Does the claustrum have a function? Lessons from human lesion and animal studies point to divergent multifunctionality

Huriye Atilgan^{*1}, Max Doody^{*1}, David K. Oliver^{*1}, Thomas M. McGrath¹, Andrew M.
Shelton¹, Irene Echeverria-Altuna², Irene Tracey³, Vladyslav V. Vyazovskiy¹, Sanjay G.
Manohar⁴, Adam M. Packer¹

¹Department of Physiology, Anatomy, and Genetics, University of Oxford, Oxford, UK

²Department of Experimental Psychology, University of Oxford, Oxford, UK

³Wellcome Centre for Integrative Neuroimaging, FMRIB Centre, Nuffield Department of
Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU,
United Kingdom

⁴Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

* Authors contributed equally to this work

Address for correspondence:

Adam Packer: adampacker@gmail.com

tel. +44 (0)1865272180

Abstract

The claustrum is the most densely interconnected region in the human brain. Despite the accumulating data from clinical and experimental studies, the functional role(s) of the claustrum remain unknown. Here, we systematically review claustrum lesion studies and discuss their functional implications. Claustral lesions are associated with an array of signs and symptoms, including changes in cognitive, perceptual and motor abilities; electrical activity; mental state; and sleep. The wide range of symptoms observed following claustral lesions suggests that the claustrum may either have a number of distinct functions, or a global function that impacts many neural processes. We further discuss the implications of these lesions in the context of recent evidence linking the claustrum to sensory perception, sleep, and salience as well as highlighting an underexplored link between the claustrum and pain. We hypothesize that the claustrum is connected to multiple brain networks, both ancient and advanced, which underly fundamental functions as well as higher cognitive processes. Extensive evidence derived from human lesion studies and animal experiments provides unequivocal evidence for a key function of the claustrum as a multifunctional node in numerous networks.

Introduction

The claustrum is a sheet-like bilateral brain region tucked beneath the insular cortex (Figure 1). Extensive anatomical work across different species, including humans, monkeys, rodents, reptiles, rabbits, and cats indicates widespread connectivity between the claustrum and the neocortex (Atlan et al., 2017, 2018; Carman et al., 1964; Goll et al., 2015; Hoover & Vertes, 2007; Jackson et al., 2018; Narikiyo et al., 2020; Sadowski et al., 1997; Helen Sherk, 1986; Tanné-Gariépy et al., 2002; Vertes, 2004; Wang et al., 2017; White et al., 2018; Zingg et al., 2014, 2018) and highlights the need for a more thorough investigation of the claustrum's circuitry. Strong reciprocal connectivity with most neocortical areas is perhaps the most noteworthy feature of the claustrum (Atlan et al., 2018; Crick & Koch, 2005; Narikiyo et al., 2020; Helen Sherk, 1986; Tanné-Gariépy et al., 2002; Zingg et al., 2014, 2018), which has the highest connectivity in the human brain by regional volume (Torgerson et al., 2015). Recent work has shown corticoclaustral and claustrrocortical connections evoke feedforward inhibition in mice (Jackson et al., 2018; J. Kim et al., 2016) similar to previous results in cats (Cortimiglia et al., 1991; Salerno et al., 1984, 1989; Tsumoto & Suda, 1982). While the anatomy, physiology, and putative functions of the claustrum have been reviewed elsewhere (S. P. Brown et al., 2017; Crick & Koch, 2005; Dillingham et al., 2017; Goll et al., 2015; Jackson et al., 2020; Mathur, 2014; Patru & Reser, 2015) this review seeks to untangle and shed new light on the functional role(s) of the claustrum.

Figure 1. The location and connectivity of the claustrum. (a) Nissl stained human coronal brain section with inset showing the location of the claustrum. (b) White matter tractography image showing outgoing connections from the claustrum adapted from Torgerson et al. 2015. (c) Mouse coronal brain section with inset showing the claustrum labelled by multi colour retrograde tracers. (d) Schematic illustration of a sagittal mouse brain section showing the relative connectivity strength between the claustrum and other brain regions. Connectivity strength was assessed based on the data provided in Zingg et al., 2018 and Wang et al. 2017. Most but not all connections are reciprocal (see reviews Mathur 2014 and Jackson et al., 2020). Abbreviations used: anterior cingulate area (ACA), anterior insular cortex (AI), auditory cortex (Aud), anterior olfactory nucleus (AON), basal forebrain (BF), claustrum (CLA), dorsal raphe (DR), entorhinal cortex (ENTI), infralimbic area (ILA), locus coeruleus (LC), motor cortex (MO), the nucleus of the lateral olfactory tract (LOT), orbital area (ORB), prelimbic area (PL), parietal cortex (PTL), piriform area (PIR), retrosplenial cortex (RSP), supramammillary (SUMI), somatosensory cortex (SS), dorsal taenia tecta (TTd), ventral tegmental area/substantia nigra (VTA/SNc), visual cortex (VIS).

Understanding the anatomy and connectivity of a brain region can provide important insights into its function. Attempts to find classic structure-function relationships are challenging in highly connected brain regions where many functions are possible due to multiple coexisting pathways. In the case of the claustrum, such widespread connectivity has led to a plethora of hypotheses regarding its function. The claustrum has been implicated in processes including the amplification of cortical oscillations (Smythies et al., 2012, 2014), attentional allocation (Atlan et al., 2018; Fodouliau et al., 2020; Goll et al., 2015; Mathur, 2014), consciousness (Koubeissi et al., 2014), cognition (Jackson et al., 2018), spatial navigation (Jankowski & O'Mara, 2015), the transfer of information across sensory modalities (Hadjikhani & Roland, 1998), sexual function (Redouté et al., 2000), and aesthetic judgement (Ishizu & Zeki, 2013).

An alternate way to investigate the role(s) of a brain region is to ask: “What happens after a lesion?” The lesion approach, including both acute and chronic interventions, has been immensely powerful in localising language, episodic memory, and even aspects of executive function in both human and animal studies (Adolphs, 2016; Wolff & Ölveczky, 2018). Loss of function approaches — when they work — enable subsequent neural activity recordings to focus on stimuli or behaviours implicated by the lost functions. Moreover, lesion studies can help reveal a region’s functional connectivity. However, the claustrum’s contorted shape and bilateral location deep in the brain renders this approach difficult. To date, there are no reports of a complete and selective claustrum knock-out in any species.

While the claustrum’s anatomy renders lesion studies challenging, examples of claustrum lesions exist within the literature. To our knowledge no review has comprehensively assessed clinical studies of human claustrum lesions. In this review, we present a meta-analysis of all studies to date that describe cases of claustrum lesions in human patients. Using these findings, in conjunction with animal studies, we consolidate evidence concerning the claustrum’s role

in sensory perception, pain, sleep, and salience. We hypothesise that the claustrum is an integral part of many different networks. We propose that the brain-wide connectivity of the claustrum may have provided a useful scaffold onto which many functional roles could subsequently be built. This may explain the apparent role of the claustrum in fundamental functions such as sleep, as well as in more evolutionarily advanced functions such as attention and salience. We argue that the claustrum is likely a multifunctional area perhaps because of its global function to regulate neural activity dynamics across the cerebral mantle. Under this schema, damage to the claustrum would disrupt diverse neurological and behavioural processes.

Diverse findings following lesion or stimulation of the human claustrum

The potential functions of the claustrum have not been comprehensively analysed by examining human lesion studies because of the relative scarcity of claustral lesions (the only reported work focused specifically on delusional states (Patru & Reser, 2015)). To tackle this, we examined claustrum lesion cases by searching the following terms on PubMed and Scopus: “claustrum AND (lesion OR contusion OR injury OR trauma)” (n = 103). Studies were then screened for cases in which reported lesions included the claustrum according to neuroimaging. Thirty-eight individual cases and fourteen cohort studies were included in this review. Details of these studies can be found in the Appendix.

Due to the claustrum’s nestled location, vascularisation, and morphology, *isolated* claustrum lesions are rare, and predominantly occur in the spectrum of autoimmune encephalitis. Unfortunately, available clinical imaging techniques lack sufficient resolution to conclusively resolve the claustrum from the external capsule. Studies that reported lesions to the claustrum

and external capsule (Figure 2B), the external capsule only (Figure 2C), and the claustrum only (Figure 2D) reveal strikingly similar imaging results. Given this diversity in the reporting of lesions, it is difficult to distinguish truly claustrum specific lesions from those which may impact both the claustrum and adjacent white matter. Disambiguating what caused the lesion can help. For example, autoimmune encephalitis might be caused by antineuronal surface antibodies that have a predilection to epitopes on the claustrum, such as VGKCA and anti-GAD (Malter et al., 2010). On the other hand, pathologies that affect white matter such as vasogenic oedema and demyelination might have a predilection for external and extreme capsules. Thus, the diagnosis offers an important clue to claustrum involvement, despite the imaging in these cases being identical. Nonetheless, the lack of isolated claustrum lesions means lesion studies are inherently problematic. It is therefore difficult to attribute particular functional role(s) to the claustrum based on lesions alone.

Figure 2. Similar lesions have been described as affecting either the claustrum, the external capsule, or both. (a) Representative T2-weighted image of a healthy human brain. (b) T2-weighted image showing a lesion reported as affecting the claustrum and external capsule, (c) FLAIR image showing a lesion reported as affecting the external capsule. (d) T2-weighted image showing a lesion reported as affecting the claustrum. (e) T2-weighted image (top) and T1-weighted image (bottom) showing a lesion reported as affecting the claustrum. Images adapted from (b) Sperner et al. 1996, (c) Mumoli et al. 2014, (d) Ishii et al. 2011, and (e) Silva et al. 2018.

Despite this difficulty, seven case studies have been identified which report relatively exclusive lesions in the claustrum with or without involvement of the external capsule. Four of these patients presented with status epilepticus and were found to have bilateral lesions

affecting the claustrum and external capsule. The four patients also had EEG abnormalities along with a variety of other symptoms including seizures, motor impairment, cognitive impairment, psychotic symptoms, and tremor (Ishii et al., 2011; Mumoli et al., 2014; Silva et al., 2018; Sperner et al., 1996). Another patient with abnormalities in the right claustrum and bilateral external capsule experienced non-epileptiform EEG abnormalities, along with motor and cognitive impairment (Hwang et al., 2014). A 55-year-old patient with an isolated left claustrum lesion following an ischaemic stroke experienced unilateral paraesthesia of the face, tongue, and head — similar to a lacunar syndrome — along with polymodal gustatory, auditory, vestibular, and visual disturbances (Maximov et al., 2018). Recently, a patient admitted to hospital with Covid-19 showed bilateral lesions to the claustrum and external capsule. He presented with aggression, cognitive impairment, disorientation, and stupor. Upon follow-up, the claustrum lesions remained despite a complete neuropsychiatric recovery (Zuhorn et al., 2020). For further details of these cases, see appendix table 1.

While the underlying cause of the claustrum damage was not always clear, the various authors suspected a range of etiologies including viral encephalitis, ischemic stroke, and seizure induced damage. Despite the similar and isolated brain abnormalities, the patients presented with a wide and inconsistent array of signs and symptoms. While difficult to interpret, these diverse cases do not point to any single hypothesis of claustrum function. Conversely, these results suggest the claustrum may instead have multiple roles.

Beyond these studies, many others have reported lesions to the claustrum in conjunction with other brain regions. Other areas commonly included the external capsule (14/38) and insula (12/38), between which the claustrum is interposed, and the hippocampus (9/38). In particular, presumed viral and non-viral encephalitides may cause relatively claustrum-specific changes

on MRI neuroimaging, sometimes in conjunction with hippocampal damage. Like the studies with the isolated claustrum lesions, these less specific lesion studies also reported a wide variety of symptoms (Table 1). The most common signs and symptoms in individual cases were nonspecific cognitive impairment (19/38), seizures (18/38), motor impairment (17/38), visual disturbances (9/38), non-seizure EEG abnormalities (8/38), loss of consciousness (8/38), speech problems (8/38), auditory disturbances (6/38), sleep disturbances (6/38), delusions (5/38), tremor (5/38), and hallucinations (4/38). We separated these observations into the following four categories: disruption in cognitive, perceptual and motor abilities; changes in electrical activities; changes in mental state; and sleep disturbance.

Table 1: Lesioned area, symptoms, and seizures reported in case studies with claustrum lesions.

Hemispheric distribution	Bilateral	22
	Unilateral (Right / Left / Undefined)	16 (9/5/2)
Extent of lesion	Clastrum-only	7
	External capsule	14
	Insula	12
	Hippocampus	9
	Other cortices	17
	Other sub-cortices	22
Signs and symptoms	Cognitive, perceptual & motor abilities	
	<i>Cognitive impairment</i>	19
	<i>Motor disturbance</i>	17
	<i>Visual disturbances</i>	9
	<i>Speech disturbances</i>	8
	<i>Auditory disturbances</i>	6
	<i>Tremor</i>	5
	<i>Paresthesia</i>	5
	Electrical activity disturbance	
	<i>Seizures</i>	18
	<i>Non-seizure EEG abnormalities</i>	8
	Mental State	
	<i>Loss of consciousness</i>	8
	<i>Hallucinations</i>	4
	<i>Delusions (Cotard delusion)</i>	5 (2)
	Sleep disturbances	6
Seizure type (patients may fit >1 severities)	1) Partial	7
	2) Generalised	15
	3) Status epilepticus	13
	4) Refractory status epilepticus	10

Claustral lesions impair cognitive, perceptual, and motor abilities

Patients with claustrum lesions were frequently reported to have perceptual and cognitive impairments. In many cases, the lesions impacted patients' ability to perceive sensory input in various ways. For example, a twelve-year-old experienced temporary loss of vision and hearing

(Sperner et al., 1996). Interestingly, another young child experienced permanent bilateral blindness due to damage to the left calcarine cortex and right claustrum, although the most parsimonious explanation for this finding is undetected damage to the right optic radiation (Albayrak & Gorgulu, 2008). In some cases, lower perceptual sensitivity (Randerath et al., 2018), and tinnitus (Matsuzono et al., 2013) were reported. Cases presumed to be driven by encephalitis often presented with deficits in episodic memory (Hiraga et al., 2014; Hwang et al., 2014; Shintaku et al., 2010), working memory, and reasoning or with disorientation in time (Chessa et al., 2017). Claustrum damage has even been described as part of neurodegenerative syndromes such as corticobasal degeneration, where it may be accompanied by disruption in visual attention functions including spatial orientation, optic ataxia (Jellinger et al., 2011), and cognitive decline in Lewy body dementia (Yoshimura et al., 1988). Left claustrum damage can lead to aphasia when accompanied by left putamen damage (Seghier et al., 2014). Despite the varied pathologies, lesion sites, and inconsistent observations across studies, each patient experienced disturbance to some aspect of their cognitive and perceptual abilities.

Clastrum lesions result in an increased incidence of electrical disturbances

Patients with claustral lesions often experienced disturbances to the electrical activity of the brain, involving generalised seizures (15/38) and status epilepticus (5 minutes of constant seizures without any return to consciousness in between, 13/38). Generalised seizures were more common when the claustrum was damaged bilaterally (10/15 studies). Several studies (Matsuzono et al., 2013; Sperner et al., 1996) reported that patients with claustral lesions developed recurrent generalised seizures, with interictal slowing (3-4 Hz) on EEG. Patients who also had claustrum-associated focal seizures reported experiencing delusions and altered mental state (discussed below), which was coupled with pathological EEG slow-wave activity (Turkalj et al., 2012). Unfortunately, the majority of the case studies reporting generalised

seizures do not report EEG recordings. The studies that did include EEG recordings typically reported generalised slow-wave activity present even in the awake state. A few of these also described generalised spikes or sharp waves (Lapenta et al., 2015; Sperner et al., 1996).

Strikingly, several patients with claustrum lesions exhibited a form of severe epilepsy (10/38) known as refractory status epilepticus. Refractory status epilepticus is a subset of these cases that fail to respond to the two frontline pharmacological treatments for seizures (benzodiazepines and one anticonvulsant) (Singh et al., 2014). Studies examining new-onset refractory status epilepticus reported lesions in the claustrum as a common pathology, concomitant with slow-wave activity, spikes and sharp waves, and periodic lateralized epileptiform discharges in EEG recordings (Choi et al., 2019; Meletti et al., 2015, 2017). Taken together, these studies suggest that claustrum dysfunction increases global synchronization of the electrical activity of the brain, and potentially leads to seizures.

Claustral lesions disturb mental state

Several studies noted altered mental states in patients with claustrum lesions even in non-medicated patients. These included non-seizure loss of consciousness, confusion, stupor, delusions, hallucinations, as well as other mild fluctuations in mental state. Loss of consciousness (LOC), defined here as an interruption in one's awareness of the self and the environment, was reported in 8 of 38 case studies. Similarly, a study of combat veterans with penetrating traumatic brain injuries reported that patients with lesions to the claustrum showed an increased duration but not frequency of LOC relative to patients with lesions in other locations (Chau et al., 2015). Recent lesion mapping has uncovered a distributed circuit associated with LOC which peaks in the bilateral claustrum (Snider et al., 2020). These findings

suggest that the claustrum may be necessary to support some aspects of maintaining one's level of consciousness. An alternative explanation is that these processes generate "selfhood", the mental representation of a distinct first person capable of agency, a role which has been associated with the nearby anterior insula (Sleigh et al., 2018) but might be extended to parts of the claustrum.

Altered mental states were reported across many claustrum lesion case studies. While some patients manifested broadly altered mental states including anhedonia, delirium, or confusion (Choi et al., 2019; Meletti et al., 2015), some had narrower neuropsychiatric features such as delusions with paranoid or religious content (McMurtray et al., 2014; Turkalj et al., 2012), visual hallucinations, and abulia (Shintani et al., 2000). One patient with claustral dysfunction attributed to COVID-19 exhibited 'delirious behavior' (Zuhorn et al., 2020). Even more specific features included delusions of jealousy (Chakraborty et al., 2014). The high frequency of visual and auditory hallucinations, confusion, and delusional states has previously been identified and discussed at length by Patru & Reser (2015). They argue persuasively that the claustrum is involved in the process of generating and filtering delusional beliefs (described later).

