



The Functional Anatomy of the Claustrum: The Net That Binds.

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Article ID: WMC003182

Article Type: Review articles

Submitted on: 25-Mar-2012, 11:14:56 PM GMT **Published on:** 26-Mar-2012, 12:36:34 PM GMT

Article URL: http://www.webmedcentral.com/article_view/3182

Subject Categories: NEUROSCIENCES

Keywords: Claustrum, Consciousness, Binding, Coincidence detection, AND gate, GABAergic interneurons, Gap-junction linked networks, Salvinorin A

How to cite the article: Smythies J , Edelstein L , Ramachandran V . The Functional Anatomy of the Claustrum: The Net That Binds. . WebmedCentral NEUROSCIENCES 2012;3(3):WMC003182

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Source(s) of Funding:

None

Competing Interests:

None

The Functional Anatomy of the Claustrum: The Net That Binds.

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Abstract

Crick and Koch suggested in 2005 that the claustrum might be engaged in sensory binding operations related to consciousness. This might involve, they suggested, widespread waves of information traveling within the claustrum that might depend on networks of gap-junction linked neurons, which were especially sensitive to the timing of inputs. But they did not suggest any specific system to do this. The purpose of this present paper is to suggest what this mechanism might be. The basic thesis is that the claustrum is a spike coincidence-detecting device, constructed of large number of small simple identical nerve nets. These function as GABA-modulated 'AND gates' that convert the separate packets of unbound information in its inputs into an efferent signal that carries the binding information essential for consciousness and other brain functions. This function may also be relevant to processing of synchronized oscillation by the claustrum. Different anatomical regions of the claustrum may exert this function for sensory binding, computation of the significance of reinforcement in a complex environment, and other higher brain functions. We also suggest the outlines of a mechanism by which the cortex may process this input from the claustrum. We review the manner in which this hypothesis explains the present data. There is at present no other detailed hypothesis in this field.

Key words: Claustrum, consciousness, binding, coincidence detection, AND gate, GABAergic interneurons, gap-junction linked networks, salvinorin A.

Introduction

A central feature of consciousness is one's sense of being a unified person despite being confronted with a diversity of sense-impressions from different sense organs. Except in disease states we also experience ourselves as a single person. Where and how this unification occurs has been a subject of considerable debate. There are philosophers who have argued that this subjective experience of unity should not be taken as evidence for anatomical convergence in some single brain location. This,

according to these philosophers, would imply the fallacy of a Cartesian theater with a homunculus inspecting it. In this paper-following the lead of Crick and Koch-we take the opposite view and argue that there may indeed be an anatomical structure (or structures) involved somehow in the unity of conscious experience. Reasonable candidates would include the angular gyrus-sitting strategically at the cross-roads between occipital (vision) temporal (hearing) and somato-sensory cortices (touch and proprioception)-and a curious, and until recently little known, structure called the claustrum. Crick and Koch (2005) shone a sudden spotlight on this hitherto much neglected organ by suggesting that the claustrum might play a key role in information processing in the brain by correlating the separate activity in the different sensory cortices into one coherent activity that 'binds' separate sensations into the unitary objects that we experience in consciousness.

The claustrum is broadly divided into three compartments (an anterior-dorsal connected with the somatosensory and motor cortices, a posterior dorsal (visual cortex) and a ventral area (auditory cortex)) (LeVay and Sherk 1981; Sherk 1986); Edelstein and Denaro 2004; Crick and Koch 2005). The claustrum has reciprocal widely distributed anatomical projections to almost all regions of the cortex, as well as to many subcortical structures. The claustrum has a well-marked retinotopically organized map of the visual field, as well as an equivalent map of the somatosensory field (LeVay and Sherk 1981; Sherk 1986). It has been claimed that areas of the claustrum in the cat sends "precisely reciprocal" projections back to those area(s) of the cortex whence its inputs derived (LeVay and Sherk 1981; Sherk 1986). Also that the projections to and from the claustrum are diffuse, but quite specific, in both directions (one point to specific points) (Divac et al. 1978; Divac 1979; Sloniewski et al. 1986). Single cells in the claustrum can send branched axons to several cortical areas. The same cells receive input from these areas (Rahman and Baizer 2007). However, there are marked species differences in the anatomy of the claustrum and others claim that the cortico-claustral projection is more diffuse. Crick and Koch summarize their view of the situation thus, "Most regions of the cortex send a projection to the claustrum, usually to many parts of it. Thus their mappings are far from

being a precise local mapping and tend to be somewhat global (that is, all to all), though not completely so.” However, as we will see, the hypothesis that we will present is not related to the question of whether the cortico-cortical projections are point-to-point or diffuse. The ventral claustrum is also connected to limbic structures, such as the amygdala, subiculum and cingulate cortex. The claustrum also has a relatively uniform microanatomical structure that would allow what Crick and Koch describe as “widespread intra-claustral interactions”. These, they suggest, may be in the form of “waves of information {that} can travel within the claustrum”. This may involve, they suggest further, dendrodendritic synapses and networks of gap-junction linked neurons. They also suggest that claustral neurons “could be especially sensitive to the timing of the inputs”. But they do not suggest any precise mechanism to perform these functions. Rahman and Bazier (2007) also suggest that the claustrum mediates “integration across compartments mediated by inhibitory interneurons”.

The present paper considers what these “waves of information” might be, and what type of timing-related, or other, computations and integrations they might perform. The task the claustrum performs is to provide the cortex with information that allows the cortex to ‘bind’ certain of its on-going activities. Our hypothesis describes a simple nerve net that may mediate these functions, as well as what functions these are.

