in the claustrum are likely to be GABAergic and display characteristics of local circuit interneurons, albeit with some variation [95].

A major question regarding the function of the claustrum relates to the organization of its internal connectivity. Does the claustrum form independent corticoclaustral loops? Do corticoclaustral loops interact across the rostral–caudal axis of the claustrum? Overall, little is known regarding the internal connectivity of the claustrum [64]. Golgi studies have revealed rich local axon arbors within the claustrum of primates and cats [8,95,96]. While some local neurons have smooth dendrites and axons with numerous collaterals that do not leave the claustrum, others have a sparse dendritic tree and axon collaterals that remain within the boundary of its dendrites [8,91,93,95,97–100]. Long-range intraclaustral connections have been reported [14,101] and the cell bodies and dendrites of interneurons appear to be preferentially oriented along the anterior–posterior axis, consistent with a potential function in communicating between the regions of the claustrum mapped to the different modalities [64].

of what are likely to be inhibitory interneurons [6,13,49,50] (Box 1).

Electrical stimulation of the claustrum in cats has been found to suppress neuronal firing in several cortical areas, including the motor cortex [51]. Typically, spontaneous activity was completely silenced for about 200 ms starting on average around 20 ms after electrical stimulation of the claustrum. In the cat oculomotor frontal eye field [52,53], as well as primary visual cortex [54,55], some neurons were briefly excited by electrical stimulation of the claustrum, with a fast burst of firing commonly followed by prolonged suppression. This effect of the claustrum on the cortex could be explained by a feedforward inhibitory loop originating in the claustrum [56]. Claustral output could directly excite cortical pyramidal neurons, explaining the rapid excitation, in parallel to excitation of cortical inhibitory interneurons. Activation of the cortical interneurons would result in delayed inhibition of pyramidal cell firing.

Box 3. Pathologies of the claustrum

Potentially, the most telling evidence for the involvement of the claustrum in allocating attention to different aspects of incoming sensory information would come from human studies. However, human patients with selective lesions in this region are rarely reported in the medical literature and when they are they justly evoke skepticism, as the structure of the claustrum renders it impossible to unambiguously identify it in human imaging studies. Still, the few cases that have been described are intriguing.

Several cases of transient lesions selective to the claustrum have been reported. One patient, a 12-year-old girl, suffered temporary bilateral lesions to her claustrum following severe transitory encephalopathy. During this time she developed epileptic seizures and loss of vision, hearing, and speech, which eventually degraded into psychotic behavior [102]. More recently, a 21-year-old man diagnosed with an infection of mumps virus that resulted in bilateral claustrum lesions suffered visual and auditory hallucinations [103].

Partial loss of claustrum function could have more subtle effects and may play a role in common diseases or mental disorders. Researchers have found negative correlations between the volume of gray matter in the claustrum and the severity of auditory hallucinations and delusions

This structure could define the output of cortical modalities, reducing the impact of prolonged stimuli [13] (Box 1). We must point out that the evidence accumulated by these early studies was obtained nearly exclusively in anesthetized cats. There is an urgent need to perform similar experiments in awake animals to understand the impact of claustral activity on cortical function. In addition, it is imperative to utilize modern techniques such as optogenetics to induce better controlled, cell type-specific, and potentially more naturalistic stimulation, since electrical stimulation could have unnatural results such as widespread inhibition. Some additional insight into the physiological functions of the claustrum may be obtained from the sparse information on human pathologies involving the claustrum (Box 3).

Neuromodulation of the claustrum

The claustrum receives a wide array of neuromodulatory afferent projections. Among others, adrenoceptors [57] and receptors for opiates [58], dopamine [59], serotonin [60], oxytocin, acetylcholine [59], and endocannabinoids [61] have been found in the claustrum, and several of these have been found to functionally affect the firing of claustral neurons *in vivo* [62,63].

Serotonergic inputs are potentially of high interest in the context of a model ascribing a role to the claustrum in attention, as we discuss below, and have been found to be spread throughout the claustrum [44,60,62,64], similar to prefrontal cortical inputs [7,32,65].