Intriguingly, claustrum dysfunction may also be linked to Cotard delusion. Patients experiencing Cotard delusion may believe that they are dead, do not exist, are decaying, or have lost internal organs (Grover et al., 2014). Intriguingly, two patients described above with claustrum lesions experienced symptoms consistent with Cotard delusion (McKay & Cipolotti, 2007; McMurtray et al., 2014). As only a few hundred instances of Cotard delusions are known worldwide, the finding that one confirmed case of Cotard delusion and another patient with highly overlapping symptoms arose from pathology involving the claustrum is highly

suggestive of an association and perhaps a disconnection with ‘self’. Although most reported cases of Cotard delusion do not include claustrum lesions (Bott et al., 2016; Debruyne et al., 2009; Kudlur et al., 2007) the claustrum was the only area of overlap between the two cases described. These examples of altered mental states following claustrum lesions suggest that the claustrum may be required to organise and integrate cognitive representations such as beliefs and desires.

Claustral lesions disturb sleep

Sleep disturbances were commonly observed in patients with claustrum lesions, usually with other symptoms present. Some studies reported hypersomnia along with altered mental state (Meletti et al., 2015; Shintani et al., 2000) while others reported restlessness along with motor disturbance (Yoshimura et al., 1988). It is unclear whether these sleep disturbances occurred as a direct result of the claustrum lesions themselves, patients’ medications, or damage to other brain structures. Additionally, these studies did not assess the polysomnographic features of the sleep disturbances or provide a systematic investigation of sleep. No details were reported about whether patients had difficulty initiating and/or maintaining sleep. Recently, a genome-wide analysis suggested a link between insomnia and a disruption in claustrum-hypothalamus-striatum circuitry (Jansen et al., 2019), pointing to the role of these areas in sleep initiation. Another mechanism by which circuit-level abnormalities might affect a patient's sleep-wake cycle is through a disturbance in waking resting-state functional connectivity in the default mode network (Lunsford-Avery et al., 2020). Although evidence points to an important functional role of the claustrum in sleep control, lesion studies are too limited to provide conclusive evidence.

Human claustrum stimulation

Like lesion studies, brain stimulation studies can provide strong evidence linking a given region to specific functional roles. The usefulness of stimulation studies is, however, limited by the possibility that observed effects result from excitation or inhibition of brain regions downstream of the region being stimulated (Bota et al., 2015). This caveat is particularly noteworthy when considering the claustrum given its widespread connectivity throughout the brain. Additionally, due to the small volume of the claustrum, stimulation will almost certainly result in depolarization of neurons in nearby tissue.

A recent study by Bickel & Parvizi (2019) obtained claustral stimulation data from five patients with pharmacologically resistant epilepsy, whose implanted electrodes partially overlapped with the claustrum. Four of the five patients experienced changes in somatosensation including ‘a strange skin sensation from the face running down to the leg’; ‘a sense of pressure in the mouth’; ‘sensation around the left knee’; ‘hot flashes’; and ‘acid-like sensation in the throat’. However, none of them reported changes in their awareness of the situation and their surroundings. In 2014, Koubeissi et al. reported that a patient with intractable epilepsy suffered a reversible disruption of consciousness after an electrode near the claustrum was stimulated. However, a few caveats apply to this finding. First, the electrode was located in the extreme capsule, near, but not within the claustrum. Second, the patient had previously undergone an ipsilateral temporal lobectomy which may have functional implications. Third, the current applied by Koubeissi was greater in both magnitude and duration than in the Bickel and Parvizi study (Bickel & Parvizi, 2019). This may have caused widespread blanket depolarisation of claustralcortical neurons, producing cortical inhibition (Jackson et al., 2018), that subsequently disrupted normal information processes.

The signs and symptoms of claustrum dysfunction caused by claustrum lesions and claustrum stimulation vary based on the pathologies and lesion/stimulation sites. Each patient experienced some aspect of disturbance in cognitive function, perceptual abilities, mental state, electrical activity, or sleep. The great variance in these symptoms suggests a structure with diverse functional roles. Remarkably, and in stark contrast to this conclusion, patients with well-delineated surgical removal of unilateral claustra for low-grade cerebral glioma had no observed long-term sensorimotor or cognitive impairment (Duffau et al., 2007). The functional role of the unilateral claustrum might be efficiently compensated by neural plasticity of the intact claustrum, explaining why these patients did not suffer any permanent cognitive-perceptual impairments. These studies suggest that due to its involvement in multiple functionally-compensated dynamic neural networks the claustrum is involved in numerous neural processes including both high-level cognitive processes as well as more fundamental processes.

Multifaceted roles of the claustrum

The results described above present the most comprehensive survey of claustrum lesions to date. Paradoxically, the most consistent feature of these claustrum lesion studies is their inconsistency. The diverse and overlapping array of clinical pathologies reported in these lesion and stimulation studies suggests that the claustrum may have either multiple functional roles or a global role. The task of attempting to draw functional conclusions from this rich and varied data is further complicated by limited and inconsistent investigational practices across human studies.

We hypothesise the widespread connectivity substrate provided by the claustrum may have been initially developed for evolutionarily ancient and fundamental homeostatic functions such as sleep and pain. Later, it became a useful framework or scaffold upon which more advanced cognitive abilities could be built as they developed over evolutionary timescales. For example, in order to generate a sleep state throughout the brain, brain-wide connectivity could be useful. Such brain-wide connectivity could then be co-opted by evolutionary pressure, taking advantage of the existing substrate in order to generate additional functionality such as salience processing that might rely on multimodal integration, for which such connectivity is particularly useful. In this way, the modern mammalian claustrum could come to play a role in numerous different behavioural processes.

In the sections below we will look more deeply into certain functional hypotheses in light of the lesion studies and propose avenues for future exploration. We briefly outline the claustrum's involvement in neural correlates of sensory processing before discussing a putative link between the insula, claustrum and pain. Next, we review the claustrum's involvement in sleep based on recent animal studies. Finally, we focus on the claustrum's role in salience as a global process that impacts many aspects of brain function.

Sensory perception

Lesion studies detailing sensory and perceptual abnormalities are suggestive of a functional role for the claustrum in sensory processing. These observations are consistent with anatomical and physiological findings in basic research. Connectivity studies have shown strong claustricocortical projections to sensory cortices and minimal corticoclaustral input from primary sensory areas (Carey & Neal, 1986; Wang et al., 2017; Zingg et al., 2018). Physiological studies have revealed somatotopic responses, retinotopic responses, and direct

responses to auditory stimuli within the claustrum (Clarey & Irvine, 1986; LeVay & Sherk, 1981; Olson & Graybiel, 1980). This anatomical connectivity, when considered in conjunction with single neuron recordings, led to the hypothesis that the claustrum is well-positioned to play a key role in multisensory integration (Crick & Koch, 2005; Smythies et al., 2012). However, individual claustrum neurons have been shown to respond predominantly to one sensory modality (Remedios et al., 2010) without any preference for the properties of the stimulus (i.e. no differences between vocalisations versus environmental sounds (Remedios et al., 2014)). These contrary findings might be partially resolved by data showing that claustrum neurons responded to *changes* in the sensory input (Remedios et al., 2014) and responded to the novelty of stimuli pairs (Reus-Garcia et al., 2021). This hints that the claustrum does not encode the physical properties of the sensory stimuli but may instead shape sensory perception. This is supported by an early animal study showing that a claustrum lesion impacted the way primary visual cortex encoded a visual feature (H Sherk & LeVay, 1983), and by more recent theories that the claustrum may reduce noise in sensory cortices (Atlan et al., 2018; Jackson et al., 2020).

The link to sensory processing is suggested by several lesion patients experiencing hallucinations and other delusions (as reviewed in-depth by Patru and Reser (Patru & Reser, 2015)). In that review, the authors argue that the claustrum is poised to act as a common centre for delusional states. They theorize how the claustrum may be involved in common models of delusion such as the glutamate/dopamine model, K-opioid receptor model, and models based on deficits in attention, sensory-gating, salience processing, and prediction. It is, however, important to note that these claustrum-related mechanisms of delusion may be directly related to the sensory abnormalities described in the lesion section.

As reported above, claustrum lesions can lead to sensory effects in multiple sensory domains, suggesting that the claustrum may either be involved in multiple parallel processes or play a more global role in sensory information processing. While it is possible that the claustrum plays a role in generating sensory perception, physiological evidence more strongly suggests a nuanced role in shaping the transition from raw sensory input to perceived output as reviewed elsewhere in detail (Mathur, 2014). Further basic research is critical to understand how the claustrum shapes sensory perception.

Pain

The lesion studies outlined above raise the intriguing possibility that the claustrum may play a role in pain perception. In the 1950s, two separate studies described patients with unilateral lesions to the claustrum, among other regions, who experienced painful sensations of hot and/or cold and presented with depression and suicidal ideation (Biemond, 1956; Obrador et al., 1957). More recently, a participant receiving claustrum stimulation reported painful sensations “like a knife jabbing” and of “burning” during claustrum stimulation (Bickel & Parvizi, 2019). This is noteworthy as brain stimulation rarely produces painful sensations, although when it does it has often been reported following stimulation of a region surrounding the posterior insula and claustrum (Mazzola et al., 2012). While these are isolated examples, numerous studies have hinted at a connection between the claustrum and pain. However, this possibility has received comparatively less attention than other brain areas.

Pain is a multifaceted sensation, involving both sensory and affective dimensions. Acutely painful sensations activate, in a flexibly accessible manner, a bilateral and widely distributed network of brain regions. These include a core set of regions, such as the thalamus, insula,

brainstem, secondary somatosensory, mid- and anterior-cingulate, and prefrontal cortices (Figure 3A, Tracey & Mantyh, 2007; Wager et al., 2013; A. Xu et al., 2020). Pain-related activity in the claustrum, which is closely connected with many of these brain regions, may be obscured by activity in the nearby insula, falsely attributed to the claustrum when genuinely within the insula, or, if in both, attributed to one or the other.

Figure 3b illustrates the classification results for physical pain within a region of the posterior insula (Wager et al., 2013). It is clear that the extent of activity from the various studies that have contributed to this map might overlap with the adjacent claustrum. Going forwards, opportunities with ultra-high field imaging, such as 7 Tesla MRI, with improved signal-to-noise, spatial resolution, and contrast effects are already illustrating for various studies, including pain, the potential it offers for better spatial discrimination between adjacent brain regions or nuclei (Faull et al., eLife 2016; Schulz et al., 2020). It will be important for future studies to better delineate the precise roles of the claustrum and divisions of the insula, as well as their interactions, in pain. Recent advances in rodent imaging now also enable further isolation of claustral and insular activity (Krimmel, Qadir, et al., 2019; Krimmel, White, et al., 2019). Notably, the insula has been identified as a potential deep brain stimulation target for treatment of pain (Segerdahl et al., 2015; Galhardoni et al., 2019); it is possible that electrodes inserted for this purpose also have contacts within the claustrum or affect it via downstream activation. Despite the challenges of isolating claustrum activity during MRI imaging, several studies of human brain activity during various modalities of experimentally-induced pain report increased activity in the claustrum, among many other regions (Coghill et al., 1994; De Groote et al., 2018; Duerden & Albanese, 2013; Gard et al., 2012; Lu et al., 2004; Martin et al., 2013; David M. Niddam et al., 2002; Ochsner et al., 2006; Scheef et al., 2012; Sevel et al., 2015; X. Xu et al., 1997).

Figure 3. The claustrum is connected with multiple brain networks. (a) Schematic illustration of a sagittal mouse brain section highlighting the connections between the claustrum and regions important in pain processing. (b) Brain activity to physical pain using multi-study data and machine learning classification tools. Adapted from Wager et al., 2013 (c) Schematic illustration of a sagittal mouse brain section highlighting the connections between the claustrum and regions important in sleep. (d) CLA and PFC stimulation both evoke slow-wave like activity adapted from Narikiyo et al., 2020 and Vyazovskiy et al., 2009 respectively. (e) Schematic illustration of a sagittal mouse brain section highlighting the connections between the claustrum and regions important in saliency. (f) Representative fMRI images showing the human and rodent saliency networks adapted from Seeley et al., 2007 and Smith et al., 2019 respectively.

As well as acute pain, claustrum activity has been reported in a few studies looking at chronic pain (D.M. Niddam et al., 2017; Smallwood et al., 2013). Furthermore, studies examining the placebo effect, catastrophizing, and empathy have also reported activity within the claustrum among other regions (Amanzio et al., 2013; Ding et al., 2020; Gracely, 2004; Jauniaux et al., 2019; Kong et al., 2008; Palermo et al., 2015). The claustrum has further been reported as active in studies investigating acupuncture, migraine, oxygen deprivation, and invasive motor cortex stimulation in patients with chronic pain (Biella et al., 2001; Jia & Yu, 2017; Liotti et al., 2001; Volkers et al., 2020; Yeo et al., 2016). Drawing strong conclusions from these studies

is challenging as the authors rarely include any discussion of the claustrum outside of data tables.

In addition to human and animal imaging studies, non-imaging evidence from animal studies also supports a link between the claustrum and pain. The claustrum expresses proteins implicated in pain-related signalling, including kappa, delta, and mu opioid receptors, (Chen et al., 2020; Florin et al., 2000; Mansour et al., 1994; Mika et al., 2011; Tempel et al., 1987) and shows increased neural activity following experimentally-induced pain in various species (Jastreboff et al., 1983; Lei et al., 2004; Sinniger et al., 2004; Słoniewski et al., 1995; Tan et al., 2017). One early study assessed the correlation between seizure-induced damage to the brain and changes in rats' pain threshold. Intriguingly, of all the structures within the diencephalon and telencephalon, damage to the claustrum explained the largest percentage of variance in the pain threshold (Persinger et al., 1997). Cautious interpretation is warranted as the pain threshold test in a rat will be confounded with movement and/or motivation deficits.

The claustrum may also play a role in the sensation of itch, a sensation that provokes the desire to scratch. While pain and itch are distinct sensations, the two are closely related (Hachisuka et al., 2018; T. Liu & Ji, 2013; Schmelz, 2010; Ständer & Schmelz, 2006). Functional neuroimaging studies have noted differences in baseline claustrum activity in patients with chronic pruritus (itching) and healthy volunteers (Cohen et al., 2011; Papoiu et al., 2014). Multiple studies have found increased claustrum activity in response to experimentally induced itch (Herde et al., 2007; Papoiu et al., 2012, 2014), and this activity correlates with itch intensity (Papoiu et al., 2012). The claustrum is also rich in K-opioid receptors which have been linked to itch reduction (Chen et al., 2020; Nguyen et al., 2021) Moreover, claustrum

deactivation is positively correlated with itch-reduction following application of butorphanol, a drug with K-opioid receptor agonist activity (Papoiu et al., 2015).

Although the claustrum is not commonly reported as active in studies of pain and itch, its potential involvement merits further investigation. The present lack of discussion, possible reporting bias, and inconsistent activation may be due to the dominance of other structures very near the claustrum that have well defined roles in pain and itch. Despite these challenges, and in light of ultra-high field MRI imaging opportunities and animal imaging techniques, further investigation of a connection between the claustrum and pain is warranted – not least because of its accessibility as a target for deep brain stimulation.

Sleep

Many of the lesion studies described above include reports of sleep disturbances. While the studies included limited details of these disruptions, recent developments from animal research support the hypothesis that the claustrum may be involved in sleep processing (for a more general review of sleep, see (R. E. Brown et al., 2012; D. Liu & Dan, 2019; Saper & Fuller, 2017; Vyazovskiy & Harris, 2013)).

The broad anatomical connectivity of the claustrum makes it well-placed to play a role in brain-wide processes such as sleep. Sleep is regulated by numerous brain regions, many of which are strongly connected to the claustrum, including those that are highlighted in Figure 3C. Of particular relevance to sleep are the enriched serotonin receptors in the claustrum (Gehlert et al., 1991; Koyama et al., 2017; Morales et al., 1998; Norimoto et al., 2020) and extensive

unidirectional inputs from serotonergic raphe neurons (Narikiyo et al., 2020; Zingg et al., 2018) which are involved in sleep-wake control (Oikonomou et al., 2019). Additionally, the claustrum's abundant reciprocal connections with the PFC, insula, and cingulate cortex (Zingg et al., 2018) — where slow waves can originate (Massimini et al., 2004; Murphy et al., 2009; Nir et al., 2011) — make the claustrum a promising candidate for regulating slow waves. These anatomical connections and physiological findings appear to support a role for the claustrum in sleep-related phenomena. Indeed, the claustrum shows increased expression of markers of neural activity following REM sleep hypersomnia, particularly in claustral neurons connected to frontal cortices such as ACC (Renouard et al., 2015).

A recent study by Narikiyo et al. causally linked the claustrum to slow-wave activity (Narikiyo et al., 2020). The authors found that stimulation of the claustrum during slow-wave sleep induced a slow wave-like down-state in the cortex followed by a synchronised transition to an up-state (Figure 3D). In keeping with this, claustrrocortical neurons were more active in slow-wave sleep, firing maximally just before and after the up-state of slow waves. Finally, slow-wave activity was reduced by genetic ablation of the claustrum. While this provides a compelling link between the claustrum and sleep, it is important to note that stimulation of the frontal cortex and thalamus (Logothetis et al., 2010; Vyazovskiy et al., 2009) as well as peripheral and TMS stimulation (Riedner et al., 2011) have both been reported to elicit similar slow-wave activity (Figure 3E). As such, further research is required to establish a unique role for the claustrum in slow-wave sleep.

Another recent study by Norimoto et al. linked the claustrum to other aspects of sleep (Norimoto et al., 2020). The authors identified a reptilian homologue of the claustrum that was important in the generation of sharp-wave ripples. These physiological events are composed of

a slow, high amplitude potential (sharp wave) followed by a burst of rapid oscillatory activity (ripple) and are implicated in memory consolidation (Joo & Frank, 2018). Increasing and decreasing serotonin levels in the claustrum led to upregulation and downregulation of spontaneous sharp-wave ripples. They did, however, note that lesions of the claustrum had no effect on the alternation between rapid eye movement (REM) and non-REM sleep. The authors conclude that while the claustrum underlies the generation of sharp-wave ripples during slow-wave sleep, it is not involved in the generation of the sleep rhythm itself.