The hypothesis

The simplest neurocomputational device to process binding is a logical {AND gate}. In this model an axon from each neural activity to be bound synapses on one neuron in such a way that neither axon by itself will activate the post-synaptic cell, but a combination of both (within a specified time) will do so. In the noisy environment of the brain, a noise reduction mechanism would improve the efficiency of the system. We therefore propose that the claustrum might contain a large number of small simple noise-protected {AND gates} (coincidence detecting neural nets or CDNNs). We will start with the simplest model. This consists of three neurons (fig. 1). One is a pyramidal (P) cell and the other two are satellite inhibitory GABAergic interneurons (INs). The module has two input axons, one derived from one sensory modality (say color), and the other from another sensory modality (say movement). (In this simplest model the binding mechanism proposed is kept within the visual system). The color input makes one synaptic contact with one

of the INs and one with the P cell. The movement input makes one synaptic contact with the other IN cell and one with the P cell. Each of these neurons requires two synaptic activations (S), delivered within a certain time limit, to fire it.

Now, if the active axon inputs are carrying the information ‘red’ in one and ‘moving to the left’ in the other, neither IN will fire (as each gets only one S): but the P neuron will fire (as it gets 2 S’s), and so transmits the information ‘red’ is bound to ‘moving to the left’ to the cortex. However, P will fire in response to any two S’s delivered within a certain time limit. So, if two ‘noisy’ impulses come down the color channel within this time limit, it will still fire, and so give a false signal. This is where the INs are relevant. Two impulses down only one channel will also activate its own IN. This will inhibit the firing of P and this will avoid the false signal. Thus the CDNNs function as logical noise-resistant GABA-modulated {AND gates}. In the real physiological situation, we would be dealing with two synchronized groups of axons in each input (and not single axons). In which case, excess noise in the input to this net arrangement would lead to statistically significant GABAergic inhibition of false positive (‘noisy’) signals by the mechanism described. The real net may well contain more complex variations of the simple model we describe.

We next propose that these modules are arranged in an orderly retinotropic manner throughout the retinotropic map that the claustrum possesses (fig. 2). Each module thus receives its main input from two small cortical areas, that each deal with a different modality in the same small portion of the visual field, and sends its information in a “precisely reciprocal” manner (Sherk 1986) back to the same areas via bifurcations in its efferent axons. In the case of the auditory cortex Beneyto and Prieto (2001) state, “Corticoclastral axons from any given area cover territories largely overlapping with those occupied by the claustrorocortical neurons projecting back to the same area. The location of cortically projecting neurons in the claustrum matches the position of the target cortical area in the cerebral hemisphere, both rostrocaudally and dorsoventrally. These findings suggest that the intermediate region of the claustrum integrates inputs from all auditory cortical areas, and then sends the result of such processing back to every auditory cortical field.” It is important to note here that the only requirement of our hypothesis is that the activated claustral P cell should project back to approximately the same cortical cells whence its main input arose. It is not relevant whether the cortico-claustral projections that carry these impulses are point-to-point or diffuse. This specificity may be

augmented by centro-surround inhibition. The axons of the neurons in layer VI of the cortex that project to the claustrum have collaterals that arborize only in layer VI and the adjacent part of layer V (Katz 1987). These may synapse on local inhibitory GABAergic interneurons and thus sharpen the projection to the claustrum. In contrast, the axons of the neurons that project to the lateral geniculate body arborize only in layer IV. We will present further evidence on this key point below in the section on deafferentation plasticity. In this way the system does not actually have to evolve codes to carry information as what type of information it is carrying for the claustrum to read. The cortex already has the information in its color center 'red' and in its movement center 'moving to the left'. What it does not 'know' is how these two pieces of information are related i.e. whether they are related spatio-temporally to the same object or not. This information is supplied by the claustrum. The necessary spatial information is carried by the location in the retinotopic map in the cortex to which the incoming claustrum-cortical axon projects. The necessary temporal information is carried by the fact that this axon is firing at all—because the module is so wired that it only fires when receiving signals delivered, within a certain time limit, by the two different afferent channels. So the signal the claustrum sends back to the cortex reads, not "Red is moving to the left" but "Whatever is going on in the color system and in the movement system in cortical location xyz belong together." This saves the system of the extra computational cost of having to send this redundant information to the claustrum, and the extra cost of the decoding and recoding systems that the claustrum would need. This hypothesis seems to fit in with the general pattern of how the cortex operates—by a very large number of different small conjoined units that all carry out the one same simple operation. DiCarlo et al. (2012) entitle such units as "canonical subunits". To deal with more than two inputs (as when color, shape and movement are bound in the visual field: and when vision (V), somatic sensation (S), and hearing (H) are being bound) more of these modules could be added, either in parallel or in sequence. For example, a net could be made up of three bimodules (VH) (VS) (HS) in parallel, or in various types of sequence. In the case of the multisensory neurons in the claustrum, the module group could be made up of trimodules (VTH). These could consist of three afferent axons and a number of IN cells arranged in a system similar to that of the two input system.

We can adapt this simple model more to the physiological situation as follows. The effective unit here is a group of action potentials carried by a

number of axons. These will activate a number of P cells and their IN satellites in a statistically significant manner, so that P cells are fired by coincident impulses in axons from each cortical areas represented, and noise will be reduced. In a description of the physiological situation we need also expand the temporal and spatial extent of the net. In the case of temporal expansion we must take note of the fact that there is a continual stream of spikes coming down the afferent axons. As soon as one particular group (A) of CDNNs in the claustrum has 'processed' (in the manner described) one congruent packet of axon spikes (that are carrying the information say 'red' and 'moving to the right'), leading to P firing, it will, after a brief refractory period, start processing the next packet leading to P firing again carrying its report to the cortex. This report to A's small part of the color area is read by the cortex as 'moving to the right': and its report to A's small part of the movement area is read by the cortex as 'red'. (A's small part of the cortical color area already has the information 'red' and A's small part of the cortical movement area already has the information 'moving to the right'). We re-emphasize that this 'processing' does not consist of the claustrum reading the information coded by the intricate spatio-temporal spike chains contained in its afferent inflow—the claustrum merely detects, and reports back, which spikes are synchronized. This process will continue until the afferent inflow from the sense organ to A's two small parts of the visual cortex changes (say to 'yellow' and 'moving to the left'). In that event group A will process its new input in the same manner and send its new message to the cortex. In the spatial dimension the actual mechanism involves the statistical behavior of groups of neurons. We also have to recognize that these massed CDNNs ('AND gates') process information from the entire visual field. There may be some increased activity at the locus of attention, but we experience binding over the whole field, not just at the locus of attention. We will return to the topic of attention later.