An additional intriguing neuromodulatory input to the claustrum is that of opiates. The claustrum contains a uniquely high concentration of kappa opioid receptors [58]. Interestingly, activation of these receptors (in other brain structures) has been found to inhibit the release of GABA [66] and the psychoactive drug salvinorin A acts on kappa opioid receptors to induce intense sensory synesthesia [67]. These results suggest the possibility that salvinorin A may disinhibit crossover between modalities by relieving inhibitory tone in the claustrum [68].

in schizophrenia patients [104,105]. In addition, it has recently been suggested that a delay in the development of the claustrum plays a role in autism [106].

To the best of our knowledge, there is only one case in which the claustrum was actively perturbed in a human patient [107]. In this study, a 54-year-old woman with intractable epilepsy underwent depth-electrode implantation and electrical stimulation mapping. One electrode included a contact adjacent to the claustrum. Stimulation of this contact while the woman was reading aloud resulted in arrest of reading, blank staring, and general unresponsiveness. The patient resumed reading immediately on cessation of the stimulation and had no recollection of what had occurred. It is interesting to note the phenotypic similarity between the results of electrical stimulation of the claustrum in the cat, causing ‘inactivation’ [108], and the effect of stimulation of the claustrum in the human patient.

Obviously, the small number of cases and the difficulty in pinpointing the effect to the claustrum limits the extent to which the results can be interpreted, yet they hint at a central role for the claustrum in defining how an individual perceives and interacts with the external world.

Box 4. Hypotheses regarding the function of the claustrum

The claustrum, its architecture, and its connectivity have attracted the interest of scientists for decades. The widespread claustracortical connections have inspired early theories to describe the claustrum as a satellite of the cortex, having some regulatory role, or acting as a relay station [8,9,13]. Other pioneers in claustrum research maintained that the claustrum is more than a simple relay station and has a role in binding information across modalities [10,109]. A decade ago, interest in this brain region was reignited, largely due to Francis Crick's last paper, co-written with Christof Koch, in which the authors singled out the claustrum as a possible hub in which sensory information is bound and integrated across and within different modalities to form a single, unified conscious experience [2]. According to the theory postulated by Crick and Koch, the claustrum receives inputs from different modalities and binds them together, implicating the claustrum as a multimodal region. This claim has motivated researchers to search for multimodal neurons in the claustrum or convergence of multimodal input within the claustrum. The prevalent findings in this regard have been negative. Electrophysiological evidence seems to point against single neurons that respond to stimuli coming from several modalities [16,47]; however, the question of whether the claustrum is an integrator or comprises segregated functional units remains open [16,32,43,47].

A modified hypothesis has been proposed whereby the claustrum acts as an amplifier for cortical oscillations [110]. According to this

hypothesis, the tight dimensions of the claustrum could cause neighboring claustral areas to oscillate in a correlated fashion, and claustrum projections from these areas are expected to induce oscillations in other cortices. The degree of amplification could be modulated by subcortical structures. The authors suggest that the claustrum can thus synchronize oscillations between distant cortical areas without the requirement for multimodal neurons. This coordination of cortical oscillatory activity was suggested to be involved in cognitive tasks. Based on a similar conceptual framework, another model proposes that control of the claustrum over cortical oscillations could enable switching between resting-state and task-associated cortical networks [65].

Recently, the claustrum has been suggested to function as a saliency detector, notifying the cortex of incoming novel stimuli [47,75]. The claustrum has further been implicated in active sensing, in which claustral inputs influence motor areas responsible for whisking or directing gaze [14–16,18]. Finally, it has been suggested that the claustrum is involved in attentional load allocation [44,45].

The hypothesis we present here is closely tied to these latter ideas and intends to provide a coherent, testable theory that explains how the claustrum may regulate allocation of attention and figure/background segregation through the architecture of its cortical connectivity.

A comprehensive model of the role of the claustrum in attention

While reading these words, you devote your attention to the text to integrate the written information and process the ideas presented. Your gaze is focused on the paper and your attention is prioritized toward the visual modality. Meanwhile, you filter out and reduce awareness to the vast majority of task-irrelevant auditory, olfactory, and somatosensory stimuli barraging your senses, as well as irrelevant visual stimuli. Nevertheless, your attention can be consciously redirected to your email or automatically redirected to the ringing of your phone. We propose that the claustrum serves the function of segregating attention between modalities, enabling us to isolate objects of current priority for attention. The concept of a role of the claustrum in attention has been raised before (Box 4) and here we elaborate on a detailed hypothesis for how the claustrum could perform this function.