These studies have carefully dissected several global and specific aspects of sleep and found that while the claustrum was involved with various aspects of sleep in different species, it did not control sleep globally. These results strongly implicate the claustrum as part of a network that subserves some of the neurophysiological correlates of sleep. While the link between the claustrum and sleep remains preliminary, the available evidence from animal studies in combination with the data from human studies presented above might lead to fruitful directions for future research.

Salience

While the heterogeneous consequences of claustrum lesions may point towards a suite of separate functions, they might instead suggest a single overarching function. Salience processing is one such possible function. Salience is the property of a stimulus that makes it noticeable. For example, a sudden loud sound carries perceptual salience, whereas the smell of food has motivational salience for a hungry organism. Put another way, salience can be seen as a process of attributing importance to information, which in turn controls information flow in the brain. In keeping with a role for the claustrum in salience processing, salience can be

linked to cognitive and perceptual functions (Dosenbach et al., 2006), delusions (Kapur, 2003; Patru & Reser, 2015) and sleep (Khazaie et al., 2017).

Findings from recent connectivity and physiology studies in animal models support the idea that the claustrum may be part of the “salience network” (Jackson et al., 2018; Smith et al., 2019). The salience network is an operationally-defined group of brain regions including the ACC, insula, amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei (Menon & Uddin, 2010; Seeley et al., 2007; Uddin, 2015). Many of these regions are closely connected with the claustrum (Figure 3 E,F). Moreover, the claustrum also receives strong input from regions linked to aversive and rewarding salience through its connections with the amygdala and dopaminergic system respectively (Anderson & Phelps, 2001; Berridge & Robinson, 1998). Recent physiological evidence from rodent models also aligns with these connectivity studies. Firstly, claustrum neurons have been reported to respond to salient sensory stimuli (S. P. Brown et al., 2017; Remedios et al., 2014). Secondly, inhibition of the claustrum decreased performance on a forced-choice task only in the presence of a distractor (Atlan et al., 2018) and regulated the behavioural sensitization to rewarding salient stimuli (Terem et al., 2020). Finally, in a classical-conditioning paradigm, claustrum responses most closely correlated with the perceptual salience (which was produced by novelty and unexpectedness) of conditioned and unconditioned stimulus associations (Reus-García et al., 2021). These studies provide further evidence of a critical role for the claustrum in salience processing.

While much evidence suggests a link, it remains unclear how the claustrum contributes to salience processing. One hypothesis suggests that the salience network is involved with *switching* between the default mode network and the central executive network (Menon &

Uddin, 2010; Uddin, 2015). This switch allows the brain to deploy the cognitive resources necessary to engage with salient stimuli. fMRI studies have suggested that the dorsal anterior insula is linked with this network switch (Menon & Uddin, 2010). However, it is possible that this process may also involve the claustrum. Furthermore, given the connectivity between the claustrum and default mode network, and the inhibitory effect of claustrum stimulation on the cortex, the claustrum is well placed to inhibit the default mode network in response to salient stimuli (Jackson et al., 2018).

The claustrum may also contribute to salience processing by acting as a *coincidence detector*. Paired recordings within the claustrum have revealed dense electrical and chemical synapses between interneurons and a relative paucity of excitatory-excitatory connections (J. Kim et al., 2016). Stimulation of corticoclaustral projections reliably evokes feed-forward inhibition in claustrrocortical projection neurons (J. Kim et al., 2016). This may explain the bimodal activity characteristic of claustrum neuron responses to cortical activation in the presence of feedforward inhibition. As such, strong input within a short temporal window is required to induce suprathreshold responses in the claustrum (Chia et al., 2020). By responding to coincident input from sensory, limbic, executive (Ettlinger & Wilson, 1990) and neuromodulatory areas, this coincidence detection architecture could allow the claustrum to signal the salience of stimuli activating multiple neural circuits simultaneously (Smythies et al., 2014).

On the other hand, claustrrocortical projections do not align well with the salience network outlined based on cortico-striatal-thalamic loops. The strong ipsilateral claustrrocortical projections (Wang et al., 2017) do not match with the strong interhemispheric projections between cortical and subcortical areas posited as crucial due to hypotheses about the salience

network (Peters et al., 2016). In addition, corticoclaustral projections provide the dominant input to the claustrum (84% of input to the claustrum from cortex reported (Zingg et al., 2018)), but saliency processing requires substantial non-cortical involvement. While supporting evidence continues to accumulate, question remains as to whether the claustrum has a role in the salience processing.

Conclusion

Recent work on the claustrum is unravelling the multifaceted nature of its role(s) in the brain. We sought to answer the classic question “What can’t you do without the claustrum?” Unfortunately, lesions to human claustra are rarely specific due to its anatomy and bilateral location. Such lesions inevitably impact neighbouring areas, resulting in heterogeneous effects ranging from impaired cognitive, perceptual, and motor abilities, to altered electrical activity in the brain, and profound disturbances to mental states and sleep. These diverse findings do not provide a clear answer regarding the role(s) of the claustrum.

While recent anatomical findings exclude the claustrum from some processes such as low-level sensory processing (given the lack of inputs from sensory thalamic nuclei and sparse inputs from primary sensory cortices) and direct generation and/or modification of motor output (given lack of connectivity with striatum), research has not yet yielded a conclusive function for the claustrum. It remains possible that the claustrum underlies many discrete functions and/or possesses an, as yet, unidentified global function that ties together these disparate findings. Given the broad connectivity of the claustrum, it is perhaps too simplistic to search for one function, regardless of how broadly defined it may be. One way forward may be to map mechanisms at the neural level, such as coordinating global brain dynamics, onto mechanisms at the cognitive level, such as processing salience.

Another possibility is to continue work on the claustrum across species, which has already usefully spanned reptiles, rodents, rabbits, cats, monkeys, and humans. This cross-species approach may be especially important considering that the role(s) of this highly connected brain area could have changed throughout evolution, while the core principles of its utility may have been conserved. While the precise evolutionary origin of the claustrum is not yet known, a claustrum-like structure has been described in all extant mammals, as well as in species of birds and reptiles (Bruguier et al., 2020; Norimoto et al., 2020). That the claustrum has been conserved across these diverse lineages over millions of years argues for a function that is both essential and fundamental. In biology, an organ's function can often be inferred from its structure. To the extent that this is possible for the brain, the extensive connectivity structure of the claustrum across species implies an “extensive” or broad function. Future work is clearly needed to refine our understanding of this enigmatic structure.

Acknowledgements

We would like to thank Armin Lak, Simon Butt, and Richard Burman for discussions and Philip Schwarz for translation assistance.

This project has received funding from the Wellcome Trust to A.M.P., the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 852765) to A.M.P., Medical Research Council (MR/S01134X/1) to V.V., Medical Research Council Clinician Scientist Fellowship (MR/P00878/X) to S.G.M., and Leverhulme grant (RPG-2018-310) to S.G.M.

680 Competing Interests statement

681 The authors declare no competing financial interests.

682

References

- Adolphs, R. (2016). Human Lesion Studies in the 21st Century. *Neuron*, 90(6), 1151–1153.
<https://doi.org/10.1016/j.neuron.2016.05.014>
- Albayrak, B. S., & Gorgulu, A. (2008). Persistent bilateral amaurosis in a child caused by damage to the calcarine cortex and the claustrum in contralateral hemispheres after a closed head injury. *The Journal of Trauma*, 64(6), E81-82.
- Amanzio, M., Benedetti, F., Porro, C. A., Palermo, S., & Cauda, F. (2013). Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Human Brain Mapping*, n/a-n/a.
<https://doi.org/10.1002/hbm.21471>
- Anderson, A. K., & Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*, 411(6835), 305–309.
<https://doi.org/10.1038/35077083>
- Atlan, G., Terem, A., Peretz-Rivlin, N., Groysman, M., & Citri, A. (2017). Mapping synaptic cortico-claustral connectivity in the mouse. *Journal of Comparative Neurology*, 525(6), 1381–1402. <https://doi.org/10.1002/cne.23997>
- Atlan, G., Terem, A., Peretz-Rivlin, N., Sehrawat, K., Gonzales, B. J., Pozner, G., Tasaka, G., Goll, Y., Refaeli, R., Zviran, O., Lim, B. K., Groysman, M., Goshen, I., Mizrahi, A., Nelken, I., & Citri, A. (2018). The Claustrum Supports Resilience to Distraction. *Current Biology*, 28(17), 2752-2762.e7. <https://doi.org/10.1016/j.cub.2018.06.068>
- Barcikowska, M. (1979). [Lesions of the insula and operculum: A syndrome]. *Neurologia i neurochirurgia polska*, 13(2), 205–209.
- Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, 28(3), 309–369. [https://doi.org/10.1016/S0165-0173\(98\)00019-8](https://doi.org/10.1016/S0165-0173(98)00019-8)

708 Bickel, S., & Parvizi, J. (2019). Electrical stimulation of the human claustrum. *Epilepsy &*
709 *Behavior*, 97, 296–303. <https://doi.org/10.1016/j.yebeh.2019.03.051>

710 Biella, G., Sotgiu, M. L., Pellegata, G., Paulesu, E., Castiglioni, I., & Fazio, F. (2001).
711 Acupuncture Produces Central Activations in Pain Regions. *NeuroImage*, 14(1), 60–
712 66. <https://doi.org/10.1006/nimg.2001.0798>

713 Biemond, A. (1956). The Conduction of Pain Above the Level of the Thalamus Opticus.
714 *A.M.A. Archives of Neurology & Psychiatry*, 75(3), 231–244.
715 <https://doi.org/10.1001/archneurpsyc.1956.02330210011001>

716 Bota, M., Sporns, O., & Swanson, L. W. (2015). Architecture of the cerebral cortical
717 association connectome underlying cognition. *Proceedings of the National Academy*
718 *of Sciences of the United States of America*, 112(16), E2093–E2101. PubMed.
719 <https://doi.org/10.1073/pnas.1504394112>

720 Bott, N., Keller, C., Kuppaswamy, M., Spelber, D., & Zeier, J. (2016). Cotard Delusion in the
721 Context of Schizophrenia: A Case Report and Review of the Literature. *Frontiers in*
722 *Psychology*, 7, 1351. <https://doi.org/10.3389/fpsyg.2016.01351>

723 Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., & McCarley, R. W. (2012).
724 Control of sleep and wakefulness. *Physiological Reviews*, 92(3), 1087–1187.
725 PubMed. <https://doi.org/10.1152/physrev.00032.2011>

726 Brown, S. P., Mathur, B. N., Olsen, S. R., Luppi, P.-H., Bickford, M. E., & Citri, A. (2017).
727 New Breakthroughs in Understanding the Role of Functional Interactions between the
728 Neocortex and the Claustrum. *The Journal of Neuroscience : The Official Journal of*
729 *the Society for Neuroscience*, 37(45), 10877–10881. PubMed.
730 <https://doi.org/10.1523/JNEUROSCI.1837-17.2017>

731 Bruguier, H., Suarez, R., Manger, P., Hoerder-Suabedissen, A., Shelton, A. M., Oliver, D. K.,
732 Packer, A. M., Ferran, J. L., García-Moreno, F., Puellas, L., & Molnár, Z. (2020). In

733 search of common developmental and evolutionary origin of the claustrum and
734 subplate. *Journal of Comparative Neurology*, 528(17), 2956–2977.
735 <https://doi.org/10.1002/cne.24922>

736 Carey, R. G., & Neal, T. L. (1986). Reciprocal connections between the claustrum and visual
737 thalamus in the tree shrew (*Tupaia glis*). *Brain Research*, 386(1–2), 155–168.
738 [https://doi.org/10.1016/0006-8993\(86\)90152-6](https://doi.org/10.1016/0006-8993(86)90152-6)

739 Carman, J. B., COWAN, W. M., & POWELL, T. P. (1964). THE CORTICAL
740 PROJECTION UPON THE CLAUSTRUM. *Journal of Neurology, Neurosurgery,*
741 *and Psychiatry*, 27(1), 46–51. PubMed. <https://doi.org/10.1136/jnnp.27.1.46>

742 Chakraborty, S., Singi, S. R., Pradhan, G., & Anantha Subramanya, H. (2014). Neuro-
743 cysticercosis presenting with single delusion: A rare psychiatric manifestation.
744 *International Journal of Applied & Basic Medical Research*, 4(2), 131–133. PubMed.
745 <https://doi.org/10.4103/2229-516X.136808>

746 Chau, A., Salazar, A. M., Krueger, F., Cristofori, I., & Grafman, J. (2015). The effect of
747 claustrum lesions on human consciousness and recovery of function. *Consciousness*
748 *and Cognition*, 36, 256–264. <https://doi.org/10.1016/j.concog.2015.06.017>

749 Chessa, E., Piga, M., Floris, A., Mathieu, A., & Cauli, A. (2017). Severe neuropsychiatric
750 systemic lupus erythematosus successfully treated with rituximab: An alternative to
751 standard of care. *Open Access Rheumatology: Research and Reviews*, Volume 9, 167–
752 170. <https://doi.org/10.2147/OARRR.S143768>

753 Chia, Z., Augustine, G. J., & Silberberg, G. (2020). Synaptic Connectivity between the
754 Cortex and Claustrum Is Organized into Functional Modules. *Current Biology : CB*,
755 30(14), 2777–2790.e4. <https://doi.org/10.1016/j.cub.2020.05.031>

756 Choi, J. Y., Kim, E. J., Moon, S. Y., Kim, T.-J., & Huh, K. (2019). Prognostic significance of
757 subsequent extra-temporal involvement in cryptogenic new onset refractory status

758 epilepticus (NORSE) initially diagnosed with limbic encephalitis. *Epilepsy Research*,
759 158, 106215. <https://doi.org/10.1016/j.eplepsyres.2019.106215>

760 Clarey, J. C., & Irvine, D. R. F. (1986). Auditory response properties of neurons in the
761 claustrum and putamen of the cat. *Experimental Brain Research*, 61(2), 432–437.
762 <https://doi.org/10.1007/BF00239531>

763 Coghill, R., Talbot, J., Evans, A., Meyer, E., Gjedde, A., Bushnell, M., & Duncan, G. (1994).
764 Distributed processing of pain and vibration by the human brain. *The Journal of*
765 *Neuroscience*, 14(7), 4095–4108. [https://doi.org/10.1523/JNEUROSCI.14-07-](https://doi.org/10.1523/JNEUROSCI.14-07-04095.1994)
766 04095.1994

767 Cohen, O. S., Chapman, J., Lee, H., Nitsan, Z., Appel, S., Hoffman, C., Rosenmann, H.,
768 Korczyn, A. D., & Prohovnik, I. (2011). Pruritus in familial Creutzfeldt–Jakob
769 disease: A common symptom associated with central nervous system pathology.
770 *Journal of Neurology*, 258(1), 89–95. <https://doi.org/10.1007/s00415-010-5694-1>

771 Cortimiglia, R., Crescimanno, G., Salerno, M. T., & Amato, G. (1991). The role of the
772 claustrum in the bilateral control of frontal oculomotor neurons in the cat.
773 *Experimental Brain Research*, 84(3), 471–477. <https://doi.org/10.1007/BF00230958>

774 Couto, B., Sedeño, L., Sposato, L. A., Sigman, M., Riccio, P. M., Salles, A., Lopez, V.,
775 Schroeder, J., Manes, F., & Ibanez, A. (2013). Insular networks for emotional
776 processing and social cognition: Comparison of two case reports with either cortical
777 or subcortical involvement. *Cortex*, 49(5), 1420–1434.
778 <https://doi.org/10.1016/j.cortex.2012.08.006>

779 Crick, F. C., & Koch, C. (2005). What is the function of the claustrum? *Philosophical*
780 *Transactions of the Royal Society of London. Series B, Biological Sciences*,
781 360(1458), 1271–1279. PubMed. <https://doi.org/10.1098/rstb.2005.1661>

782 De Groote, S., De Jaeger, M., Van Schuerbeek, P., Sunaert, S., Peeters, R., Loeckx, D.,

783 Goudman, L., Forget, P., De Smedt, A., & Moens, M. (2018). Functional magnetic
784 resonance imaging: Cerebral function alterations in subthreshold and suprathreshold
785 spinal cord stimulation. *Journal of Pain Research, Volume 11*, 2517–2526.
786 <https://doi.org/10.2147/JPR.S160890>

787 Debruyne, H., Portzky, M., Van den Eynde, F., & Audenaert, K. (2009). Cotard's syndrome:
788 A review. *Current Psychiatry Reports, 11*(3), 197–202.
789 <https://doi.org/10.1007/s11920-009-0031-z>

790 Dillingham, C. M., Jankowski, M. M., Chandra, R., Frost, B. E., & O'Mara, S. M. (2017).
791 The claustrum: Considerations regarding its anatomy, functions and a programme for
792 research. *Brain and Neuroscience Advances, 1*, 2398212817718962.
793 <https://doi.org/10.1177/2398212817718962>

794 Ding, R., Ren, J., Li, S., Zhu, X., Zhang, K., & Luo, W. (2020). Domain-general and domain-
795 preferential neural correlates underlying empathy towards physical pain, emotional
796 situation and emotional faces: An ALE meta-analysis. *Neuropsychologia, 137*,
797 107286. <https://doi.org/10.1016/j.neuropsychologia.2019.107286>

798 Dodgson, M. C. H. (1955). A congenital malformation of insular cortex in man, involving the
799 claustrum and certain subcortical centres. *Journal of Comparative Neurology, 102*(2),
800 341–364. <https://doi.org/10.1002/cne.901020203>

801 Dosenbach, N. U. F., Visscher, K. M., Palmer, E. D., Miezin, F. M., Wenger, K. K., Kang, H.
802 C., Burgund, E. D., Grimes, A. L., Schlaggar, B. L., & Petersen, S. E. (2006). A core
803 system for the implementation of task sets. *Neuron, 50*(5), 799–812.
804 <https://doi.org/10.1016/j.neuron.2006.04.031>

805 Duerden, E. G., & Albanese, M.-C. (2013). Localization of pain-related brain activation: A
806 meta-analysis of neuroimaging data. *Human Brain Mapping, 34*(1), 109–149.
807 <https://doi.org/10.1002/hbm.21416>