This mechanism may explain why the claustrum needs both sensory specific 'maps' (visual, somatosensory and auditory) and an apparently common amorphous area. The maps may operate in the manner described above. We can then suppose that each small retinotopically defined area consists of a distributed 'domain' (or sheet) with its base in the map and the rest orthogonally located in the adjacent amorphous area, both composed of a mixture of pyramidal cells and INs, into which domain these modules are packed. The multisensory neurons in these columns receive input from more than one sensory modality. The

afferent axons carrying the three unbound inputs could likely be distributed along each vertical (orthogonal) domain. There is also some anatomical evidence for orientation domains in the claustrum. [14C]-2-deoxyglucose uptake during visual exposure to vertical stripes resulted in two dense, wormlike regions of label running in a rostrocaudal direction through the visual zone of the claustrum (Sherk and LeVay, 1981). This may explain the fact, which so impressed Crick and Koch, that each line in the cortex projects to an orthogonally oriented sheet in the claustrum. Thus we propose that this mechanism allows the cortex to 'bind' its sensory input and thus forms the neural correlate of consciousness (NCC) as proposed in the Crick-Koch hypothesis.

Cortical processing of the claustral input:

This hypothesis now needs to be extended to explain how the cortex would integrate the 'binding' information it gets from its claustral input with its own computations, so as to obtain the final products—a fully bound visual field in consciousness and an executive message to the decisions centers for action. In other words we need to explain how the information from the claustrum, 'bound' in the manner described, is processed by the cortex. We know from the work of Schilder and others (Schilder 1942) on the manner in which sight returns following injury to the occipital lobe, that the visual field in consciousness is constructed by a tripartite mechanism. After such an injury, the first aspect of sight to recover is movement perception. In this the subject sees pure motion, usually rotary, without any shape or color. Then 'space' or 'film' colors appear floating about in visual space unattached to any objects. Next, the subjects starts seeing parts of objects, say the handle of a teacup. Lastly these parts join up to form complete objects into which the space colors enter. So activity in the visual field in consciousness can be driven solely by one of these parameters. Their binding into one complete colored, moving object comes later.

The three different visual parameters—color, shape and movement—are initially processed by separate cortical mechanisms. Feed-forward over-lapping projections from these areas to the higher visual cortex synapse on single neurons. These can thus react to stimuli from all three lower centers. One neuron may receive inputs from say a lower 'red' reactive cell, a 'round' receptive cell, and a 'moving to the left' sensitive cell. So it has the necessary information for 'binding' this input into 'a red, round object is moving left'. However, these cells have progressively wider receptive fields the higher in the cortex one goes. Thus these nets may possess the

necessary information for binding, but they have poor, or no, information as to where in the visual field these bindings are located. Perhaps this information is supplied by the claustrum, whose projection to the visual cortex is retinotopically ordered. Our hypothesis suggests that this input supplies, not only the missing location information, but spatio-temporal binding information as well (e.g 'red' and 'moving to the right' go together). So perhaps the claustral projections to layer IV neurons in the higher visual cortex might provide a type of retinotopically ordered 'template' to which the multidomain cells in the higher visual cortex can 'refer' in some way. This 'referral' might be mediated in some way by interaction of some sort between the binding information carried by each system. The claustral input to the cortex will reactivate the neurons that started the cycle, so the re-entry cycle will continue. These cycles may form the NCCs of consciousness and presumably activate the decision-making centers in the brain so that the appropriate behavior results. We will take up this matter again later.

The relevance of information from cortical deafferentation experiments:

Any hypothesis as to the nature of the neural correlates of consciousness (NCCs) needs to account for some recent findings from cortical deafferentation plasticity experiments. There is now evidence to indicate that the modality of a cortical sensory neuron is determined, not by where in the cortex the neuron is located (e.g. the visual versus the auditory cortex), but from where the sensory input to the neuron originates (e.g. the eye or the ear: or, more accurately in that case, the lateral or the medial geniculate nuclei). For example, in experiments on blind subjects skilled in Braille, Ptito et al. (2008) showed that magnetic transcranial stimulation of neurons of loci in the optic cortex results in a somatosensory, and not a visual, experience in these subjects (Ptito et al. 2008). In these cases, some differentiated 'visual' cells are 'taken over' by the somatosensory system, and start to process somatic information instead. This activity generates somatosensory sensations in consciousness (sensations that the fingers are being touched) in place of the normal visual sensations. These authors conclude "Our data show that the qualitative character of the subject's experience is not determined by the area of cortex that is active (cortical dominance), but by the source of input to it (cortical deference)."