Our attention is modulated by two major sources: top-down and bottom-up processing. Top-down processing is defined as the flow of information from 'higher' to 'lower' centers, carrying knowledge derived from previous experience rather than sensory stimulation. Top-down modulation, sometimes called the endogenous system, is controlled by cognitive factors such as knowledge, expectation, and current goals and is believed to depend on activity in prefrontal cortical regions [69]. Bottom-up modulation, or the exogenous system, refers to the rapid and involuntary shifting of attention toward salient sensory stimuli of potential importance [70,71]. The bottom-up system is faster than the top-down system [71,72]. Peripheral cues grab bottom-up attention in an automatic, stimulus-driven manner and are typically effective within a time window of 80–130 ms after the cue onset, whereas the allocation of top-down attention is slower, becoming effective within about 300 ms [72]. Increased efficacy of cortical responses and improved signal/noise ratio have been shown to be the main effects of increased attention [73,74].

We propose that the claustrum acts to control the output from the cortical representations of each of the sensory modalities. The claustrum may control which cortical output is attended, promoting the preferred modality, while reducing the efficacy of other, competing cortical modalities. Our model further implicates the claustrum as a hub for attention, where top-down attentional strategies, as well as bottom-up interventions, are implemented. For possible analogies between the role of the claustrum and a similarly interconnected structure, the thalamus, see Box 5.

According to our model (Figure 2), the 'attentional strategy' at any given time is defined by the prefrontal input to the claustrum (top down), modulating the output of the claustrum to the various cortical modalities. Projections from the claustrum are to cortical layers I&II, IV, and VI and have been reported to innervate pyramidal neurons in all layers (layers I&II, IV, and VI), with preferential input onto local inhibitory interneurons in layer IV. This architecture may generate feedforward inhibition whereby claustral activation causes fast excitation of layer IV pyramidal neurons followed by prolonged inhibition of the defined cortical circuit through activation of local interneurons. This circuit organization would tone down output from cortical modalities not privileged for attention. In parallel, output from the claustrum to layers I and VI may enhance the responsiveness and efficacy of selected cortical outputs (Box 1).

Claustral neurons fire at low basal frequency and respond optimally to motion at the periphery of the visual field or the onset of noisy stimuli. This implies that the claustrum is recruited on salient shifts in the sensory input and is tuned to respond to the onset of a novel stimulus rather than its content [75]. Salient sensory experiences could override the attentional strategy imposed by the prefrontal cortex through direct rerouting of claustral activity, reallocating attention (bottom up) to those cortical modalities reporting the sensory experience. In addition,

Box 5. The claustrum and the thalamus: how similar/how different?

The claustrum shares several characteristics with the thalamus, suggesting that there may be analogies between the two structures and raising the question of what distinguishes their impact on cortical processing and attention. The thalamus acts as the relay station for sensory information on its way to the primary sensory regions in the cortex and the sensory modalities map with clear spatial segregation in the thalamus [111]. Each of the primary sensory relay areas in the thalamus receives strong feedback connections from the cortex [111,112]. These connections have been shown to impact information processing in the thalamus, demonstrating that the flow of information to the cortex can be modulated within the thalamus [112,113]. Furthermore, the thalamic reticular nucleus (TRN), which forms a lateral capsule around the thalamus, is a GABAergic nucleus whose function is to provide strong inhibitory drive onto thalamic nuclei, selectively limiting their relay of information to the cortex. Potentially, this could provide a mechanism for selective attention by blocking information from the modalities even before they reached the cortex. The TRN has been shown to participate in intrathalamic as well as corticothalamic feedforward loops, impacting the output from the thalamus in a top-down fashion. While the effects are modest, there is evidence that the impact of the TRN on thalamic output could promote task-oriented selective attention [114–117]. Comparisons of the cortical projections to the thalamus and the claustrum demonstrate that while they originate from the same cortical layer, they arise from different neuronal

populations [8,9,33]. Thus, while spatially defined visual information arrives at the LGN, the claustrum receives information preferably pertaining to motion in the periphery of the visual field [5,11,34]. In addition, the claustrum and the thalamus share projections to common frontal cortical targets [118].