808 Duffau, H., Mandonnet, E., Gatignol, P., & Capelle, L. (2007). Functional compensation of
809 the claustrum: Lessons from low-grade glioma surgery. *Journal of Neuro-Oncology*,
810 81(3), 327–329. <https://doi.org/10.1007/s11060-006-9236-8>

811 Ettlinger, G., & Wilson, W. A. (1990). Cross-modal performance: Behavioural processes,
812 phylogenetic considerations and neural mechanisms. *Behavioural Brain Research*,
813 40(3), 169–192. [https://doi.org/10.1016/0166-4328\(90\)90075-p](https://doi.org/10.1016/0166-4328(90)90075-p)

814 Faull, O. K., Jenkinson, M., Ezra, M., & Pattinson, K. T. (2016). Conditioned respiratory
815 threat in the subdivisions of the human periaqueductal gray. *eLife*, 5, e12047.
816 <https://doi.org/10.7554/eLife.12047>

817 Fodouliau, L., Gschwend, O., Huber, C., Mutel, S., Salazar, R. F., Leone, R., Renfer, J.-R.,
818 Ekundayo, K., Rodriguez, I., & Carleton, A. (2020). The claustrum-medial prefrontal
819 cortex network controls attentional set-shifting. *BioRxiv*, 2020.10.14.339259.
820 <https://doi.org/10.1101/2020.10.14.339259>

821 Freedman, M., Alexander, M. P., & Naeser, M. A. (1984). Anatomic basis of transcortical
822 motor aphasia. *Neurology*, 34(4), 409. <https://doi.org/10.1212/WNL.34.4.409>

823 Galhardoni, R., Aparecida da Silva, V., García-Larrea, L., Dale, C., Baptista, A. F., Barbosa,
824 L. M., Menezes, L. M. B., de Siqueira, S. R. D. T., Valério, F., Rosi, J., de Lima
825 Rodrigues, A. L., Reis Mendes Fernandes, D. T., Lorencini Selingardi, P. M.,
826 Marcolin, M. A., Duran, F. L. de S., Ono, C. R., Lucato, L. T., Fernandes, A. M. B.
827 L., da Silva, F. E. F., ... Ciampi de Andrade, D. (2019). Insular and anterior cingulate
828 cortex deep stimulation for central neuropathic pain. *Neurology*, 92(18), e2165.
829 <https://doi.org/10.1212/WNL.00000000000007396>

830 Gard, T., Holzel, B. K., Sack, A. T., Hempel, H., Lazar, S. W., Vaitl, D., & Ott, U. (2012).
831 Pain Attenuation through Mindfulness is Associated with Decreased Cognitive
832 Control and Increased Sensory Processing in the Brain. *Cerebral Cortex*, 22(11),

833 2692–2702. <https://doi.org/10.1093/cercor/bhr352>

834 Gehlert, D., Gackenhimer, S., Wong, D., & Robertson, D. (1991). Localization of 5-HT₃
835 receptors in the rat brain using [3H]LY278584. *Brain Research*, 553(1), 149–154.
836 PubMed. [https://doi.org/10.1016/0006-8993\(91\)90242-n](https://doi.org/10.1016/0006-8993(91)90242-n)

837 Goll, Y., Atlán, G., & Citri, A. (2015). Attention: The claustrum. *Trends in Neurosciences*,
838 38(8), 486–495. <https://doi.org/10.1016/j.tins.2015.05.006>

839 Gracely, R. H. (2004). Pain catastrophizing and neural responses to pain among persons with
840 fibromyalgia. *Brain*, 127(4), 835–843. <https://doi.org/10.1093/brain/awh098>

841 Grover, S., Aneja, J., Mahajan, S., & Varma, S. (2014). Cotard’s syndrome: Two case reports
842 and a brief review of literature. *Journal of Neurosciences in Rural Practice*, 5(Suppl
843 1), S59–S62. PubMed. <https://doi.org/10.4103/0976-3147.145206>

844 Hachisuka, J., Chiang, M. C., & Ross, S. E. (2018). Itch and neuropathic itch. *Pain*, 159(3),
845 603–609. PubMed. <https://doi.org/10.1097/j.pain.0000000000001141>

846 Hadjikhani, N., & Roland, P. E. (1998). Cross-modal transfer of information between the
847 tactile and the visual representations in the human brain: A positron emission
848 tomographic study. *The Journal of Neuroscience : The Official Journal of the Society*
849 *for Neuroscience*, 18(3), 1072–1084. [https://doi.org/10.1523/JNEUROSCI.18-03-](https://doi.org/10.1523/JNEUROSCI.18-03-01072.1998)
850 01072.1998

851 Herde, L., Forster, C., Strupf, M., & Handwerker, H. O. (2007). Itch Induced by a Novel
852 Method Leads to Limbic Deactivations—A Functional MRI Study. *Journal of*
853 *Neurophysiology*, 98(4), 2347–2356. <https://doi.org/10.1152/jn.00475.2007>

854 Hiraga, A., Watanabe, O., Kamitsukasa, I., & Kuwabara, S. (2014). Voltage-gated Potassium
855 Channel Antibody-associated Encephalitis with Claustrum Lesions. *Internal*
856 *Medicine*, 53(19), 2263–2264. <https://doi.org/10.2169/internalmedicine.53.2701>

857 Hoover, W. B., & Vertes, R. P. (2007). Anatomical analysis of afferent projections to the

858 medial prefrontal cortex in the rat. *Brain Structure & Function*, 212(2), 149–179.
859 <https://doi.org/10.1007/s00429-007-0150-4>

860 Hwang, K. J., Park, K.-C., Yoon, S. S., & Ahn, T.-B. (2014). Unusual lesion in the bilateral
861 external capsule following status epilepticus: A case report. *Journal of Epilepsy*
862 *Research*, 4(2), 88–90. PubMed. <https://doi.org/10.14581/jer.14019>

863 Ishida, H., Hattori, H., Takaura, N., Yoshida, T., Tanaka, K., Otani, S., Matsuoka, O.,
864 Takahashi, Y., & Yamano, T. (2006). [A child with non-herpetic acute limbic
865 encephalitis affecting the claustrum and hippocampus]. *No to hattatsu = Brain and*
866 *development*, 38(6), 443–447.

867 Ishii, K., Tsuji, H., & Tamaoka, A. (2011). Mumps Virus Encephalitis with Symmetric
868 Claustrum Lesions. *American Journal of Neuroradiology*, 32(7), E139.
869 <https://doi.org/10.3174/ajnr.A2603>

870 Ishizu, T., & Zeki, S. (2013). The brain’s specialized systems for aesthetic and perceptual
871 judgment. *The European Journal of Neuroscience*, 37(9), 1413–1420. PubMed.
872 <https://doi.org/10.1111/ejn.12135>

873 Jackson, J., Karnani, M. M., Zemelman, B. V., Burdakov, D., & Lee, A. K. (2018). Inhibitory
874 Control of Prefrontal Cortex by the Claustrum. *Neuron*, 99(5), 1029-1039.e4.
875 <https://doi.org/10.1016/j.neuron.2018.07.031>

876 Jackson, J., Smith, J. B., & Lee, A. K. (2020). The Anatomy and Physiology of Claustrum-
877 Cortex Interactions. *Annual Review of Neuroscience*, 43(1), 231–247.
878 <https://doi.org/10.1146/annurev-neuro-092519-101637>

879 Jankowski, M. M., & O’Mara, S. M. (2015). Dynamics of place, boundary and object
880 encoding in rat anterior claustrum. *Frontiers in Behavioral Neuroscience*, 9.
881 <https://doi.org/10.3389/fnbeh.2015.00250>

882 Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., de

883 Leeuw, C. A., Benjamins, J. S., Muñoz-Manchado, A. B., Nagel, M., Savage, J. E.,
 884 Tiemeier, H., White, T., Agee, M., Alipanahi, B., Auton, A., Bell, R. K., Bryc, K.,
 885 Elson, S. L., ... The 23andMe Research Team. (2019). Genome-wide analysis of
 886 insomnia in 1,331,010 individuals identifies new risk loci and functional pathways.
 887 *Nature Genetics*, 51(3), 394–403. <https://doi.org/10.1038/s41588-018-0333-3>
 888 Jastreboff, P., Sikora, M., Frydrychowski, A., & Słoniewski, P. (1983). Claustal single cell
 889 reactions to tooth pulp stimulation in cats. *Acta Neurobiologiae Experimentalis*, 43(4–
 890 5), 291–298.
 891 Jauniaux, J., Khatibi, A., Rainville, P., & Jackson, P. L. (2019). A meta-analysis of
 892 neuroimaging studies on pain empathy: Investigating the role of visual information
 893 and observers’ perspective. *Social Cognitive and Affective Neuroscience*, 14(8), 789–
 894 813. <https://doi.org/10.1093/scan/nsz055>
 895 Jellinger, K. A., Grazer, A., Petrovic, K., Ropele, S., Alpi, G., Kapeller, P., Ströbel, T., &
 896 Schmidt, R. (2011). Four-repeat tauopathy clinically presenting as posterior cortical
 897 atrophy: Atypical corticobasal degeneration? *Acta Neuropathologica*, 121(2), 267–
 898 277. <https://doi.org/10.1007/s00401-010-0712-z>
 899 Jia, Z., & Yu, S. (2017). Grey matter alterations in migraine: A systematic review and meta-
 900 analysis. *NeuroImage: Clinical*, 14, 130–140.
 901 <https://doi.org/10.1016/j.nicl.2017.01.019>
 902 Joo, H. R., & Frank, L. M. (2018). The hippocampal sharp wave–ripple in memory retrieval
 903 for immediate use and consolidation. *Nature Reviews Neuroscience*, 19(12), 744–757.
 904 <https://doi.org/10.1038/s41583-018-0077-1>
 905 Kapur, S. (2003). Psychosis as a State of Aberrant Salience: A Framework Linking Biology,
 906 Phenomenology, and Pharmacology in Schizophrenia. *American Journal of*
 907 *Psychiatry*, 160(1), 13–23. <https://doi.org/10.1176/appi.ajp.160.1.13>

908 Khazaie, H., Veronese, M., Noori, K., Emamian, F., Zarei, M., Ashkan, K., Leschziner, G.
909 D., Eickhoff, C. R., Eickhoff, S. B., Morrell, M. J., Osorio, R. S., Spiegelhalder, K.,
910 Tahmasian, M., & Rosenzweig, I. (2017). Functional reorganization in obstructive
911 sleep apnoea and insomnia: A systematic review of the resting-state fMRI.
912 *Neuroscience & Biobehavioral Reviews*, 77, 219–231.
913 <https://doi.org/10.1016/j.neubiorev.2017.03.013>

914 Kim, J., Matney, C. J., Roth, R. H., & Brown, S. P. (2016). Synaptic Organization of the
915 Neuronal Circuits of the Claustrum. *The Journal of Neuroscience*, 36(3), 773–784.
916 <https://doi.org/10.1523/JNEUROSCI.3643-15.2016>

917 Kim, T. S., Kim, I. O., Kim, W. S., Choi, Y. S., Lee, J. Y., Kim, O. W., Yeon, K. M., Kim, K.
918 J., & Hwang, Y. S. (1997). MR of childhood metachromatic leukodystrophy. *AJNR*.
919 *American Journal of Neuroradiology*, 18(4), 733–738.

920 Kong, J., Gollub, R. L., Polich, G., Kirsch, I., LaViolette, P., Vangel, M., Rosen, B., &
921 Kaptchuk, T. J. (2008). A Functional Magnetic Resonance Imaging Study on the
922 Neural Mechanisms of Hyperalgesic Nocebo Effect. *Journal of Neuroscience*, 28(49),
923 13354–13362. <https://doi.org/10.1523/JNEUROSCI.2944-08.2008>

924 Koubeissi, M. Z., Bartolomei, F., Beltagy, A., & Picard, F. (2014). Electrical stimulation of a
925 small brain area reversibly disrupts consciousness. *Epilepsy & Behavior*, 37, 32–35.
926 <https://doi.org/10.1016/j.yebeh.2014.05.027>

927 Koyama, Y., Kondo, M., & Shimada, S. (2017). Building a 5-HT3A Receptor Expression
928 Map in the Mouse Brain. *Scientific Reports*, 7, 42884–42884. PubMed.
929 <https://doi.org/10.1038/srep42884>

930 Krimmel, S. R., Qadir, H., Hesselgrave, N., White, M. G., Reser, D. H., Mathur, B. N., &
931 Seminowicz, D. A. (2019). Resting State Functional Connectivity of the Rat
932 Claustrum. *Frontiers in Neuroanatomy*, 13, 22.

933 <https://doi.org/10.3389/fnana.2019.00022>

934 Krimmel, S. R., White, M. G., Panicker, M. H., Barrett, F. S., Mathur, B. N., & Seminowicz,
935 D. A. (2019). Resting state functional connectivity and cognitive task-related
936 activation of the human claustrum. *NeuroImage*, 196, 59–67.
937 <https://doi.org/10.1016/j.neuroimage.2019.03.075>

938 Kudlur, S. N. C., George, S., & Jaimon, M. (2007). An overview of the neurological
939 correlates of Cotard syndrome. *The European Journal of Psychiatry*, 21, 99–116.

940 Kurokawa, K., Sato, H., Nakajima, K., Kawanami, T., & Kato, T. (2005). [Clinical,
941 neuroimaging and electroencephalographic findings of encephalopathy occurring after
942 the ingestion of “sugihiratake” (*Pleurocybella porrigens*), an autumn mushroom: A
943 report of two cases]. *Rinsho shinkeigaku = Clinical neurology*, 45(2), 111–116.

944 Lapenta, L., Frisullo, G., Vollono, C., Brunetti, V., Giannantoni, N. M., Sandroni, C., Di
945 Lella, G., & Della Marca, G. (2015). Super-Refractory Status Epilepticus: Report of a
946 Case and Review of the Literature. *Clinical EEG and Neuroscience*, 46(4), 335–339.
947 <https://doi.org/10.1177/1550059414534418>

948 Lei, L.-G., Zhang, Y.-Q., & Zhao, Z.-Q. (2004). Pain-related aversion and Fos expression in
949 the central nervous system in rats: *NeuroReport*, 15(1), 67–71.
950 <https://doi.org/10.1097/00001756-200401190-00014>

951 Leroy, J. G., Lyon, G., Fallet, C., Amiel, J., De Praeter, C., Van Den Broecke, C., &
952 Vanhaesebrouck, P. (2007). Congenital pontocerebellar atrophy and telencephalic
953 defects in three siblings: A new subtype. *Acta Neuropathologica*, 114(4), 387–399.
954 <https://doi.org/10.1007/s00401-007-0248-z>

955 LeVay, S., & Sherk, H. (1981). The visual claustrum of the cat. I. Structure and connections.
956 *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*,
957 1(9), 956–980. <https://doi.org/10.1523/JNEUROSCI.01-09-00956.1981>

958 Liotti, M., Brannan, S., Egan, G., Shade, R., Madden, L., Abplanalp, B., Robillard, R.,
 959 Lancaster, J., Zamarripa, F. E., Fox, P. T., & Denton, D. (2001). Brain responses
 960 associated with consciousness of breathlessness (air hunger). *Proceedings of the*
 961 *National Academy of Sciences*, 98(4), 2035–2040.
 962 <https://doi.org/10.1073/pnas.98.4.2035>
 963 Liu, D., & Dan, Y. (2019). A Motor Theory of Sleep-Wake Control: Arousal-Action Circuit.
 964 *Annual Review of Neuroscience*, 42(1), 27–46. [https://doi.org/10.1146/annurev-neuro-](https://doi.org/10.1146/annurev-neuro-080317-061813)
 965 080317-061813
 966 Liu, T., & Ji, R.-R. (2013). New insights into the mechanisms of itch: Are pain and itch
 967 controlled by distinct mechanisms? *Pflügers Arch*, 15.
 968 Logothetis, N. K., Augath, M., Murayama, Y., Rauch, A., Sultan, F., Goense, J., Oeltermann,
 969 A., & Merkle, H. (2010). The effects of electrical microstimulation on cortical signal
 970 propagation. *Nature Neuroscience*, 13(10), 1283–1291.
 971 <https://doi.org/10.1038/nn.2631>
 972 Lu, C.-L., Wu, Y.-T., Yeh, T.-C., Chen, L.-F., Chang, F.-Y., Lee, S.-D., Ho, L.-T., & Hsieh,
 973 J.-C. (2004). Neuronal correlates of gastric pain induced by fundus distension: A 3T-
 974 fMRI study. *Neurogastroenterology and Motility*, 16(5), 575–587.
 975 <https://doi.org/10.1111/j.1365-2982.2004.00562.x>
 976 Lunsford-Avery, J. R., Damme, K. S. F., Engelhard, M. M., Kollins, S. H., & Mittal, V. A.
 977 (2020). Sleep/Wake Regularity Associated with Default Mode Network Structure
 978 among Healthy Adolescents and Young Adults. *Scientific Reports*, 10(1), 509.
 979 <https://doi.org/10.1038/s41598-019-57024-3>
 980 Malter, M. P., Helmstaedter, C., Urbach, H., Vincent, A., & Bien, C. G. (2010). Antibodies to
 981 glutamic acid decarboxylase define a form of limbic encephalitis. *Annals of*
 982 *Neurology*, 67(4), 470–478. <https://doi.org/10.1002/ana.21917>

983 Mansour, A., Fox, C. A., Burke, S., Meng, F., Thompson, R. C., Akil, H., & Watson, S. J.
 984 (1994). Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in
 985 situ hybridization study. *The Journal of Comparative Neurology*, 350(3), 412–438.
 986 <https://doi.org/10.1002/cne.903500307>

987 Martin, L., Borckardt, J. J., Reeves, S. T., Frohman, H., Beam, W., Nahas, Z., Johnson, K.,
 988 Younger, J., Madan, A., Patterson, D., & George, M. (2013). A Pilot Functional MRI
 989 Study of the Effects of Prefrontal rTMS on Pain Perception. *Pain Medicine*, 14(7),
 990 999–1009. <https://doi.org/10.1111/pme.12129>

991 Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow
 992 oscillation as a traveling wave. *The Journal of Neuroscience : The Official Journal of*
 993 *the Society for Neuroscience*, 24(31), 6862–6870. PubMed.
 994 <https://doi.org/10.1523/JNEUROSCI.1318-04.2004>