Sensory input rerouting (diverting the sensory inflow of one system to the cortex of another system by neonatal diversion of e.g. retinal axons to the auditory

thalamus (cross-modal rewiring)) leads to profound changes on diverse components of cortical circuitry, both at the anatomical and functional levels (Gao and Pallas, 1999; Sharma and Angelucci, 2000). Rerouting visual inputs to the auditory thalamus can also reorganize callosal connections in the auditory cortex, causing both a reduction in their extent and a reorganization of the pattern (Pallas et al. 1999). Sensory input rerouting can also lead to changes in intracolumnar information processing in the post-synaptic neuron. For example, if the input to an auditory neuron is replaced by a visual input, then the response characteristics of information processing in its cortical columns changes so as to mimic the systems employed in a visual neuron. Auditory cortical cells develop visual response properties such as direction selectivity, orientation tuning and simple/complex receptive-field structure (Roe et al., 1992). The auditory cortex also develops retinotopic maps (Roe et al., 1990; and see Linden and Schreiner (2003) for a comprehensive review). Chowdhury and DeAngelis (2008) have extended the range of cortical plasticity by showing, in depths perception discrimination experiments, that the contribution of particular brain areas to task performance can change dramatically as a result of learning new tasks. These changes must be the result of some signaling system in the afferent axons. The nature of this system is not currently known.

The efferent outflow to the claustrum from that part of the deafferented visual cortex, that now performs somatosensory processing (as in the case of the blind subjects skilled in Braille), must enter the claustrum via its medial optic compartment. Here, in spite of being in the 'optic' pathway, it is 'recognized', by the claustrum as carrying, in this case, somatosensory information. How could the claustrum do this? There seem to be two possible answers. The first answer is that the claustrum has a mechanism to recognize the unknown modular specific code carried by the afferent axon. The second answer is simpler. The claustral efferent returns to the same neuron (or neuronal group) that gave rise to the afferent axon. This neuron (or group) is now processing somatosensory information and belongs to the somatosensory system. So the sensation in consciousness that results from this neural cortico-claustral cycling will be a touch on the face, and not a visual sensation. We mentioned earlier that our hypothesis requires only that the efferent outflow from a claustral P cell (or a small group of functionally related P cells) should project mainly to the cortical neurons that activated those claustral cells. This is clearly what is happening in the case of the blind subjects skilled in Braille.

A role for the claustrum in synchronized oscillations:

The {AND gate} system we propose identifies synchronous spikes in axons afferent to the claustrum. If the parent neurons of these axons have synchronous oscillations then the {AND gates} will be fully 'open'. If these neurons are not oscillating the {AND gates} will be less active. If these pairs of neurons have regular, but not synchronous, oscillations the outcome will be more complex. Therefore, the signal returned by these gates to the cortex can also carry the information "A and B are firing in synchrony." In general, synchronized activation of claustral P cells by corticoclaustral afferents will increase the signal-noise ratio of the claustral {AND gates}, and thus lead to a sharpening of claustral binding (for an informative review of the role of noise and noise-abating systems in the brain see Clarke (2012)). Many roles have been proposed for synchronized oscillations in the nervous system, including binding (Uhihaas et al. 2009). In cases of long-range interactions the mechanism for synchronizing the oscillations is usually attributed to corticocortical axons. In such cases, there is considerable variability in the length of these axons. For example, the distance between the caudal somatosensory neurons in the parietal lobe and the rostral visual neurons in the occipital lobe is considerably shorter than the distance between the rostral somatosensory neurons and the caudal visual neurons in these two lobes. In addition, these axons have sinuous paths dictated by the geometry of the cerebral gyri and sulci. In contrast, in the case of corticoclaustral connections, the equivalent pathways, are all approximately equidistant and straight. This is because the claustrum forms a thin curved sheet molded, as it were, under the curved plate of the cortex, and located closer to the center of the hemisphere formed by the cortex (fig. 3). This may have beneficial effects on the accuracy of the timing of synchronicity in the corticoclaustral path.

Another possible role of synchronized oscillations in claustral function:

There is another possible role for synchronized oscillations in claustral function. In a magnetoencephalographic study Emrich et al. (2012) examined the effect on synchronous oscillations in the brain associated with object perception (shape-from-motion) in six normal volunteers. The stimulus was a computer generated 'object' seen against background noise. Each lasted for 4 seconds. During the MOVE epoch, the object and background moved in counter phase, followed by one of two

stationary epochs. In the first—STOP—the motion stopped, and the object remained in the display along with the stationary background noise?. In the second—VANISH—the motion stopped and the object was removed from the display, leaving only the stationary background noise. During the MOVE epoch synchronized gamma oscillations (35-45 Hz) appeared in the right insula, right claustrum, right superior temporal gyrus (RSTG), and right parahippocampal gyrus (RHG). During the STOP epoch the gamma synchronization remained but changed to a higher frequency (55-72 Hz). The authors propose that claustral activity during the MOVE epoch may be related to conscious awareness of the object, and/or motion cues, and/or memory processes: and that claustral activity during the STOP epoch might be related to awareness of the object only (since the object is not moving). However, it could be objected that the absence of movement of a previously moving object carries information just as much as the presence of movement does, and both are recorded in memory processes. Therefore, this experiment may actually be relevant to the binding of form and movement, rather than, or in addition to, the “conscious awareness” of an object. Furthermore, in their analysis, the action of the claustrum during the MOVE epoch involves binding of form and movement, but, during the STOP epoch, there is no binding, since the only input to the claustrum, in their analysis, involves form only. Using an fMRI technique (that provides evidence of activation but not synchronization) Kavounoudias et al. (2007) demonstrated that, in the case of integrating proprioceptive and tactile information resulting in kinesthetic illusions of a clockwise rotation of the right hand, activation of the superior temporal gyrus, the inferior parietal lobe and the claustrum resulted. In an fMRI investigation of color synesthesia activation of the color area V4 resulted (Nunn et al. 2002).