In our view, sensory selectivity is one of the most important functions of the brain. Defining what features or objects will be attended, and more importantly (and potentially dangerously) what can be ignored, is crucial for efficient interaction with the surrounding world. Therefore, it may be beneficial that multiple circuits work to achieve this goal. We propose that both the thalamus and the claustrum have the capacity to focus attention, albeit at different stages of sensory processing. The thalamus can gate the access of information to the cortex early in the process of sensory selection [116], while the function of the claustrum may be to define gain control on information after it has been processed in the cortex, limiting the access of this information from the cortex to the rest of the brain. According to this hypothesis, the claustrum would enable parallel cortical processing of many different sensory objects in a given scene, while only the representation of the selected object would be allowed to project out from the cortex. This structure would enable rapid shifts in attention as the sensory processing is continuously occurring for multiple objects in parallel. Different circumstances may entail the utilization of different attentional strategies – which could be broader (thalamic) or more selective (claustral).

subcortical input from the amygdala, entorhinal cortex, and hippocampus could play a role in subconscious coordination of attention with regard to spatial, social, and emotional elements. The projections of the claustrum to motor and oculomotor centers could allow the claustrum to

promote motor responses important for focusing attention toward salient stimuli by supporting shifts in gaze or head/body orientation. In relation to the neuromodulatory input to the claustrum, recent studies of the function of the major serotonergic nucleus, the dorsal raphe, show that serotonin