995 Mathur, B. N. (2014). The claustrum in review. *Frontiers in Systems Neuroscience*, 8.
 996 <https://doi.org/10.3389/fnsys.2014.00048>

997 Matsuzono, K., Kurata, T., Deguchi, S., Yamashita, T., Deguchi, K., Ikeda, Y., & Abe, K.
 998 (2013). Two Unique Cases with Anti-GluR Antibody-Positive Encephalitis. *Clinical*
 999 *Medicine Insights. Case Reports*, 6, 113–117. PubMed.
 1000 <https://doi.org/10.4137/CCRep.S11890>

1001 Maximov, G. K., Hinova-Palova, D. V., Iliev, A. A., Kotov, G. N., Kirkov, V. K., Landzhov,
 1002 B. V., & Maksimov, K. G. (2018). Ischemic stroke of the left claustrum in a 55-year-
 1003 old female: A case report. *Claustrum*, 3(1), 1528135.
 1004 <https://doi.org/10.1080/20023294.2018.1528135>

1005 Mazzola, L., Isnard, J., Peyron, R., & Mauguière, F. (2012). Stimulation of the human cortex
 1006 and the experience of pain: Wilder Penfield's observations revisited. *Brain*, 135(2),
 1007 631–640. <https://doi.org/10.1093/brain/awr265>

- 1008 McKay, R., & Cipolotti, L. (2007). Attributional style in a case of Cotard delusion.
 1009 *Consciousness and Cognition*, 16(2), 349–359.
 1010 <https://doi.org/10.1016/j.concog.2006.06.001>
- 1011 McMurtray, A., Tseng, B., Diaz, N., Chung, J., Mehta, B., & Saito, E. (2014). Acute
 1012 Psychosis Associated with Subcortical Stroke: Comparison between Basal Ganglia
 1013 and Mid-Brain Lesions. *Case Reports in Neurological Medicine*, 2014, 428425–
 1014 428425. PubMed. <https://doi.org/10.1155/2014/428425>
- 1015 Meletti, S., Giovannini, G., d’Orsi, G., Toran, L., Monti, G., Guha, R., Kirytopoulos, A.,
 1016 Pascarella, M. G., Martino, T., Alexopoulos, H., Spilioti, M., & Slonkova, J. (2017).
 1017 New-Onset Refractory Status Epilepticus with Claustrum Damage: Definition of the
 1018 Clinical and Neuroimaging Features. *Frontiers in Neurology*, 8, 111–111. PubMed.
 1019 <https://doi.org/10.3389/fneur.2017.00111>
- 1020 Meletti, S., Slonkova, J., Mareckova, I., Monti, G., Specchio, N., Hon, P., Giovannini, G.,
 1021 Marcian, V., Chiari, A., Krupa, P., Pietrafusa, N., Berankova, D., & Bar, M. (2015).
 1022 Claustrum damage and refractory status epilepticus following febrile illness.
 1023 *Neurology*, 85(14), 1224–1232. PubMed.
 1024 <https://doi.org/10.1212/WNL.0000000000001996>
- 1025 Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network
 1026 model of insula function. *Brain Structure and Function*, 214(5–6), 655–667.
 1027 <https://doi.org/10.1007/s00429-010-0262-0>
- 1028 Mizutani, A. U., Shindo, A., Arikawa, S., Shimada, T., Matsuura, K., Ikejiri, K., Suzuki, K.,
 1029 Imai, H., & Tomimoto, H. (2020). Reversible splenial lesion in a patient with new-
 1030 onset refractory status epilepticus (NORSE). *ENeurologicalSci*, 18, 100220.
 1031 <https://doi.org/10.1016/j.ensci.2019.100220>
- 1032 Morales, M., Battenberg, E., & Bloom, F. E. (1998). Distribution of neurons expressing

1033 immunoreactivity for the 5HT3 receptor subtype in the rat brain and spinal cord.
 1034 *Journal of Comparative Neurology*, 402(3), 385–401.
 1035 [https://doi.org/10.1002/\(SICI\)1096-9861\(19981221\)402:3<385::AID-](https://doi.org/10.1002/(SICI)1096-9861(19981221)402:3<385::AID-)
 1036 [CNE7>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1096-9861(19981221)402:3<385::AID-CNE7>3.0.CO;2-Q)
 1037 Mumoli, L., Labate, A., Palamara, G., Sturniolo, M., & Gambardella, A. (2014). Reversible
 1038 symmetrical external capsule hyperintensity as an early finding of autoimmune
 1039 encephalitis. *Neurological Sciences*, 35(7), 1147–1149.
 1040 <https://doi.org/10.1007/s10072-014-1708-6>
 1041 Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009).
 1042 Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences*
 1043 *of the United States of America*, 106(5), 1608–1613. PubMed.
 1044 <https://doi.org/10.1073/pnas.0807933106>
 1045 Narikiyo, K., Mizuguchi, R., Ajima, A., Shiozaki, M., Hamanaka, H., Johansen, J. P., Mori,
 1046 K., & Yoshihara, Y. (2020). The claustrum coordinates cortical slow-wave activity.
 1047 *Nature Neuroscience*, 23(6), 741–753. <https://doi.org/10.1038/s41593-020-0625-7>
 1048 Nguyen, E., Lim, G., Ding, H., Hachisuka, J., Ko, M.-C., & Ross, S. E. (2021). Morphine
 1049 acts on spinal dynorphin neurons to cause itch through disinhibition. *Science*
 1050 *Translational Medicine*, 13(579), eabc3774.
 1051 <https://doi.org/10.1126/scitranslmed.abc3774>
 1052 Niddam, David M., Yeh, T.-C., Wu, Y.-T., Lee, P.-L., Ho, L.-T., Arendt-Nielsen, L., Chen,
 1053 A. C. N., & Hsieh, J.-C. (2002). Event-Related Functional MRI Study on Central
 1054 Representation of Acute Muscle Pain Induced by Electrical Stimulation. *NeuroImage*,
 1055 17(3), 1437–1450. <https://doi.org/10.1006/nimg.2002.1270>
 1056 Niddam, D.M., Lee, S.-H., Su, Y.-T., & Chan, R.-C. (2017). Brain structural changes in
 1057 patients with chronic myofascial pain. *European Journal of Pain*, 21(1), 148–158.

1058 <https://doi.org/10.1002/ejp.911>

1059 Nir, Y., Staba, R. J., Andrillon, T., Vyazovskiy, V. V., Cirelli, C., Fried, I., & Tononi, G.
 1060 (2011). Regional slow waves and spindles in human sleep. *Neuron*, 70(1), 153–169.
 1061 PubMed. <https://doi.org/10.1016/j.neuron.2011.02.043>

1062 Nixon, J., Bateman, D., & Moss, T. (2001). An MRI and neuropathological study of a case of
 1063 fatal status epilepticus. *Seizure*, 10(8), 588–591.
 1064 <https://doi.org/10.1053/seiz.2001.0553>

1065 Nomoto, T., Seta, T., Nomura, K., Shikama, Y., Katagiri, T., Katsura, K., Kato, T., &
 1066 Katayama, Y. (2007). A Case of Reversible Encephalopathy Accompanied by
 1067 Demyelination Occurring after Ingestion of Sugihiratake Mushrooms. *Journal of*
 1068 *Nippon Medical School*, 74(3), 261–264. <https://doi.org/10.1272/jnms.74.261>

1069 Norimoto, H., Fenk, L. A., Li, H.-H., Tosches, M. A., Gallego-Flores, T., Hain, D., Reiter, S.,
 1070 Kobayashi, R., Macias, A., Arends, A., Klinkmann, M., & Laurent, G. (2020). A
 1071 claustrum in reptiles and its role in slow-wave sleep. *Nature*, 578(7795), 413–418.
 1072 <https://doi.org/10.1038/s41586-020-1993-6>

1073 Obara, K., Wada, C., Yoshioka, T., Enomoto, K., Yagishita, S., & Toyoshima, I. (2008).
 1074 Acute encephalopathy associated with ingestion of a mushroom, *Pleurocybella*
 1075 *porrigens* (angel’s wing), in a patient with chronic renal failure. *Neuropathology*,
 1076 28(2), 151–156. <https://doi.org/10.1111/j.1440-1789.2007.00819.x>

1077 Obrador, S., Dierssen, G., & Ceballos, R. (1957). Consideraciones clinicas, neurológicas y
 1078 anatómicas sobre el llamado dolor talámico. *Acta Neurológica Latinoamericana*, 3,
 1079 58–77.

1080 Ochsner, K. N., Ludlow, D. H., Knierim, K., Hanelin, J., Ramachandran, T., Glover, G. C., &
 1081 Mackey, S. C. (2006). Neural correlates of individual differences in pain-related fear
 1082 and anxiety: *Pain*, 120(1–2), 69–77. <https://doi.org/10.1016/j.pain.2005.10.014>

1083 Oikonomou, G., Altermatt, M., Zhang, R.-W., Coughlin, G. M., Montz, C., Gradinaru, V., &
 1084 Prober, D. A. (2019). The Serotonergic Raphe Promote Sleep in Zebrafish and Mice.
 1085 *Neuron*, 103(4), 686-701.e8. PubMed. <https://doi.org/10.1016/j.neuron.2019.05.038>
 1086 Okamoto, K., Yamazaki, T., Banno, H., Sobue, G., Yoshida, M., & Takatama, M. (2008).
 1087 Neuropathological Studies of Patients with Possible Non-Herpetic Acute Limbic
 1088 Encephalitis and So-called Acute Juvenile Female Non-Herpetic Encephalitis.
 1089 *Internal Medicine*, 47(4), 231–236. <https://doi.org/10.2169/internalmedicine.47.0547>
 1090 Olson, C. R., & Graybiel, A. M. (1980). Sensory maps in the claustrum of the cat. *Nature*,
 1091 288(5790), 479–481. <https://doi.org/10.1038/288479a0>
 1092 Palermo, S., Benedetti, F., Costa, T., & Amanzio, M. (2015). Pain anticipation: An activation
 1093 likelihood estimation meta-analysis of brain imaging studies: Pain Anticipation an
 1094 Activation Likelihood Estimation Meta-Analysis. *Human Brain Mapping*, 36(5),
 1095 1648–1661. <https://doi.org/10.1002/hbm.22727>
 1096 Papoiu, A. D. P., Coghill, R. C., Kraft, R. A., Wang, H., & Yosipovitch, G. (2012). A tale of
 1097 two itches. Common features and notable differences in brain activation evoked by
 1098 cowhage and histamine induced itch. *NeuroImage*, 59(4), 3611–3623.
 1099 <https://doi.org/10.1016/j.neuroimage.2011.10.099>
 1100 Papoiu, A. D. P., Emerson, N. M., Patel, T. S., Kraft, R. A., Valdes-Rodriguez, R.,
 1101 Nattkemper, L. A., Coghill, R. C., & Yosipovitch, G. (2014). Voxel-based
 1102 morphometry and arterial spin labeling fMRI reveal neuropathic and neuroplastic
 1103 features of brain processing of itch in end-stage renal disease. *Journal of*
 1104 *Neurophysiology*, 112(7), 1729–1738. <https://doi.org/10.1152/jn.00827.2013>
 1105 Papoiu, A. D. P., Kraft, R. A., Coghill, R. C., & Yosipovitch, G. (2015). Butorphanol
 1106 Suppression of Histamine Itch Is Mediated by Nucleus Accumbens and Septal Nuclei:
 1107 A Pharmacological fMRI Study. *Journal of Investigative Dermatology*, 135(2), 560–

1108 568. <https://doi.org/10.1038/jid.2014.398>

1109 Patru, M. C., & Reser, D. H. (2015). A New Perspective on Delusional States – Evidence for
 1110 Claustum Involvement. *Frontiers in Psychiatry*, 6.
 1111 <https://doi.org/10.3389/fpsy.2015.00158>

1112 Persinger, M. A., Peredery, O., Bureau, Y. R., & Cook, L. L. (1997). Emergent properties
 1113 following brain injury: The claustrum as a major component of a pathway that
 1114 influences nociceptive thresholds to foot shock in rats. *Perceptual and Motor Skills*,
 1115 85(2), 387–398. <https://doi.org/10.2466/pms.1997.85.2.387>

1116 Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-Striatal-Thalamic Loop Circuits of
 1117 the Salience Network: A Central Pathway in Psychiatric Disease and Treatment.
 1118 *Frontiers in Systems Neuroscience*, 10, 104–104. PubMed.
 1119 <https://doi.org/10.3389/fnsys.2016.00104>

1120 Randerath, J., Finkel, L., Shigaki, C., Burriss, J., Nanda, A., Hwang, P., & Frey, S. H. (2018).
 1121 Does it fit? – Impaired affordance perception after stroke. *Neuropsychologia*, 108,
 1122 92–102. <https://doi.org/10.1016/j.neuropsychologia.2017.11.031>

1123 Redouté, J., Stoléru, S., Grégoire, M. C., Costes, N., Cinotti, L., Lavenne, F., Le Bars, D.,
 1124 Forest, M. G., & Pujol, J. F. (2000). Brain processing of visual sexual stimuli in
 1125 human males. *Human Brain Mapping*, 11(3), 162–177. PubMed.
 1126 [https://doi.org/10.1002/1097-0193\(200011\)11:3<162::aid-hbm30>3.0.co;2-a](https://doi.org/10.1002/1097-0193(200011)11:3<162::aid-hbm30>3.0.co;2-a)

1127 Remedios, R., Logothetis, N. K., & Kayser, C. (2010). Unimodal Responses Prevail within
 1128 the Multisensory Claustrum. *The Journal of Neuroscience*, 30(39), 12902.
 1129 <https://doi.org/10.1523/JNEUROSCI.2937-10.2010>

1130 Remedios, R., Logothetis, N. K., & Kayser, C. (2014). A role of the claustrum in auditory
 1131 scene analysis by reflecting sensory change. *Frontiers in Systems Neuroscience*, 8,
 1132 44–44. PubMed. <https://doi.org/10.3389/fnsys.2014.00044>

- 1133 Renouard, L., Billwiller, F., Ogawa, K., Clément, O., Camargo, N., Abdelkarim, M., Gay, N.,
 1134 Scoté-Blachon, C., Touré, R., Libourel, P.-A., Ravassard, P., Salvert, D., Peyron, C.,
 1135 Clausturat, B., Léger, L., Salin, P., Malleret, G., Fort, P., & Luppi, P.-H. (2015). The
 1136 supramammillary nucleus and the claustrum activate the cortex during REM sleep.
 1137 *Science Advances*, 1(3), e1400177. <https://doi.org/10.1126/sciadv.1400177>
- 1138 Reus-García, M. M., Sánchez-Campusano, R., Ledderose, J., Dogbevia, G. K., Treviño, M.,
 1139 Hasan, M. T., Gruart, A., & Delgado-García, J. M. (2021). The Claustrum is Involved
 1140 in Cognitive Processes Related to the Classical Conditioning of Eyelid Responses in
 1141 Behaving Rabbits. *Cerebral Cortex*, 31(1), 281–300.
 1142 <https://doi.org/10.1093/cercor/bhaa225>
- 1143 Riedner, B. A., Hulse, B. K., Murphy, M. J., Ferrarelli, F., & Tononi, G. (2011). Temporal
 1144 dynamics of cortical sources underlying spontaneous and peripherally evoked slow
 1145 waves. *Progress in Brain Research*, 193, 201–218. PubMed.
 1146 <https://doi.org/10.1016/B978-0-444-53839-0.00013-2>
- 1147 Sadowski, M., Moryś, J., Jakubowska-Sadowska, K., & Narkiewicz, O. (1997). Rat's
 1148 claustrum shows two main cortico-related zones. *Brain Research*, 756(1–2), 147–152.
 1149 [https://doi.org/10.1016/s0006-8993\(97\)00135-2](https://doi.org/10.1016/s0006-8993(97)00135-2)
- 1150 Saito, Y., Maegaki, Y., Okamoto, R., Ogura, K., Togawa, M., Nanba, Y., Inoue, T.,
 1151 Takahashi, Y., & Ohno, K. (2007). Acute encephalitis with refractory, repetitive
 1152 partial seizures: Case reports of this unusual post-encephalitic epilepsy. *Brain and*
 1153 *Development*, 29(3), 147–156. <https://doi.org/10.1016/j.braindev.2006.08.005>
- 1154 Salerno, M. T., Cortimiglia, R., Crescimanno, G., & Amato, G. (1989). Effect of claustrum
 1155 activation on the spontaneous unitary activity of frontal eye field neurons in the cat.
 1156 *Neuroscience Letters*, 98(3), 299–304. [https://doi.org/10.1016/0304-3940\(89\)90418-7](https://doi.org/10.1016/0304-3940(89)90418-7)
- 1157 Salerno, M. T., Cortimiglia, R., Crescimanno, G., Amato, G., & Infantellina, F. (1984).