How does our hypothesis explain these findings? Firstly we can note that, Emrich et al. (2012) found that the effect they report does not involve the whole cortex, but only the RSTG and the RHR. This suggests that these two loci have a special importance for object recognition of the type examined in this experiment. The STG contains both auditory and polysensory areas (Smiley and Falchier, 2009; Cappe and Barone, 2005). In particular, it contains visual neurons sensitive to both form and the direction of movement (Oram and Perrett 1996) and projections to the frontal eye fields (Scalaidhe et al. 1997). The RHR contains a higher visual area that processes topographic scenes. The insula has multiple involvements in interoceptive awareness, emotions

and salience.

We suggested earlier that the claustral {AND gates} relay back to the cortex information about the state of synchrony of its inputs from those areas of the cortex: the greater the synchrony, the more effective the signal. This signal may be the effective trigger that synchronizes oscillations of all the neurons belonging to the system. Therefore our account of the function of the cortico-claustral network, that we described above in terms of binding by synchrony detection, may need extension. The network may provide in addition both the neural connectivity needed for its components to align their oscillations in synchrony, and the trigger to promote this synchrony. When the neurons in these areas are not oscillating, traffic through the {AND gates} will have a low signal/noise ratio. As each group starts to oscillate at its own preferred frequency, the target neurons in the claustrum will be bombarded by two spike trains, each one oscillating at its own preferred frequency. This might provide the mechanism, involving the dynamic interaction between cell assemblies, for the oscillations of the efferent targeted claustral neurons to align their frequencies. This alignment might increase with further cycles of the system. So the claustrum may be engaged not only in detecting synchrony, but also in providing the pathways that carry this synchrony, and a mechanism for aligning the frequency of the oscillations. One function of these synchronized oscillations may be to focus and sharpen the binding operation of the {AND gate} functions of the claustrum onto the most salient stimuli at that moment in consciousness. Synchrony propagates through networks (Bruno 2011). The cortico-claustral projection may form a strong fast forward inhibitory system (FFI) as described by Bruno (2011). However, the evidence is currently lacking as to whether cortico-claustral axons provide the needed greater synaptic input to the inhibitory neurons than to the excitatory neurons needed for a strong FFI system.

The role of GABAergic neurons:

Our hypothesis allots a key role to GABAergic interneurons (INs) in the claustrum. The INs in each CDNN are likely to interact with other adjacent GABAergic INs. The latter may modulate activity in the former. In the cortex and the lateral geniculate nucleus GABAergic interneurons have been found to form extensive polysynaptic bidirectional networks linked by electrical junctions (Fukuda et al. 2006). These authors suggest that these networks support “...the precise synchronization of neuronal populations with differing feature preferences thereby providing a temporal frame for the generation of distributed representations.” Such gap junction linked networks

can either promote network synchronization, or trigger rapid network desynchronization, depending on the synaptic input (Vervaeke et al. 2010).

Rahman and Bazier (2007) also note that the claustrum contains a rich variety of neurochemically defined types. Each type is found throughout the entire claustrum, and in all functionally defined divisions. All five types contained mRNAs for glutamic acid decarboxylase 65 and cholecystokinin, whereas only type 5 neurons were somatostatin positive. Kowianski et al. (2009) report the following co-localizations of neuropeptides in the interneurons of the claustrum in rat brain:

- neuropeptide Y with calbindin D28k, calretinin or parvalbumin;
- somatostatin with calbindin D28k;
- vasoactive intestinal polypeptide with calretinin.

A further subdivision of GABAergic interneurons into 5 types (in the lateral amygdala) using electronic and electrogenetic parameters has been described by Sosulina et al. (2010). If this same, or similar, subdivisions are found in the claustrum, this might offer scope for further neurocomputational mechanisms. This detailed arrangement suggested to Rahman and Bazier (2007) that many claustral neurons make extensive inter cell type and interclaustral connections. These connections between the GABAergic network and the INs in the CDNN may serve to allow many modulatory functions as to the fine tuning of the CDNN by neuromodulators, such as norepinephrine and others (Douchette et al. 2010).

Kappa opioid receptors:

An interesting clue may be provided by recent findings concerning the psychoactive drug salvinorin A. This is a specific agonist at kappa opioid receptors. Psychologically it induces an intense sensory synesthesia in which subjects claim that they see sounds and hear sights (Babu et al. 2008; and see Hubbard and Ramachandran (2005) and Baron-Cohen (2008)). This may be interpreted as an inhibition of sensory binding. In our present context it is interesting that activation of the kappa opioid receptor has been shown to inhibit the release of GABA in the bed nucleus of the stria terminalis by a pre-synaptic mechanism (Li et al. 2012). If the same holds in the claustrum, this would provide direct evidence that the GABAergic system in the claustrum is related to sensory binding. The claustrum contains particularly high levels of mRNA for the kappa receptor (Mansour et al. 1993; Meng et al. 1993). The binding of kappa1 opioid-stimulated [35S]GTPgammaS (a marker of the kappa opioid receptor) is also particularly high in the

ventral claustrum (Sim-Selley et al. 1999).

Discussion

In the CDNN system postulated in our hypothesis, the claustrum does not need to process the information content of its afferent input axons. The information it supplies to the cortex is composed of the output of a simple (AND gate) or coincidence detector.

The claustrum has a massive input from all the major neuromodulator circuits (Baizer 2001; Edelstein and Denaro 2004, Das, 2010). The ventral claustrum also has extensive connections with limbic areas such as the anterior cingulate gyrus, amygdala, hippocampus and others. Why would this information, relating largely to emotions, reinforcement and motivation, be required by a system concerned with sensory binding? One answer might be that the claustrum is also involved in binding between limbic operations (emotions, etc.) and the sensory and motor systems. Another answer (not competitive) could be that this neuromodulatory input to the claustrum might be modulating claustral activity in relation to the attentional state of the brain, in which these neuromodulatory circuits play an extensive role. Attention plays a prominent role in binding. Vohn et al. (2007) have shown that the claustrum is involved in within-modal and cross-modal divided attention performance.