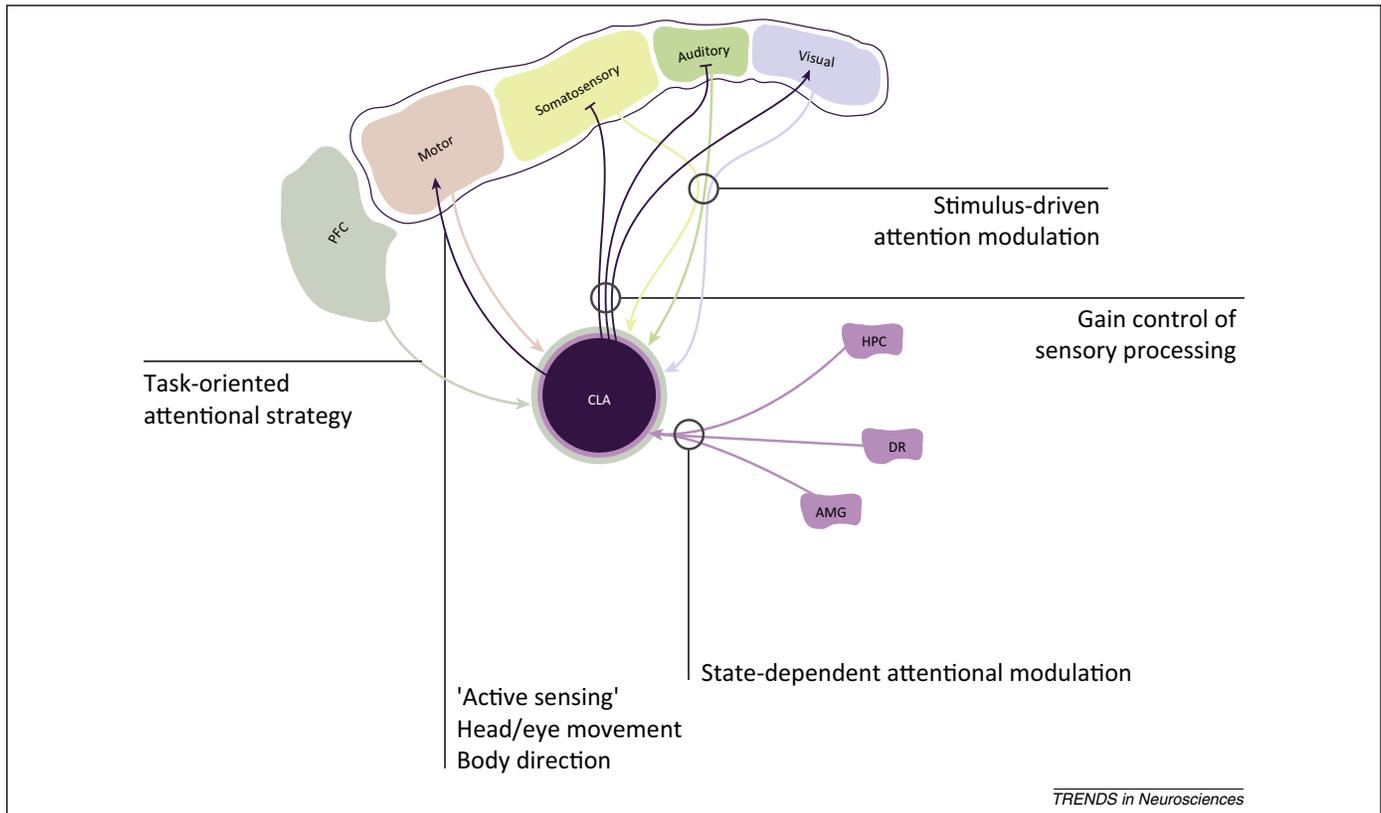


Figure 2. The role of the claustrum in attention (a model). We propose a scheme for the function of the claustrum in modulating attention. The figure illustrates our hypothesis in the case of preferential attention to an object in the visual modality. In top-down modulation of attention, prefrontal inputs, spanning the extent of the claustrum, dictate a task-oriented attentional strategy and define the focus of attention. The claustrum implements the strategy by providing gain control of sensory processing, enhancing the cortical efficacy of a selected visual object, while suppressing the report of competing stimuli from other sensory regions in the cortex. A salient input from one of the modalities may override the attentional strategy, acting in a bottom-up, stimulus-dependent fashion to redefine the hierarchy of attentional segregation. Additional mechanisms for modulation of attention could come from subcortical inputs, including neuromodulation (dorsal raphe), context (hippocampus and entorhinal cortex), and emotion (amygdala), providing state-dependent attentional modulation.

may be necessary for completion of tasks demanding behavioral persistence and prolonged attention [76]. It will be interesting to study whether this depends on the serotonergic projection to the claustrum.

The model we describe above is potentially oversimplified. The reason for this is that while attention can be directed toward global information from modalities, it is often focused on individual objects (a face, a word, an item we recognize by touch) [77]. A refinement of the model could therefore propose that the claustrum enables attention to selected objects while reducing the output from the cortical representation of irrelevant information. The inhibition could be within the same modality, as well as across modalities, via the vast (yet highly understudied) local connectivity within the claustrum (Box 2). This model implies that the claustrum interacts with higher-order sensory areas which encode of an 'object' rather than a 'feature' [77]. This fine-tuning of the model also allows the formation of parallel representations of multiple competing objects in the cortex although only one is selected for attention at any point in time. The ignored representations may be kept in short-term memory and rapidly registered 'retrospectively' on release from inhibition by the claustrum. In principle, a similar model for the logic of claustral connectivity and impact on cortical physiology could explain a role for the claustrum in figure/background separation in the context of segregation between modalities or between objects. However, the model that ascribes a function to the claustrum in the selection of objects implies that the claustrum would preferentially project to (and impact) higher-order sensory processing areas where sensory objects have already been formed [78–80].

We summarize our hypothesis for the function of the claustrum with the following example. Imagine you are directing the television broadcast of a football game. You watch 24 screens displaying the information from different cameras set around the field and at each moment you are responsible for selecting which camera is going to go 'live'. You have certain rules/strategies you must follow – for example, you should never miss a touchdown – and sometimes you need to broadcast a replay while the match is going on, only to jump back to the game when an important play occurs. Simultaneously screening 24 channels, you cannot see the detailed expression on the face of each player and you might even have difficulty identifying individual players. Attention works this way: based on simultaneous, potentially low-resolution input from multiple channels, an ongoing decision has to be taken at short-timescale intervals to allow proper processing of the relevant information. Our model proposes that the prefrontal input to the claustrum defines the attentional strategy, which is implemented primarily through the feedforward inhibition that the claustrum exerts on the cortical modalities. The input from the prefrontal cortex to the claustrum may promote cortical processing of task-relevant information (potentially through claustrorocortical afferents to layers I&II and VI), while most of the impact of the claustrum on the cortex is through selective activation of cortical inhibitory interneurons in layer IV, reducing the output of the cortical representations not currently selected for attention. The introduction of an unexpected