1158 Effects of claustrum stimulation on spontaneous bioelectrical activity of motor cortex
 1159 neurons in the cat. *Experimental Neurology*, 86(2), 227–239.
 1160 [https://doi.org/10.1016/0014-4886\(84\)90183-3](https://doi.org/10.1016/0014-4886(84)90183-3)
 1161 Saper, C. B., & Fuller, P. M. (2017). Wake-sleep circuitry: An overview. *Current Opinion in*
 1162 *Neurobiology*, 44, 186–192. PubMed. <https://doi.org/10.1016/j.conb.2017.03.021>
 1163 Saper, A., Kaplan, J. B., He, B. J., & Corbetta, M. (2007). Anatomical correlates of
 1164 directional hypokinesia in patients with hemispatial neglect. *The Journal of*
 1165 *Neuroscience : The Official Journal of the Society for Neuroscience*, 27(15), 4045–
 1166 4051. PubMed. <https://doi.org/10.1523/JNEUROSCI.0041-07.2007>
 1167 Scheef, L., Jankowski, J., Daamen, M., Weyer, G., Klingenberg, M., Renner, J., Mueckter, S.,
 1168 Schürmann, B., Musshoff, F., Wagner, M., Schild, H. H., Zimmer, A., & Boecker, H.
 1169 (2012). An fMRI study on the acute effects of exercise on pain processing in trained
 1170 athletes: *Pain*, 153(8), 1702–1714. <https://doi.org/10.1016/j.pain.2012.05.008>
 1171 Schmelz, M. (2010). Itch and pain. *Touch, Temperature, Pain/Itch and Pleasure*, 34(2), 171–
 1172 176. <https://doi.org/10.1016/j.neubiorev.2008.12.004>
 1173 Schulz, E., Stankewitz, A., Winkler, A. M., Irving, S., Witkovský, V., & Tracey, I. (2020).
 1174 Ultra-high-field imaging reveals increased whole brain connectivity underpins
 1175 cognitive strategies that attenuate pain. *ELife*, 9, e55028.
 1176 <https://doi.org/10.7554/eLife.55028>
 1177 Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A.
 1178 L., & Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for
 1179 Salience Processing and Executive Control. *The Journal of Neuroscience*, 27(9),
 1180 2349. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>
 1181 Segerdahl, A. R., Mezue, M., Okell, T. W., Farrar, J. T., & Tracey, I. (2015). The dorsal
 1182 posterior insula subserves a fundamental role in human pain. *Nature Neuroscience*,

1183 18(4), 499–500. <https://doi.org/10.1038/nn.3969>

1184 Seghier, M. L., Bagdasaryan, J., Jung, D. E., & Price, C. J. (2014). The Importance of
 1185 Premotor Cortex for Supporting Speech Production after Left Capsular-Putaminal
 1186 Damage. *Journal of Neuroscience*, 34(43), 14338–14348.
 1187 <https://doi.org/10.1523/JNEUROSCI.1954-14.2014>

1188 Sener, R. N. (1998). Lesions affecting the claustrum. *Computerized Medical Imaging and*
 1189 *Graphics*, 22(1), 57–61. [https://doi.org/10.1016/S0895-6111\(97\)00043-8](https://doi.org/10.1016/S0895-6111(97)00043-8)

1190 Serrano-Castro, P. J., Quiroga-Subirana, P., Payán-Ortiz, M., & Fernandez-Perez, J. (2013).
 1191 The expanding spectrum of febrile infection-related epilepsy syndrome (FIRES).
 1192 *Seizure - European Journal of Epilepsy*, 22(2), 153–155.
 1193 <https://doi.org/10.1016/j.seizure.2012.11.006>

1194 Sevel, L. S., O’Shea, A. M., Letzen, J. E., Craggs, J. G., Price, D. D., & Robinson, M. E.
 1195 (2015). Effective connectivity predicts future placebo analgesic response: A dynamic
 1196 causal modeling study of pain processing in healthy controls. *NeuroImage*, 110, 87–
 1197 94. <https://doi.org/10.1016/j.neuroimage.2015.01.056>

1198 Sherk, H., & LeVay, S. (1983). Contribution of the cortico-claustral loop to receptive field
 1199 properties in area 17 of the cat. *The Journal of Neuroscience*, 3(11), 2121.
 1200 <https://doi.org/10.1523/JNEUROSCI.03-11-02121.1983>

1201 Sherk, Helen. (1986). The Claustrum and the Cerebral Cortex. In E. G. Jones & A. Peters
 1202 (Eds.), *Sensory-Motor Areas and Aspects of Cortical Connectivity* (pp. 467–499).
 1203 Springer US. https://doi.org/10.1007/978-1-4613-2149-1_13

1204 Shiihara, T., Kato, M., Ichiyama, T., Takahashi, Y., Tanuma, N., Miyata, R., & Hayasaka, K.
 1205 (2006). Acute encephalopathy with refractory status epilepticus: Bilateral mesial
 1206 temporal and claustral lesions, associated with a peripheral marker of oxidative DNA
 1207 damage. *Journal of the Neurological Sciences*, 250(1), 159–161.

1208 <https://doi.org/10.1016/j.jns.2006.07.002>

1209 Shintaku, M., Kaneda, D., Tada, K., Katano, H., & Sata, T. (2010). Human herpes virus 6
 1210 encephalomyelitis after bone marrow transplantation: Report of an autopsy case.
 1211 *Neuropathology*, 30(1), 50–55. <https://doi.org/10.1111/j.1440-1789.2009.01020.x>

1212 Shintani, S., Tsuruoka, S., & Shiigai, T. (2000). Serial positron emission tomography (PET)
 1213 in gliomatosis cerebri treated with radiotherapy: A case report. *Journal of the*
 1214 *Neurological Sciences*, 173(1), 25–31. [https://doi.org/10.1016/S0022-](https://doi.org/10.1016/S0022-510X(99)00296-8)
 1215 [510X\(99\)00296-8](https://doi.org/10.1016/S0022-510X(99)00296-8)

1216 Silva, G., Jacob, S., Melo, C., Alves, D., & Costa, D. (2018). Claustrum sign in a child with
 1217 refractory status epilepticus after febrile illness: Why does it happen? *Acta*
 1218 *Neurologica Belgica*, 118(2), 303–305. <https://doi.org/10.1007/s13760-017-0820-9>

1219 Singh, S. P., Agarwal, S., & Faulkner, M. (2014). Refractory status epilepticus. *Annals of*
 1220 *Indian Academy of Neurology*, 17(5), 32–36.

1221 Sinniger, V., Porcher, C., Mouchet, P., Juhem, A., & Bonaz, B. (2004). C-fos and CRF
 1222 receptor gene transcription in the brain of acetic acid-induced somato-visceral pain in
 1223 rats: *Pain*, 110(3), 738–750. <https://doi.org/10.1016/j.pain.2004.05.014>

1224 Sleigh, J., Warnaby, C., & Tracey, I. (2018). General anaesthesia as fragmentation of
 1225 selfhood: Insights from electroencephalography and neuroimaging. *British Journal of*
 1226 *Anaesthesia*, 121(1), 233–240. <https://doi.org/10.1016/j.bja.2017.12.038>

1227 Słoniewski, P., Moryś, J., & Pilgrim, C. (1995). Stimulation of glucose utilization in the rat
 1228 claustrum by pain. *Folia Neuropathologica*, 33(3), 163–168.

1229 Smallwood, R. F., Laird, A. R., Ramage, A. E., Parkinson, A. L., Lewis, J., Clauw, D. J.,
 1230 Williams, D. A., Schmidt-Wilcke, T., Farrell, M. J., Eickhoff, S. B., & Robin, D. A.
 1231 (2013). Structural Brain Anomalies and Chronic Pain: A Quantitative Meta-Analysis
 1232 of Gray Matter Volume. *The Journal of Pain*, 14(7), 663–675.

1233 <https://doi.org/10.1016/j.jpain.2013.03.001>

1234 Smith, J. B., Watson, G. D. R., Liang, Z., Liu, Y., Zhang, N., & Alloway, K. D. (2019). A
 1235 Role for the Claustrum in Salience Processing? *Frontiers in Neuroanatomy*, 13, 64.
 1236 <https://doi.org/10.3389/fnana.2019.00064>

1237 Smythies, J., Edelstein, L., & Ramachandran, V. (2012). Hypotheses relating to the function
 1238 of the claustrum. *Frontiers in Integrative Neuroscience*, 6, 53.
 1239 <https://doi.org/10.3389/fnint.2012.00053>

1240 Smythies, J., Edelstein, L., & Ramachandran, V. (2014). Hypotheses relating to the function
 1241 of the claustrum II: does the claustrum use frequency codes? *Frontiers in Integrative*
 1242 *Neuroscience*, 8, 7–7. PubMed. <https://doi.org/10.3389/fnint.2014.00007>

1243 Snider, S. B., Hsu, J., Darby, R. R., Cooke, D., Fischer, D., Cohen, A. L., Grafman, J. H., &
 1244 Fox, M. D. (2020). Cortical lesions causing loss of consciousness are anticorrelated
 1245 with the dorsal brainstem. *Human Brain Mapping*, 41(6), 1520–1531.
 1246 <https://doi.org/10.1002/hbm.24892>

1247 Sperner, J., Sander, B., Lau, S., Krude, H., & Scheffner, D. (1996). Severe transitory
 1248 encephalopathy with reversible lesions of the claustrum. *Pediatric Radiology*, 26(11),
 1249 769–771. <https://doi.org/10.1007/BF01396197>

1250 Ständer, S., & Schmelz, M. (2006). Chronic itch and pain-Similarities and differences.
 1251 *European Journal of Pain*, 10(5), 473–473.
 1252 <https://doi.org/10.1016/j.ejpain.2006.03.005>

1253 Tan, L. L., Pelzer, P., Heintz, C., Tang, W., Gangadharan, V., Flor, H., Sprengel, R., Künér,
 1254 T., & Künér, R. (2017). A pathway from midcingulate cortex to posterior insula gates
 1255 nociceptive hypersensitivity. *Nature Neuroscience*, 20(11), 1591–1601.
 1256 <https://doi.org/10.1038/nn.4645>

1257 Tanné-Gariépy, J., Boussaoud, D., & Rouiller, E. M. (2002). Projections of the claustrum to

1258 the primary motor, premotor, and prefrontal cortices in the macaque monkey. *The*
1259 *Journal of Comparative Neurology*, 454(2), 140–157.
1260 <https://doi.org/10.1002/cne.10425>

1261 Tempel, A., & Zukin, R. S. (1987). Neuroanatomical patterns of the mu, delta, and kappa
1262 opioid receptors of rat brain as determined by quantitative in vitro autoradiography.
1263 Proceedings of the National Academy of Sciences of the United States of America,
1264 84(12), 4308–4312. PubMed. <https://doi.org/10.1073/pnas.84.12.4308>

1265 Terem, A., Gonzales, B. J., Peretz-Rivlin, N., Ashwal-Fluss, R., Bleistein, N., del Mar Reus-
1266 Garcia, M., Mukherjee, D., Groysman, M., & Citri, A. (2020). Claustral Neurons
1267 Projecting to Frontal Cortex Mediate Contextual Association of Reward. *Current*
1268 *Biology*, 30(18), 3522–3532.e6. <https://doi.org/10.1016/j.cub.2020.06.064>

1269 Torgerson, C. M., Irimia, A., Goh, S. Y. M., & Van Horn, J. D. (2015). The DTI connectivity
1270 of the human claustrum: Claustrum Connectivity. *Human Brain Mapping*, 36(3), 827–
1271 838. <https://doi.org/10.1002/hbm.22667>

1272 Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its
1273 Modulation. *Neuron*, 55(3), 377–391. <https://doi.org/10.1016/j.neuron.2007.07.012>

1274 Tsumoto, T., & Suda, K. (1982). Effects of stimulation of the dorsocaudal claustrum on
1275 activities of striate cortex neurons in the cat. *Brain Research*, 240(2), 345–349.
1276 [https://doi.org/10.1016/0006-8993\(82\)90233-5](https://doi.org/10.1016/0006-8993(82)90233-5)

1277 Turkalj, I., Stojanovic, S., Petrovic, K., Njagulj, V., Mikov, I., & Spanovic, M. (2012).
1278 Psychosis following stab brain injury by a billiard stick. *Hippokratia*, 16(3), 275–277.
1279 PubMed.

1280 Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction.
1281 *Nature Reviews Neuroscience*, 16(1), 55–61. <https://doi.org/10.1038/nrn3857>

1282 Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the

1283 rat. *Synapse (New York, N.Y.)*, 51(1), 32–58. <https://doi.org/10.1002/syn.10279>

1284 Volkers, R., Giesen, E., Heiden, M., Kerperien, M., Lange, S., Kurt, E., Dongen, R., Schutter,
1285 D., Vissers, K. C. P., & Henssen, D. (2020). Invasive Motor Cortex Stimulation
1286 Influences Intracerebral Structures in Patients With Neuropathic Pain: An Activation
1287 Likelihood Estimation Meta-Analysis of Imaging Data. *Neuromodulation:
1288 Technology at the Neural Interface*, 23(4), 436–443.
1289 <https://doi.org/10.1111/ner.13119>

1290 Vyazovskiy, V. V., Faraguna, U., Cirelli, C., & Tononi, G. (2009). Triggering slow waves
1291 during NREM sleep in the rat by intracortical electrical stimulation: Effects of
1292 sleep/wake history and background activity. *Journal of Neurophysiology*, 101(4),
1293 1921–1931. <https://doi.org/10.1152/jn.91157.2008>

1294 Vyazovskiy, V. V., & Harris, K. D. (2013). Sleep and the single neuron: The role of global
1295 slow oscillations in individual cell rest. *Nature Reviews. Neuroscience*, 14(6), 443–
1296 451. PubMed. <https://doi.org/10.1038/nrn3494>

1297 Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An
1298 fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of
1299 Medicine*, 368(15), 1388–1397. <https://doi.org/10.1056/NEJMoa1204471>

1300 Wang, Q., Ng, L., Harris, J. A., Feng, D., Li, Y., Royall, J. J., Oh, S. W., Bernard, A., Sunkin,
1301 S. M., Koch, C., & Zeng, H. (2017). Organization of the Connections Between
1302 Clastrum and Cortex in the Mouse. *The Journal of Comparative Neurology*, 30.
1303 White, M. G., Panicker, M., Mu, C., Carter, A. M., Roberts, B. M., Dharmasri, P. A., &
1304 Mathur, B. N. (2018). Anterior Cingulate Cortex Input to the Clastrum Is Required
1305 for Top-Down Action Control. *Cell Reports*, 22(1), 84–95.
1306 <https://doi.org/10.1016/j.celrep.2017.12.023>

1307 Wolff, S. B., & Ölveczky, B. P. (2018). The promise and perils of causal circuit

1308 manipulations. *Current Opinion in Neurobiology*, 49, 84–94. PubMed.
 1309 <https://doi.org/10.1016/j.conb.2018.01.004>
 1310 Xu, A., Larsen, B., Baller, E. B., Scott, J. C., Sharma, V., Adebimpe, A., Basbaum, A. I.,
 1311 Dworkin, R. H., Edwards, R. R., Woolf, C. J., Eickhoff, S. B., Eickhoff, C. R., &
 1312 Satterthwaite, T. D. (2020). Convergent neural representations of experimentally-
 1313 induced acute pain in healthy volunteers: A large-scale fMRI meta-analysis.
 1314 *Neuroscience & Biobehavioral Reviews*, 112, 300–323.
 1315 <https://doi.org/10.1016/j.neubiorev.2020.01.004>
 1316 Xu, X., Fukuyama, H., Yazawa, S., Mima, T., Hanakawa, T., Magata, Y., Kanda, M.,
 1317 Fujiwara, N., Shindo, K., Nagamine, T., & Shibasaki, H. (1997). Functional
 1318 localization of pain perception in the human brain studied by PET. *Neuroreport*, 8(2),
 1319 555–559. <https://doi.org/10.1097/00001756-199701200-00035>
 1320 Yasui, K., Ieda, T., Arahata, Y., Suzuki, Y., & Sobue, G. (1999). [An adult patient of Reye’s
 1321 syndrome—The possible background mechanism of lesions in claustrum, striatum and
 1322 limbic system and limbic dementia]. *Rinsho shinkeigaku = Clinical neurology*, 39(9),
 1323 920–924.
 1324 Yeo, S., Rosen, B., Bosch, P., van den Noort, M., & Lim, S. (2016). Gender Differences in
 1325 the Neural Response to Acupuncture: Clinical Implications. *Acupuncture in Medicine*,
 1326 34(5), 364–372. <https://doi.org/10.1136/acupmed-2015-011025>
 1327 Yoshimura, N., Yoshimura, I., Asada, M., Hayashi, S., Fukushima, Y., Sato, T., & Kudo, H.
 1328 (1988). Juvenile Parkinson’s disease with widespread Lewy bodies in the brain. *Acta*
 1329 *Neuropathologica*, 77(2), 213–218. <https://doi.org/10.1007/BF00687434>
 1330 Zingg, B., Dong, H.-W., Tao, H. W., & Zhang, L. I. (2018). Input-output organization of the
 1331 mouse claustrum. *Journal of Comparative Neurology*, 526(15), 2428–2443.
 1332 <https://doi.org/10.1002/cne.24502>

1333 Zingg, B., Hintiryan, H., Gou, L., Song, M. Y., Bay, M., Bienkowski, M. S., Foster, N. N.,
1334 Yamashita, S., Bowman, I., Toga, A. W., & Dong, H.-W. (2014). Neural networks of
1335 the mouse neocortex. *Cell*, 156(5), 1096–1111. PubMed.
1336 <https://doi.org/10.1016/j.cell.2014.02.023>
1337 Zuhorn, F., Omainen, H., Ruprecht, B., Stellbrink, C., Rauch, M., Rogalewski, A.,
1338 Klingebiel, R., & Schäbitz, W.-R. (2020). Parainfectious encephalitis in COVID-19:
1339 “The Claustrum Sign.” *Journal of Neurology*, 1–4. PubMed.
1340 <https://doi.org/10.1007/s00415-020-10185-y>
1341

Appendix - Supplementary information

Study selection: The meta analysis was conducted on Scopus and PubMed by searching “((claustrum) AND (lesion)) OR ((claustrum) AND (injury)) OR ((claustrum) AND (contusion)) OR ((claustrum) AND (trauma))”. From this search, 103 studies were found. 5 inclusion and exclusion criteria were used for the study selection in this review. (1) Studies have to be primary sources (clinical) and (2) conducted on humans. (3) The claustrum lesion has to be defined explicitly. (4) The claustrum lesion has to be confirmed with neuroimaging and/or post-mortem techniques. (5) Major lesion and trauma resulting in death were excluded. For case studies, details of the case study has to be given explicitly. Studies written in the English language (unless translated) were included only. There was no preference in age or sex in study selection. We have also extended our searched by checking papers on the first ten pages of Google Scholar by searching “claustrum lesion in humans” and “external capsule lesions in humans” as well as PubMed by searching “(external capsule[Title/Abstract]) AND (lesions)”. These extra studies found by this extended search were included if they met the criteria as ‘Studies found through extended search’.