Also relevant to the binding problem is the question of "illusory conjunctions" (Triesmann and Schmidt 1982; Crick and Koch 2003). If separate features of an object (e.g. 'red square'/'moving left') are processed in different brain areas (i.e. the color area V4 and the motion area MT), which results in the loss of their topographic location label, and if two objects are simultaneously presented – e.g. a red one moving left and a green one moving right, then how does the brain compute which color goes with which motion? One possibility is that Crick's "searchlight" of attention is directed toward different portions of the visual scene at an early stage of processing when topographical information is still present (e.g. area 17 of the primary visual cortex, or the claustrum). If the spotlight permits 'red' and 'left' to go through, then they will be bound. This explains why, if a red triangle and green square are briefly presented and masked, subjects see illusory conjunctions in 50% of trials. This is because there has been enough time to process the features separately, but not enough time for (in our scheme) claustro-striate iterations to ensure correct binding through attention. Crick and Treisman suggest that that the nucleus reticularis thalami is involved. We

would argue, from the current evidence, that ascending brainstem efferents to the claustrum interacting iteratively with topographically organized area 17 may constitute the searchlight (see also Smythies 1997). Some difference in the motor and sensory functions of the claustrum may be suggested by the observations that the claustral neurons projecting to the contralateral motor cortex are predominantly pyramidal in shape, whereas the predominant claustral neurons projecting to the somatosensory, visual and auditory cortices are mainly oval on shape (Sadowski et al, 1997).

Naghavi et al. (2007) have reported that the claustrum failed to be activated by attentionally-focussed non-congruent stimuli from the same location in external space e.g. the visual stimulus of a cat's face with the contemporaneous auditory stimulus of a dog's bark. They suggest that this indicates that the claustrum must be involved in the "analysis of the content of stimuli". However, it must be noted that the claustrum did not react at all to the cat's face/dog's bark. So it can hardly be said to have extracted the information 'cat' from its visual input, and 'dog' from its auditory input, compared the two, computed that they are incongruent and rejected them from its binding operation. Furthermore, we suggest that the claustrum simply does not have the computational capacity to decipher all the immense flow of information that passes through it. The decision that 'cat' and 'bark' do not go together must have been made in the higher cortex before it activates the claustrum.

So we could suggest that the claustrum does not react in this experiment to 'cat/bark' and 'dog/miow' because these improbable signals have been suppressed upstream. This would be an example of the same sort of mechanism that operates in the experiment reported by Kovács et al. 1996). In this experiment they took two photographs, one of a monkey's face and the second of a leafy tropical jungle. They converted these into two pastiches each composed of portions of each photo, so that in the location where one photo showed part of the monkey's face the other showed leafy jungle. Then each pastiche was shown separately to each retina, so that retinal rivalry occurred. Under these circumstances, the subject did not see what was actually there — that is the two pastiches alternating — but rather a complete monkey face alternating with a complete leafy jungle. Clearly the brain had suppressed the improbable mixed pastiche in favor of what it was familiar with (and thus computed to be more probable). Many other experiments, based on stimuli such as moving plaid patterns, have shown this phenomenon, where the perception of an improbable input is

suppressed by the brain, and replaced with the perception of what it computes to be a more probable one (see Ramachandran and Anstis, 1983).

What functions does the claustrum bind?

So far we have discussed only the original Crick-Koch hypothesis that is based on the idea that the claustrum is involved in binding features of the sensory stimulus. We have suggested that a spike coincidence detector mechanism is involved. However, spike timing codes may carry information in addition to that relating to the properties of the stimulus. Douchette et al. (2010) suggest another account of what information synchronized spikes are carrying. This leads to a wider concept of what the function of the postulated spike coincidence detection mechanism of the claustrum might be. Douchette et al. (2011) studied spike-timing codes in the olfactory system and came up with a challenging result. They report that the number of synchronous spikes (SS) fired by pairs of olfactory bulbar neurons signals, not stimulus properties, but whether the odor is associated with reward or not. The SS fall below the spontaneous activity level for unrewarded odors, and rise above it in the case of rewarded odors. The authors suggest that this is an easily understood and implemented population temporal code, the decoding of which simply requires downstream coincidence detectors, connected to decision-making networks, that take input from both members of the neuron pair. Douchette et al. (2011) then found that the SS rate is modulated by noradrenergic input to the bulb. In this way the SS code can signal the reinforcement significance of the stimulus. Katz and Maier (2011) comment in the same issue of *Neuron* "It is also unclear whether, when coherently firing neurons are studied in larger ensembles, the observable patterns will become more complicated." Katz and Maier conclude, "Thus, these are important, novel data added to a growing corpus suggesting that "sensory" coding is as much about the stimulus in context as what the stimulus physically is." That is to say that the reinforcement significance of most stimuli will be affected by other events happening in the environment. For example, the last meal chosen and eaten by a condemned prisoner will not carry the same reinforcement value that it should.

Perhaps, then, the claustrum could be functioning as such a reinforcement related 'downstream coincidence detector' on a global scale in larger assemblies? In some areas (such as the anterior and part of the ventral claustrum) the spikes impinging on the coincidence detectors in our postulated CDNN may carry information relating to the reinforcement value of the stimulus rather than to the sensory properties of

the stimulus. The function of this might be to provide a metastable network that enables the brain to compute the significance of a stimulus in its complex global context. That is, a stimulus can be signalling reward, or the opposite, depending on its contextual environment—on what surrounds it. In other words the brain must have a global mechanism that needs input from other sensory systems to evaluate the reinforcement significance of a single stimulus presented in a complex environment.