Box 6. Outstanding questions

- The claustrum is one of the most intriguing structures in the brain. The literature regarding the claustrum has so far contributed to enhancing the mystery as it has provided tantalizing hints regarding the vast connectivity of the claustrum and its impact on cortical function and behavior.
- Obviously, a priority in the field is the development of multiple transgenic models, which will enable genetic access to claustral neurons, facilitating the application of powerful new tools to address the function of the claustrum and the rules governing its input–output connectivity. Genetic access to the claustrum would open a universe of possibilities, of which we describe two urgent experiments. One experiment of interest would be to inactivate claustral projection neurons (by conditional expression of an inhibitory opsin or inhibitory DREADD [119,120]) in mice and test their ability to perform a task that requires attention in the presence of a sensory interference. An additional informative experiment would be to optogenetically activate claustral output neurons while recording activity from excitatory and inhibitory neurons in a sensory cortical region. These experiments (and their extensions) would test the basic premises of the hypothesis proposed here and would provide important insight into the function of the claustrum and the principles of its interaction with the cortex.
- The local circuit connectivity of the claustrum is also a topic on which very little information exists and that will obviously benefit from application of genetic access to the claustrum.
- Additional questions involve identifying the role of neuromodulation in regulating the function of the claustrum, the significance of the interaction of the claustrum with frontal and associational cortices, and the question of multimodal integration in the claustrum – do single claustral neurons integrate information from different modalities?

stimulus from the periphery may overcome the attentional strategy in a bottom-up fashion, imposing a new hierarchy of object representation and driving motor commands to focus on the source of the stimulus, and inhibit cortical representations of objects newly redefined as irrelevant. In sum, our hypothesis ascribes a role to the claustrum in figure/background separation – providing deeper contrast for the representation of the selected object while further fading the representation of irrelevant information.

The model presented here sets the stage for well-defined experiments to test the potential function of the claustrum in modulating cortical function during attention. Crick and Koch likened the claustrum to a conductor of an orchestra [2]. According to our hypothesis, the claustrum may act as a spotlight operator, implementing the moment-to-moment choice of which aspects of the external world are featured center stage in the theatre of our mind.

Concluding remarks

The claustrum has been fascinating neuroscientists for decades. Whether it is responsible for attention or consciousness or has a completely distinct function remains an open question. This review proposes a detailed model for the role of the claustrum in attention, providing the substrate for focusing future research in the field (Box 6).

Directly testing the role of the claustrum in the context of attention is an experiment yet to be conducted and the closest evidence acquired so far ascribes a role to the claustrum in salience detection in primates [75]. As championed by Crick and Koch, it is clear that for the next decade to provide more concrete results about the function of the claustrum, genetic access to claustral neurons

is essential. Such access, in the context of the rapidly developing optogenetic and pharmacogenetic toolbox, is expected to revolutionize the field, as it will enable manipulation of the activity of claustral neurons to test their behavioral consequences as well as the rules governing the interaction of the claustrum with cortical modalities (Box 4). Similar strategies have recently been implemented in investigating the role of the cingulate cortex in top-down modulation of visual attention [81]. To quote the final words of Francis Crick and Christof Koch's famous review, 'What could be more important, so why wait?' [2].

Acknowledgments

The authors thank their friends, especially Drs Mickey London, Inbal Goshen, Brian Mathur, and Zhiping Pang, for their comments, which channeled the manuscript into its current form. Work in the Citri laboratory for Experience-Dependent Plasticity is funded by the Edmond and Lily Safra Center for Brain Sciences, the Brain and Behavior Foundation (NARSAD #18795), the German-Israel Foundation (GIF #2299-2291.1/2011), the Binational Israel-USA Foundation (BSF #2011266), the EU Marie Curie Career Integration Grant (CIG #PCIG13-GA-2013-618201), the Israel Anti-Drug Authority, the Israel Science Foundation (ISF #393/12), and the Adelis Award in Neuroscience. A.C. is a supported member of the Israeli Center for Research Excellence (iCORE) Program of the Israel Science Foundation (#1796/12).

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