Seizure categorisation: The word table includes standardised seizure reporting according to ILAE 2017. ‘*Non-seizure disturbance of consciousness*’ used as a general term includes LOC/reduced conc not associated with a seizure, consciousness disturbance, Electroencephalogram (EEG) showed a diffuse slow wave of 3–4 Hz, slight drowsiness

Seizure and symptom categorisation: 12 main categories were used to summarise the symptoms. The inclusion of each categories as below; (1) *Cognitive impairment* includes deficits in memory, retaining information, learning, concentrating, decision-making and/or disorientation; severe cognitive dysfunction in simple and complex attention, reasoning, problem solving and memory, being even unable to recall her age and the exact date; consciousness disturbance, cognition gradually became impaired, disorientation with regard to time and place, loss of short-term memory, disorientation in time, abulia, cognitive impairment, bradypsychia, impaired attention and concentration functions and impaired judgement (2) *Motor disturbance* includes hemiparesis; was not able to walk without support; hemiplegia (3) *Visual disturbance* includes trouble seeing, visual hallucinations, nystagmus, diplopia, persistent bilateral amaurosis, temporary loss of vision (4) *Auditory disturbances* includes trouble hearing, auditory hallucinations, hearing loss, tinnitus (5) *Speech disturbances* includes any change in language abilities, dysarthria, loss of speech (6) *Non-seizure EEG abnormality* as results of EEG signals compared to health people (7) *Sleep disturbance* includes change in sleep quality or quantity, somnolence, hypersomnia, sleep disturbance, restlessness (8) *Hallucinations* includes psychosis, experiencing something that is not there, visual hallucinations and reported seeing cats and people who were not present, auditory hallucinations: clicking sounds and strange voices, psychotic behaviour, Cotard delusion (a belief that you are dead) (9) *Delusion* includes A belief directly contradicted by reality, psychotic behaviour; delusion of infidelity; delusions with paranoid and religious content; repeatedly stated that she was dead (10) *Tremor* includes involuntary, rhythmic muscle contraction leading to shaking movements in one or more parts of the body, a tongue tremor of 5-6 Hz; tremors of the finger (11) *Paraesthesia* includes abnormal skin sensations including tingling, pricking, chilling, burning, numbness without local cause, Abnormal gustatory sensations.

Table 1: Details of the case studies that reported claustrum-only lesion studies (n=7)

Study	Hemisphere	Other lesion sites	Pathology	Seizure classification	Observations	Case evolution
Hwang et al. 2014	Unilateral, right	Bilateral external capsule	Unknown	Age - 28 Convulsive Status Epilepticus (CSE) (A.I.c Unknown whether focal or generalised) Seizure-free (IV phenytoin, lamotrigine, levetiracetam) EEG showed generalised spikes. Modulation and effect of intervention on EEG not recorded.	Cognitive impairment (Confusion, cognitive impairment, short term memory impairments.) Non-seizure EEG abnormality (Diffuse slow-wave discharges on EEG.) Unilateral non-tremor motor disturbance (Transient postural instability) Non-seizure disturbance of consciousness (Gradual worsening of status epilepticus of unknown aetiology over 3 days without full recovery of consciousness in the latter stages.)	Recovery 20 days later after first seizure.
Ishii et al. 2011	Bilateral		Mumps encephalitis	Age - 21 Day 1 Unknown onset, motor (tonic-clonic), Convulsive status epilepticus (A.I.c. Unknown whether focal or generalised) Day 14 Focal to bilateral tonic clonic. Periodic discharges on EEG. Day 65 Seizure-free (acute IV Midazolam, intermediate IV midazolam, chronic oral sodium valproate and phenytoin) Location, morphology, time-related features, modulation and effect of intervention on EEG unspecified.	Cognitive impairment (confusion and disorientation) Hallucinations (visual and auditory) Visual disturbances (visual hallucinations) Auditory disturbances (auditory hallucinations) Tremor (tongue) Other (Flu-like symptoms - fever, headache, vomiting)	Complete recovery, control of seizures at day 65 by anticonvulsant (phenytoin and sodium valproate)
Maximov et al. 2018 ^a	Left		Ischaemic stroke	Age - 55	Visual disturbances (mixed horizontal and rotary nystagmus to the right side) Auditory disturbances (decreased hearing) Paresthesia (abnormal gustatory sensations on the left-hand side of tongue and peribuccal region, spread to left hand side of face and head) Other (Dizziness, static ataxia and ataxic gait)	4 weeks of therapy elicited full recovery
Mumoli et al. 2014 ^a	Bilateral	Bilateral external capsule	Febrile infection-related epilepsy syndrome (FIRES)	Age - 14 Unknown onset, motor Convulsive status epilepticus (CSE) (A.I.b. Focal onset evolving into bilateral convulsive SE) EEG showed focal rhythmic spikes and delta activity with generalisation. Treatment failure (IV valproate and midazolam) Modulation and effect of intervention on EEG not recorded.	Cognitive impairment (confusion) Non-seizure EEG abnormality Visual disturbances (visual disturbances) Auditory disturbances Other (Fever, generalised seizures, EEG revealed focal rhythmic spikes at 5–10 Hz, auditory disturbances, visual disturbance, refractory development with poor response to drugs.	Still some seizures
Silva et al. 2018 ^a	Bilateral		New-onset refractory status epilepticus (NORSE)	Age - 6 Day 1 Unknown onset, convulsive status epilepticus Seizure free (IV diazepam) but mental status non recovery Day 2 Seizure free (oral valproate, phenytoin and levetiracetam) “Focal tonic-clonic movements in the left superior limb”	Non-seizure EEG abnormality (occipital intermittent rhythmic delta activity) Other (Flu-like symptoms, fever, headache)	Complete recovery, control of seizures within a day of anticonvulsants (valproate, phenytoin, and levetiracetam, seizure free for 6 months).
Sperner et al. 1996	Bilateral	Bilateral external capsule	Transient non-viral encephalitis	Age - 12 On admission, Convulsive Status Epilepticus (CSE) (A.I.c Unknown whether focal or generalised) Hospitalised, focal-onset impaired awareness. Seizure-free (IV phenytoin and diazepam).	Cognitive impairment (severe cognitive impairment) Non-seizure EEG abnormality (EEG displayed generalised slowing and right-sided sharp slow waves for 4 weeks.) Delusions (psychosis) Visual disturbances (temporary loss of vision)	Complete recovery

				EEG showed right-lateralized sharp waves. Modulation and effect of intervention on EEG not recorded.	Auditory disturbances (temporary loss of hearing) Speech disturbances (temporary loss of speech) Unilateral non-tremor motor disturbance (Not able to walk without support - limb weakness.)	
Zuhorn et al. 2020	Bilateral	Bilateral external capsule	Parainfectious autoimmune encephalitis	Age - 54	Cognitive impairment (disorientation, stupor, delirious behaviour, mild cognitive impairment)	Complete recovery in neurological and cognitive status. However, the claustrum lesions persisted.

^a Studies found through extended search

^b Studies in which individual patient details are not provided; data is presented as aggregate

^c Studies in foreign language; abstract in English only

^d Poor lesion specificity and so has been excluded from case study table and analysis

Table 2: Details of the case studies that reported claustrum lesion along with other regions (n=31)

Study	Hemisphere	Other lesion sites	Pathology	Seizure classification	Observations	Case evolution
Albayrak et al. 2008	Unilateral, right	Left calcarine cortex, right external capsule	Closed head injury		Visual disturbances (Bilateral amaurosis, but pupils isocoric and reactive to light bilaterally. Cortical. Visual pathways intact.)	Resolution of lesions, but no clinical recovery of vision
Barcikowska et al. 1979 ^{a,c}	Unilateral, side not specified	Lower part of the cortex of the insula, capsula extrema, uncinate and fronto-occipital fascicles	Dejérine-Roussy syndrome		Unilateral non-tremor motor disturbance (Transient hemiparesis, thalamic position of hand) Paresthesia (hemihypoesthesia, lancinating pains of a hand)	
Biemond 1956 ^a	Unilateral, right	3 confluent small foci of softening in the opposite sides of the insula and parietal operculum; area of secondary degeneration in the ventral part of the thalamocortical radiation; marked cellular loss in the posterolateral and posteromedial ventral nuclei of the thalamus. Operative lesion on the right inferior parietal lobe and softening of the medulla.	Special type of thalamic syndrome resulting from a slight vascular accident.		Unilateral non-tremor motor disturbance (Powerlessness in the left arm and left leg. Hemiparesis on the left side improved over 4 weeks. Heightened achilles tendon reflex on left; reflex of Mayer could not be elicited on left. Abdominal reflexes lower than right. Proprioceptive disturbance in left arm and hand after operation for 3 weeks. Hyperpathia) Paresthesia (Gradual increase in pain on left side, cold sensation on left side of abdomen - persisted throughout investigation. Increasing sensitivity to touch - persistent (typical hyperpathia). Could not differentiate touch of pin head or point.) Other (Depression, suicidal ideation greater left side perspiration)	IV sodium iodide had no change on prognosis. Excision of part of the right posterior parietal cortex. Diminished pain and hypersensitivity, but persisted. Suicide 1.5 years after first observation - gas.
Biemond 1956 ^a	Unilateral, right (claustrum not found)	Tumour in region of right external capsule - well defined, no infiltration. Brain distinctly flattened, pressure cone at the tonsils	Necrotic tumour (glioma), suggested		Cognitive impairment (Bradyphrenia and disorientation.) Unilateral non-tremor motor disturbance (Minimal paresis of left facial nerve and left arm.)	Death after a few months.

		of the cerebellum. Displacement of the insula to the outside and striatum dorsomedially. Internal capsule medially displaced and stretched longitudinally. Compression of the greater part of the right lateral ventricle. Partial demyelination of the putamen and pallidum. External capsule not recognised. Demyelination of corona radiata.	origin being claustrum.		Paresthesia (Pain localised to the right eye and radiated to the right side of neck - hyperalgesia and hypothermia of the left side of the body.) Other (Bilateral papilloedema)	
Chakraborty et al. 2014 ^a	Left	Multiple cortical (insular, medial and lateral frontal cortex), and periventricular (caudate head) discrete ring enhancing lesions and associated surrounding oedema	Multiple parenchymal neurocysticercosis		Sleep disturbances (Sleep disturbances) Delusions (Delusion of jealousy) Unilateral non-tremor motor disturbance (left-sided hemiplegia)	Recovered
Chessa et al. 2017	Bilateral	Extensive: white matter of semioval centres, temporal lobe, external capsule, claustrum, subinsular regions and midbrain	Neuropsychiatric systemic lupus erythematosus (NPSLE)		Cognitive impairment (Severe cognitive dysfunction in simple and complex attention, reasoning, problem solving and memory, being even unable to recall her age and the exact date.) Visual disturbances (Bilateral nystagmus, diplopia) Speech disturbances (dysarthria) Unilateral non-tremor motor disturbance (lower-limb ataxia and bilateral sixth and left seventh cranial nerve palsies were found. She also had weakness in the right side of her body, lower limbs sensory loss and hyper-reactive deep tendon reflexes with left foot dorsiflexion deficit.)	Recovered
Couto et al. 2013	Unilateral, right	Right putamen and external capsule	Right subcortical haemorrhagic stroke		Unilateral non-tremor motor disturbance (Left sided hemiparesis and hemianaesthesia.) Other (No neurological deficits, only complained about pain in left arm, leg and foot.)	Recovered after 4 months
Dodgson 1955 ^a	Bilateral	Bilateral insular microgyria, abnormal frontal and temporal sulci adjacent to the insula	Neurodevelopmental abnormality		Other (Infantile death, significant brain malformation, musculoskeletal abnormalities, cyanosis and stridor breathing.)	Died shortly after birth
Hiraga et al. 2014	Bilateral	Bilateral medial temporal lobes	VGK (voltage-gated potassium channel) antibody-associated encephalitis	Age - 65 Unknown onset motor (other motor) Nature of the intervention and mode of application unspecified. No EEG.	Cognitive impairment (Acute consciousness disturbance, comatose with clonic seizures. Memory loss.)	Recovered with some memory dysfunction

Ishida et al. 2006 ^{a,c}	Bilateral	Right hippocampus	Non-herpetic acute limbic encephalitis (NHALE)	Generalised onset, motor (tonic-clonic) seizure; seizure free in response to intervention with undetermined adverse effects (1C). Anti-epileptic agents regime not specified. No EEG.	Cognitive impairment (Disturbance of short-term memory) Speech disturbances (Ataxia) Unilateral non-tremor motor disturbance (Ataxia) Non-seizure disturbance of consciousness (Consciousness disturbance) Other (Change of character)	Resolution of symptoms spontaneously, but short-term memory disturbance persisted
Jellinger et al. 2011	Bilateral	Diffuse tauopathy: parietal, temporal, occipital cortex, frontal cortex, hippocampus, putamen, thalamus and subthalamus, white matter.	Tauopathy		Cognitive impairment (Progressive decline in spatial orientation and visual functions for 2 years. Preserved memory and motor perception, gradually progressing to dementia, without extrapyramidal signs.) Visual disturbances (He showed impaired optic fixation, optic ataxia, agraphia, acalculia, ideomotor apraxia, disturbed right-left differentiation but preserved colour matching)	Deceased
Kurokawa et al. 2005 ^{a,c}	Bilateral	Subcortical white matter of insular cortex, external capsule, putamen and globus pallidus	Encephalopathy with unknown cause - sugihiratake mushroom	Focal onset (motor), with progression to generalised convulsive status epilepticus (A.1.a); treatment failure in response to intervention with undetermined adverse effects (1C). Anti-epileptic agent regime not specified. No EEG.	Non-seizure EEG abnormality (EEG in comatose state showed periodic synchronous discharge (PSD)) Speech disturbances (Dysarthria) Unilateral non-tremor motor disturbance (Weakness and involuntary movements of extremities)	Improvement of seizures gradually
Lapenta et al. 2015 ^a	Bilateral	Bilateral hippocampus	New-onset refractory status epilepticus (NORSE)	Age - 17 Generalised onset, motor (tonic-clonic). Subsequent Focal motor Status Epilepticus (A.3.a. Repeated focal motor seizures (Jacksonian)) Treatment failure (diazepam and valproic acid) Development into Myoclonic Status Epilepticus (prominent epileptic myoclonic jerks) (A.2.a. With coma) Treatment failure (phenytoin, valproic acid, levetiracetam, lacosamide, carbamazepine). EEG showed lateralised (left) seizure onset with periodic discharges and sharp waves. Mode of application of intervention unspecified. Modulation and effect of intervention on EEG not recorded.	Cognitive impairment (frontal cognitive impairment) Tremor (bilateral intention tremor) Other (Fever)	When discharged, patient had bilateral intentional tremor of the hands and myoclonic seizures without loss of consciousness. Slight impairment in frontal functions.
Matsuzono et al. 2013	Bilateral	Periventricular	Non-herpetic acute limbic encephalitis		Cognitive impairment (impaired cognition) Non-seizure EEG abnormality (EEG diffuse wave of 3-4 Hz) Auditory disturbances (Hearing loss and tinnitus) Unilateral non-tremor motor disturbance (myoclonus) Tremor (unstable and wide-based gait - Parkinsonism) Non-seizure disturbance of consciousness (Consciousness stupor - GCS 11)	Complete recovery
McKay and Cipolotti 2006 ^a	Unilateral, right	Bilateral insula (but less severe changes in left insular cortex), right adjacent white matter	Herpes simplex encephalitis	Age - 24 Focal and motor onset, Convulsive Status Epilepticus (CSE) (A.1.b. Focal onset evolving into bilateral convulsive SE) No EEG. No discussion of anti-epileptic medication.	Cognitive impairment (Short term memory impairment for faces, words and visual information.) Hallucinations (musical, tactile and visual) Cotard (Cotard delusion) Delusions (Cotard delusion)	Complete recovery

McMurtray et al. 2014 ^a	Left	Left basal ganglia with adjacent oedema likely affecting the corona radiata and possibly extending to the optic radiations Small periventricular hyperintensities	Haemorrhagic stroke		Hallucinations (visual and auditory hallucinations) Cotard (hemicotard) Delusions (delusions of rotting/decaying of the right (paralysed) side of his body) Visual disturbances (visual hallucinations) Auditory disturbances (auditory hallucinations) Unilateral non-tremor motor disturbance (Right-sided weakness, hemiparesis)	Treated with antipsychotics
Mizutani et al. 2020	Bilateral	Reversible splenial lesion (corpus callosum), also hippocampus, amygdala, insula, perisylvian operculum and basal ganglia.	New-onset refractory status epilepticus (NORSE)	Age - 30 Generalised onset, motor (tonic-clonic) Drug-resistant ("antiepileptics") Status Epilepticus EEG generalized rhythmic high-voltage slow-background activity, frequent multifocal spikes and sharp waves. Nature of the intervention and mode of application unspecified. Modulation and effect of intervention on EEG not recorded.	No other observations.	Reversible splenial lesion, lasting hyperintensities in claustrum and other regions. Seizures remitted and continued for 1.5 months before improvement.
Nixon et al. 2001	Unilateral, right	Bilateral temporal lobe, hippocampi atrophy	Idiopathic	Age - 35 Unknown onset, motor Subsequent generalised onset, motor (tonic-clonic). Progression to Convulsive Status Epilepticus (CSE) (A.I.a. Generalised convulsive). Drug resistance with treatment failure (IV phenytoin, acyclovir, phenobarbitone, thiopentone) EEG showed generalised slow-wave activity, progressed to generalised periodic discharges. Modulation and effect of intervention on EEG not recorded.	Cognitive impairment (confusion, disorientation in time) Non-seizure disturbance of consciousness (LOC, slight drowsiness)	Death by cardiovascular and respiratory complications
Nomoto et al. 2007 ^a	Bilateral	Bilateral medial temporal lobe, insulae, putamen	Sugihiratake Mushrooms, acute encephalopathy		Sleep disturbances (somnolent) Speech disturbances (Dysarthria) Unilateral non-tremor motor disturbance (mild right hemiparesis including face, tetraplegia) Non-seizure disturbance of consciousness (coma)	Recovered
Obara et al. 2008 ^a	Bilateral	Bilateral putamen, caudate nuc, nuc accumbens, cysts in cerebral cortex, hindbrain damage too	Sugihiratake / Angel's wing mushroom	Age - 65 Unknown onset, motor (tonic-clonic) Convulsive Status Epilepticus (CSE) (A.I.a Generalised convulsive) Seizure free (diazepam and phenytoin) Mode of application unspecified. No EEG.	Speech disturbances (Dysarthria) Non-seizure disturbance of consciousness (Consciousness disturbance, Comatose).	Regained consciousness but could only communicate with simple sentences
Obrador et al. 1956 ^a	Unilateral, right	Inferoexternal part of the putamen, external capsule	Arterial/vascular lesion		Unilateral non-tremor motor disturbance (Hemiparesis in left arm and leg, progression into hemiplegia. 24 hours since first symptoms, relief and movement of left hand restored. Limb - upper and lower - movement restored more slowly.) Paraesthesia (Numbness in left lower limb, followed by acute radiation to left upper limb. Paraesthetic sensations months later in left face and upper limb. Gradual increase in intensity)	Patient died by suicide following failed surgery to alleviate pain, prodromal depression.