It is possible, therefore, that the claustrum might perform both functions described above—computing binding and computing global reinforcement—at the same time. If it functions by some mechanism akin to the simple CDNN system described in our hypothesis, this system could supply the information it generates to other targets besides the sensory-motor cortex. The claustrum has bidirectional connections with the limbic, temporal and frontal cortices, as well as with the sensory-motor cortex. The dorsal claustrum has connections mainly with sensory and motor cortices, the ventral claustrum has connections mainly with limbic cortex and subcortical structures, and the rostral claustrum projects mainly with frontal cortex (LeVay and Sherk 1981; Sherk 1986). If the function of the claustrum is to detect synchrony between spikes by means of what Douchette et al. (2011) call a “downstream coincidence detector” acting on a “simple population temporal code”, its subdivisions could export the results to more than one target. The anterior dorsal, posterior dorsal and part of the ventral subdivisions could be concerned with sensory-motor binding. The anterior and another part of the ventral subdivisions could be concerned with reinforcement and other limbic functions. Thus the claustrum could cooperate with the sensory cortex for sensory binding, with the limbic system for emotional coordination to allow modulation of behavior by complex patterns of reinforcement, and with the decision-making mechanisms in the prefrontal cortex to coordinate ‘higher brain’ functions (in response in each case to specific inputs from these different loci).

Recent research suggests that what some of these ‘higher brain functions’ may be. Volz et al. (2010) carried out fMRI studies of retrieval fluency in normal subjects. This is defined as how long it takes to retrieve a trace from long-term memory. If one of two objects is retrieved more quickly this indicates that that one has a higher value than the other. This measure was accompanied by another that assessed the emotional feeling in the subject of the ‘rightness’ of that memory (a feeling-of-knowing judgment). The authors suggest that a number of brain processes could contribute to these measures including “...the

ease with which such memories are bound together”. Their results were that these procedures were associated with activation of the dorsal claustrum, but not the ventromedial prefrontal cortex. The authors suggest that their findings indicate that the claustrum may also bind semantic and emotional information in addition to sensory information. Tian et al. (2011) have investigated another possible function in which the claustrum may play a role—the mental preparation of successful insight problem solving (that is the “Aha” experience as exemplified by Archimedes). Using fMRI they showed that successful preparation coding was associated with activation of a circuit that included the parts of the frontal and temporal cortices, the cerebellum and the bilateral claustrum. The postulated claustral CDNN mechanism may be plugged in to a number of different neural circuits engaged in different distributed computations. The claustrum is also engaged in the rapid interhemispheric of information needed for the bilateral coordination of movement regulation (Smith and Alloway 2010). The {AND gate} mechanism we propose might effect this by ‘binding’ information from two inputs, one from each ipsilateral motor system.

Advantages of the hypothesis:

The advantages of our hypothesis seem to us to be:

- its simplicity of action. It does not need any complex mechanisms such as axonal spike time pattern analysis,

- its low neurocomputational cost. The claustrum is not concerned with the informational content of the spike trains fed into it, only with their timing.

- it accounts for how one simple piece of mechanism can exert functions that affects many ‘higher’ brain functions.

- the fact that it uses two principles well established in neuroscience—the multiple use of a simple net to perform complex computations, and the use of conjoint inhibition.

- the fact that it may explain such data such as the line-plane cortico-claustral projection, the need for retinotropic and somatosensory maps in the claustrum, and the deafferentation plasticity data.

- it gives a key role to the GABAergic interneuron system in claustral function.

- it allows for more accurate judgments of the presence of synchronized oscillations between groups of neurons located in different lobes in the cortex.

We feel that we should mention that we have carried an extensive exploration of other possible hypotheses, in relation to the ‘binding’ function of the claustrum, based on other fixed nerve net systems, spike train spatio-temporal codes, and non-linear dynamics, but

failed to develop any promising candidates in those fields.

Problems with the hypothesis?

Only about 10% of neurons in the claustrum are INs (Rahman and Biazar 2007; Kowianski et al. 2008). This compares with a 20-25% rate in the cerebral cortex (Druga 2009). In our model there are two INs for every P cell. Do we have to modify our model to account for this fact? Perhaps not. In mouse frontal cortex Fino and Youste (2011) report dense connectivity of GABAergic somatostatin-positive INs. They found that every IN was connected to every pyramidal cell within the range of its axonal tree. They say, "In fact, the complete connectivity that we observe appears in some cases deterministic, as if the circuit has been built to ensure that every interneuron is connected to every single local PC cell... in this way neighboring neurons would have overlapping but not identical connectivity patterns." If this applies also to INs in the claustrum, then a 1-10 IN/P cell might be ample to ensure that no P cell was left unprotected from noise. It seems doubtful if any P neurons could function efficiently without any form of noise protection. Some other factors may be relevant. The INs in the {AND gates} are linked to each other via the GABAergic gap-linked syncytium. This may allow rapid movements of electrolytes and current between them and possibly lessen the number of INs needed to work the system. Electrical synapses between interneurons have been reported to contribute to synchronized firing and network oscillations in the brain (Vervaeke et al. 2010). Other mechanisms for noise reduction may be operative (see for example Kleene 1997; Middleton et al. 2007). In the bushy cells of the cochlear nucleus Chanda and Xu-Friedman (2010) have shown that the activation of GABAergic receptors adjust the function of these cells by suppressing the relaying of individual inputs and requiring the coincident activity of multiple inputs. If this same system operates in the claustrum, this might provide a powerful mechanism for GABAergic receptors to increase the signal-noise ratio of the operation of its {AND gates}.