					for a couple of months, spread to entire left side of body. Hyperalgesia to touch.) Other (5 years prodromal arterial hypertension. Dizziness, pain in right frontotemporal region. Headache rising in severity. Fever persistent for 48 hours. Muscle tone normal, normal neurological limb examination. No cog impairment. Normal EEG. Autopsy for claustrum lesion.)	
Okamoto et al. 2007 ^a	Bilateral	Bilateral medial temporal lobes, insula, basal ganglia, hippocampus	Non-herpetic acute limbic encephalitis (NHALE)	Age - 43 Unknown onset, motor (tonic-clinic) Convulsive status epilepticus (CSE) (A.I.c. unknown whether focal or generalised) Treatment failure ("anticonvulsants"). EEG showed periodic sharp waves. Nature of the intervention and mode of application unspecified. Location of discharges, modulation and effect of intervention on EEG not recorded.	Non-seizure EEG abnormality (EEG showed periodic sharp waves.)	Fatal 28 days after onset
Saito et al. 2007 ^a	Bilateral	Diffuse cortical atrophy appeared during the recovery phase, decrease in bifrontal blood flow.	Bronchopneumonia Acute encephalitis	Age - 10 Unknown onset, motor (tonic clonic) Initial drug failure (IV midazolam and barbiturates). Seizure-free (oral phenytoin and clonazepam) EEG showed partial suppression of multifocal spikes with IV high-dose pentobarbital; tapering of dose revealed pattern again. Generalised periodic discharges persisted; IV zonisamide and potassium bromide revealed burst-suppression pattern.	Non-seizure disturbance of consciousness (fluctuation of consciousness) Other (Headache, fever, EEG and brain appearance normal.)	At 60 days, therapeutics resolved fever; seizures persisted. Complete recovery
Seghier et al. 2014	Unilateral, left	All on the left side: putamen, most of the globus pallidus, a dorsal part of caudate nucleus, anterior internal capsule, external capsule, superior occipitofrontal fasciculus and the corona radiata.	Stroke in the left lentiform nucleus		Speech disturbances (Only aphasic for auditory repetition of words and non-words 15 months after stroke.) Other (Initial observations not specified.)	Not specified
Serrano-Castro et al. 2013 ^a	Bilateral	Bilateral insula	Febrile infection-related epilepsy syndrome (FIRES)	Age - 19 Focal onset, motor onset, aware Focal motor Status Epilepticus (A.3.a. Repeated focal motor seizures (Jacksonian)) EEG showed generalised spikes and sharp waves. Seizure free (IV levetiracetam, clonazepam, methylprednisolone) Modulation and effect of intervention on EEG not recorded.	Speech disturbances (dysarthria) Sleep disturbances (nocturnal seizures) Other (Flu-like symptoms, fever)	Recovered
Shihara et al. 2006	Bilateral	Bilateral hippocampus, amygdala, bilateral mesial temporal	Acute encephalopathy with refractory	Age - 12 Focal onset, aware, motor onset. Convulsive Status Epilepticus CSE (Focal onset evolving into bilateral convulsive SE)	Speech disturbances (seven months after the onset, she could not speak) Non-seizure disturbance of consciousness (Consciousness disturbance without focal neurological signs)	Severe atrophy developed. Seven months after the onset, she could not speak or sit alone.

			status epilepticus	EEG showed multifocal spikes or sharp waves. Treatment failure with progression to drug resistant CSE (phenobarbital, phenytoin, valproate, midazolam, thiamylal, propofol). Mode of application unspecified. Modulation and effect of intervention on EEG not recorded.		Anti-epileptics caused leukopenia, hypotension, atelectasis, thrombophlebitis, renal failure and liver failure
Shintaku et al. 2010	Bilateral	Widespread atrophy and lesions to: cerebral cortex (medial temporal lobe), insular cortex, hippocampus, amygdala, mamillary body, thalamus, pontine base, lumbar cord, cerebellar white matter, midbrain.	Human herpes virus 6 (HHV6) induced encephalomyelitis following an allogenic bone marrow transplant (BMT) to treat acute myeloid leukaemia.		Cognitive impairment (At 35 days post-BMT: short term memory deficits, space and time disorientation, STM deficit) Sleep disturbances (At 35 days post-BMT: somnolence) Tremor (At 35 days post-BMT: tremors of the fingers.)	4 months after BMT, increased severity of sensory aphasia and tremor. Death after a clinical course of 6 months.
Shintani et al. 2000	Unilateral, right	Left thalamus, right temporal lobe, and pons	Gliomatosis cerebri		Cognitive impairment (abulia) Sleep disturbances (hypersomnia) Unilateral non-tremor motor disturbance (Bilateral hemiparesis)	Recovered
Turkalj et al. 2012 ^a	Left	A 10 cm tubular area of posttraumatic encephalomalacia of the left hemisphere (left orbitofrontal region, insula, putamen, deep white matter and parietal lobe with consecutively slightly enlarged left lateral	Stabbing injury from a billiard stick		Cognitive impairment (bradypsychia anosognosia) Non-seizure EEG abnormality (showed slow left temporal activity.) Hallucinations (visual hallucinations) Delusions (Delusions with paranoid and religious content, Psychosis) Visual disturbances (left mydriasis, visual hallucinations)	Recovered from hallucinations
Yoshimura et al. 1988	Not specified, just "claustrum"	Widespread Lewy bodies – diencephalon, brain stem, sympathetic ganglia, entire cerebral cortex.	Juvenile Parkinson's		Cognitive impairment (Memory loss in later disease) Sleep disturbances (restlessness) Unilateral non-tremor motor disturbance (weakness of his extremities) Tremor (tremor) Other (Full signs and symptoms of classical Parkinson's disease – tremor and rigidity of neck and extremities, loss of associated movement, stooped posture, facial masking and pro- and retropulsion. Gait disturbances, stiffness and weakness of extremities, treated well for 4 years with L-DOPA before hospitalisation, hypersexuality)	Progressive worsening of condition until death 14 years after diagnosis.
Yasui et al. 1999 ^{a,c}	Not defined, likely to be unilateral	Hippocampus, amygdala	Post-infectious encephalitis in limbic system	Unknown onset and unclassified status epilepticus; treatment failure in response to intervention with undetermined adverse effects (1C). Anti-epileptic agents regime not specified. No EEG.	Cognitive impairment (Limbic dementia)	Improved dramatically but limbic dementia persisted

			after Reye's syndrome			
--	--	--	-----------------------	--	--	--

^a Studies found through extended search

^b Studies in which individual patient details are not provided; data is presented as aggregate

^c Studies in foreign language; abstract in English only

^d Poor lesion specificity and so has been excluded from case study table and analysis

Table 3: Details of the cohort studies that reported claustrum lesion along with other areas (n=14)

Study	Patients (n)	Hemisphere	Other areas	Pathology	Observations	Case evolution
Chau et al. 2015 ^{a,b}	171		Variable and undefined on aggregate; most limited to cortex and white matter	Penetrating head injury	Non-seizure disturbance of consciousness (Loss of consciousness (Prolonged N=16, transient N=91, none N=64) "Claustrum damage was associated with the duration, but not frequency, of loss of consciousness, indicating that the claustrum may have an important role in regaining, but not maintaining, consciousness")	
Choi et al. 2019	10/13	Bilateral	3/10 neocortex, 2/10 bilateral pulvinar 1) Bilateral mesial temporal 2) Bilateral mesial temporal 3) Bilateral mesial temporal 4) Bilateral mesial temporal, multiple neocortex sites and pulvinar 6) Bilateral mesial temporal 7) Bilateral mesial temporal, multiple neocortex sites and pulvinar 10) Bilateral mesial temporal and frontal cortex 11) Bilateral mesial temporal 12) Bilateral mesial temporal 13) Bilateral mesial temporal	New-onset refractory status epilepticus (NORSE)	Prodromal symptoms: 1) fever, headache, myalgia, memory impairment 2) Fever, upper respiratory tract infection, memory impairment, confusion, Bi-LPD 3) Fever, myalgia, headache, memory impairment, language impairment, somnolence, Bi-LPD 4) myalgia, upper respiratory tract infection, confusion, GPD 6) fever, nausea, memory impairment, GPD 7) fever, myalgia, somnolence, confusion, language impairment, Bi-LPD 10) headache, confusion, language impairment, GPD 11) fever, headache, myalgia, memory impairment, language impairment, Bi-LPD 12) fever, headache, myalgia, somnolence, confusion, labile mood, LPD 13) fever, myalgia, upper respiratory tract infection, confusion, GPD All presented with status epilepticus. GPD = generalised periodic discharge Bi-LPD = bilateral independent lateralised periodic discharge LPD = lateralised periodic discharge	Poor prognosis (with extratemporal/claustrum involvement) BUT scarce data available about the prognostic significance of claustrum involvement. Differs between patient. Range: ICU day 4-129 Hospital day 26-129
Duffau et al. 2007 ^{a,b}	42	12 left 30 right Complete removal of affected claustrum during surgery	Insula	WHO grade II glioma	All had seizures postoperatively. No description of seizure type and outcome. No EEG. No description; mention conspicuous absence of Sx on CLA lesion.	39 patients recovered a normal neurological examination in 3 months 3 patients had permanent left hemiparesis (stroke).
Freedman et al. 1984	3	Unilateral, left	Anterolateral to the left frontal horn, anterior portion of the head of the caudate, anterior limb of the internal capsule, anterior	Infarction, transcortical motor aphasia (TCMA)	Mild auditory comprehension problems. 9) Moderate hemiparesis 12) Infarction, facial weakness, stuttering 13) Infarction, facial weakness	Not specified

			putamen, anterior portion of external capsule, insula			
Gustafson et al. 1998 ^{a, d}	2 IV:2 IV:9	Not specified	Varied and extensive. IV:2 and IV:9 experienced atrophy and degeneration in all following regions, although to different degrees: hypothalamus, corpora mamillaria, central thalamic nuclei, brain stem, substantia nigra, pontine nuclei, cortex - temporoparietal, frontal, anterior cingulate, posterior cingulate, sensory motor	Alzheimer encephalopathy (presenile dementia)	IV:2 and IV:9 Generalised motor onset (tonic-clonic) and other motor (myoclonia). No EEG. IV:2 Cognitive impairment (Early amnesia (spatial orientation, but preserved insight) Sypracia, dysgnosia, Logoclonia, Psychomotor slowness) Delusions (suspiciousness) Visual disturbances (Dyslexia) Speech disturbances (Late mutism, Expr and rec dysphasia) Unilateral non-tremor motor disturbance (Increased muscular tension, Gait disturbance (bent forwards with long slow steps, "curtseying" at the knees, stiffly and heavily", Late incontinence) Other (Rapid loss of weight) IV:9 Cognitive impairment (Early amnesia (spatial orientation, but preserved insight), Sypracia, dysgnosia) Sleep disturbances (Restlessness - agitation) Delusions (suspiciousness) Visual disturbances (Dyslexia) Speech disturbances (Expr and rec dysphasia, Vocally disruptive, Late mutism) Unilateral non-tremor motor disturbance (Psychomotor slowness, Increased muscular tension, Gait disturbance, Late incontinence) Other (Rapid loss of weight)	IV:2 death 51yrs after 3 years of condition IV:9 death 56yrs after 7 years of condition
Kim et al. 1997	4	Not specified, "claustrum" only	Bilateral periventricular white matter and centrum semiovale demylination in all. 3) Posterior limb of internal capsule, descending pyramidal tracts, cerebellar deep white matter, diffuse corticosubcortical atrophy 5) Genu of corpus callosum, splenium of corpus callosum, posterior limb of internal capsule, descending pyramidal tracts, diffuse low T2 intensity in thalami 6) Genu of corpus callosum, splenium of corpus callosum, diffuse low T2 intensity in thalami 7) Posterior limb of internal capsule, cerebellar deep white matter, diffuse corticosubcortical atrophy, subcortical U fibres.	Late-infantile metachromatic leukodystrophy	All normal developmental processes until onset of symptoms, between 9 and 28 months. Regression of motor development (loss of head control, inability to sit alone, gait disorders, speech disturbances, quadriparesis).	Deceased, not specified.
Leroy et al. 2007 ^a	3	Bilateral	Ponto-cerebellar atrophy, cortical changes in insula, decreased brain size	Pontocerebellar hypoplasia (PCH) novel subtype	Fatal seizures in all three cases	Fatal
Meletti et al. 2015	6	Bilateral	1) Insular cortex 2) None 3) None	New-onset refractory status epilepticus (NORSE)	1) Confusion/stupor – staring/eye deviation and focal hemiclonic (uncountable) seizures, then generalised myoclonic state. Status epilepticus evolution was super-refractory.	1) Normal life, mild deficits in executive functions. Focal epilepsy.

			4) None 5) Right posterior thalamus 6) None		2) Confusion/sleepiness – focal hemiconic, myoclonic, then generalised (uncountable) seizures. Status epilepticus evolution was refractory. 3) Confusion/stupor – focal hemiconic, myoclonic, then generalised (uncountable) seizures. Status epilepticus evolution was super-refractory. 4) Seizures (uncountable) – eye deviation and focal hemiconic, with alternating side, then generalised. Status epilepticus evolution was refractory. 5) Headache/sleepiness – focal hemiconic, with alternating side, then generalised (uncountable) seizures. Status epilepticus evolution was super-refractory. 6) Stupor/severe sleep disruption – focal motor, tonic, chewing and complex automatisms (isolated) seizures. Status epilepticus evolution was super-refractory.	2) Cognitive and behavioural deficits. Focal epilepsy. 3) Death 4) Normal life, slight attentional deficits. Focal epilepsy. 5) Normal life. 6) Mild cognitive deficit, attention deficit. Seizure-free final follow up.
Meletti et al. 2017	31	Bilateral	Various	New-onset refractory status epilepticus (NORSE)	For sudden onset altered mental status, ranging from mild fluctuations in mental status to stupor. Status epilepticus was refractory/super-refractory in 74% of the patients, requiring	Differs between patient
Morys et al. 1988 ^{a,b,c}	No detail on which patient has claustrum lesion, 12	Unilateral	Not specified	Not specified	Other (Absence of somatosensory evoked potentials contralateral to the side of the lesion and ipsilateral to the stimulated nerve)	
Randerath et al. 2018 ^{a,b}	34	17 Left 17 Right		Unilateral infarction or haemorrhagic stroke	Cognitive impairment (Anosognosia for motor impairment) Visual disturbances (visuo-spatial disturbance) Unilateral non-tremor motor disturbance (Motor impairment (limb apraxia), hemiparesis (unaffected ipsilesional hand was used in those patients)) Other (Neglect symptoms. Assessment of visuo-spatial and motor function indicated right brain damage patients performed worse than those with left-sided damage.)	
Sapir et al. 2007	29	Unilateral	Ventral lateral putamen, white matter beneath the frontal lobe (likely others but not specified for each patient)	Stroke	Hemispatial neglect with directional hypokinesia (individual observations not given)	Not specified
Sener et al. 1997	7	(1) Bilateral (2) Bilateral (3) Bilateral (4) Unilateral, left (5) Unilateral, left (6) Unilateral, left (7) Unilateral, left	(1) Globi palladi, putamen, head of caudate nuclei (2) Parenchyma (3) Periventricular (4) Left thalamus (5) Left putamen, left caudate nucleus, left opercular region (6) Widespread (7) Widespread	(1) Asphyxia (2) Wilson's disease (3) Ischaemic white matter disease (4) Thalamic arteriovenous malformation (5) MELAS syndrome (6) Viral encephalitis (7) Parkinson's disease	Neurological symptoms are not "attributable to exclusively the claustrum"	Not specified
Snider et al. 2020 ^{a,b}	171	Bilateral peak in functional connectivity	Variable and undefined on aggregate; most limited to cortex and white matter	Penetrating head injury	Non-seizure disturbance of consciousness (Loss of consciousness (Prolonged N=16, transient N=91, none N=64) "Suggests that functional anticorrelation with the dorsal brainstem, rather than anatomical intersection with the claustrum, may be the more critical factor, explaining why many penetrating lesions outside the claustrum also cause LOC")	

^a Studies found through extended search

^b Studies in which individual patient details are not provided; data is presented as aggregate

^c Studies in foreign language; abstract in English only

^d Poor lesion specificity and so has been excluded from case study table and analysis

Lesion Table References

(Albayrak & Gorgulu, 2008; Barcikowska, 1979; Biemond, 1956; Chakraborty et al., 2014; Chessa et al., 2017; Couto et al., 2013; Dodgson, 1955; Freedman et al., 1984; Hiraga et al., 2014; Hwang et al., 2014; Ishida et al., 2006; Ishii et al., 2011; Jellinger et al., 2011; T. S. Kim et al., 1997; Kurokawa et al., 2005; Lapenta et al., 2015; Leroy et al., 2007; Matsuzono et al., 2013; Maximov et al., 2018; McKay & Cipolotti, 2007; McMurtray et al., 2014; Mizutani et al., 2020; Mumoli et al., 2014; Nixon et al., 2001; Nomoto et al., 2007; Obara et al., 2008; Obrador et al., 1957; Okamoto et al., 2008; Saito et al., 2007; Sapir et al., 2007; Seghier et al., 2014; Sener, 1998; Serrano-Castro et al., 2013; Shiihara et al., 2006; Shintaku et al., 2010; Shintani et al., 2000; Silva et al., 2018; Sperner et al., 1996; Turkalj et al., 2012; Yasui et al., 1999; Yoshimura et al., 1988)