Conclusion

This paper presents a specific hypothesis on the mechanism of action of the claustrum. We propose that it consists of a large number of simple coincidence detectors (inhibition modulated {AND gates}) that detect and react to the temporal coincidence between impulses in selective input axons, and conveys this 'binding' information back to the cortex. This activity repeats as a series of

cortico-claustral-cortical cycles. The information contained in these selective inputs may relate to the properties of the sensory input in the case of the dorsal claustrum. In the case of the ventral claustrum the information may relate to the reinforcement value of stimuli and other higher brain functions of the claustrum. These cycles may function as the neural correlates of consciousness. We also suggest a mechanism by which the cortex incorporates the information fed into it by the claustrum. This involves supplying the higher visual cortex with a retinotopic map that it lacks, and supplying it with additional binding information. The net we describe may also be involved in mediating transient synchronous oscillations between the neuronal groups it connects. The fine details of the mode of operation of any actual noise-protected {AND gate} is very likely to be more complex than the simple model we have outlined. Therefore we will express our basic element hypothesis in the following manner—the binding function of the claustrum exerts may be by means of arrays of noise-protected [AND gates} that respond to the reception of simultaneous impulses in the afferent axons they are monitoring in the macro-manner we have outlined. The micro-details of the mode of operation of the gate remain to be determined. This gate may also modulate synchronized oscillations in the manner described.

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Acknowledgement(s)

We are grateful to Elizabeth Seckel for her aid in preparing the figures.

Illustrations

Illustration 1

Figure 1. A diagram of the proposed GABA-modulated 'AND gate' (two input). P: pyramidal cell, IN: GABAergic interneuron. C: input from color center of cortex. M: input from movement center of brain.

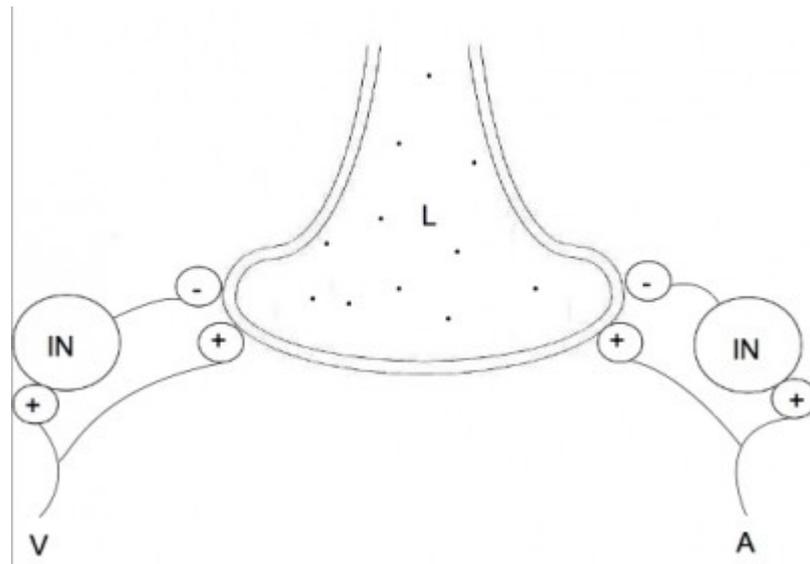


Illustration 2

Figure 2. A diagram of the proposed grid net for cortico-claustral connections. In this instance the arrangement for two different cortical sensory modules (V visual; S somatic) is shown. The same arrangement applies for submodules in the visual cortex. Traffic is bidirectional.

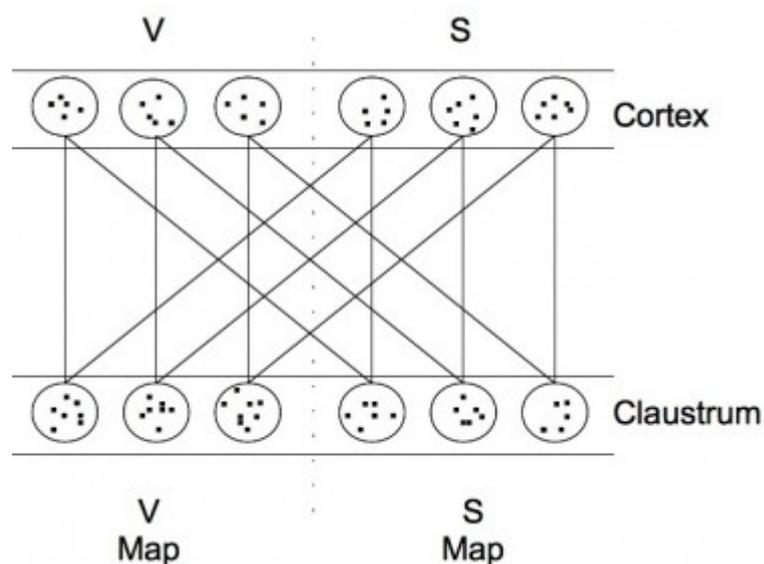
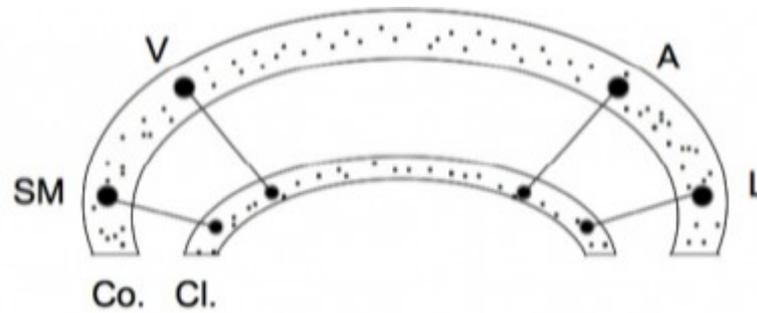


Illustration 3

Figure 3. A diagram of the axonal connections between the sensory and limbic cortices, and their correlated regions of the claustrum.



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