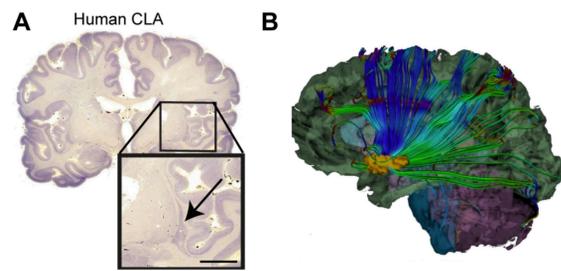


What can human lesion studies tell us about the function of the claustrum?

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Introduction

The claustrum is a sheet-like bilateral brain region tucked beneath the insular cortex. Its function remains unknown, making it one of the final frontiers in brain anatomy. It has the highest connectivity of any brain region by volume. A wide variety of hypotheses of function surrounding the claustrum have been generated from modulating nociception to being proposed as the seat of consciousness by the late Francis Crick.



(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 reprinted with permission from John Wiley and Sons: Human Brain Mapping, Torgerson et al., 2015, Copyright © 2015.

Aim

We wondered if human lesion case studies could help to elucidate the function of the claustrum. This has never before been carried out comprehensively due to the relative scarcity of claustral lesions.

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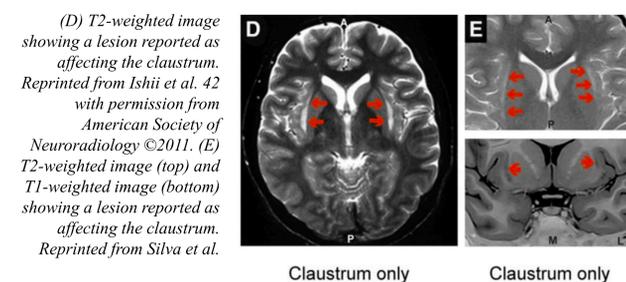
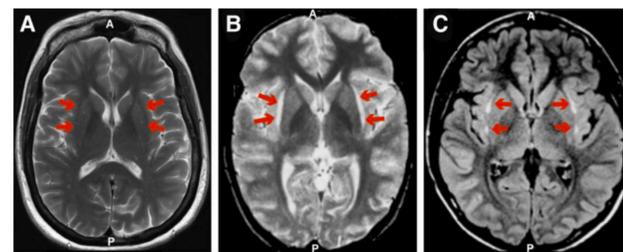
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Method

- To perform a literature search, we examined claustrum lesion cases by searching the following terms on PubMed and Scopus: 'claustrum AND (lesion OR contusion OR in- jury OR trauma)'.
- Studies were then screened for cases in which reported lesions included the claustrum according to neuroimaging.
- We grouped cases according to pre-determined terms of interest and by our findings as we progressed through the literature.

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. Reprinted from Sperner et al. 45 with permission from Springer Nature ©1996. (C) Fluid-attenuated inversion recovery (FLAIR) image showing a lesion reported as affecting the external capsule. Reprinted from Mumoli et al. 43 with permission from Springer Nature ©2014.



(D) T2-weighted image showing a lesion reported as affecting the claustrum. Reprinted from Ishii et al. 42 with permission from American Society of Neuroradiology ©2011. (E) T2-weighted image (top) and T1-weighted image (bottom) showing a lesion reported as affecting the claustrum. Reprinted from Silva et al.

Results

In total our search uncovered 103 cases.

Thirty-eight individual cases and 14 cohort studies were included. The results of these studies are tabulated below.

Only seven cases reported lesions exclusive to the claustrum, so patients were included with damage to neighbouring structures such as the insula and external capsule.

Hemispheric distribution	Bilateral	22
	Unilateral (Right / Left / Undefined)	16 (9/5/2)
Extent of lesion	Claustrum-only	7
	External capsule	14
	Insula	12
	Hippocampus	9
	Other cortices	17
	Other sub-cortices	22
Signs and symptoms	Cognitive, perceptual and motor abilities	
	Cognitive impairment	19 (50%)
	Motor disturbance	17 (45%)
	Visual disturbances	9 (24%)
	Speech disturbances	8 (21%)
	Auditory disturbances	6 (16%)
	Tremor	5 (13%)
	Paresthesia	5 (13%)
	Electrical activity disturbance	
	Seizures	18 (47%)
	Non-seizure EEG abnormalities	8 (21%)
	Mental State	
	Loss of consciousness	8 (21%)
	Hallucinations	4 (11%)
	Delusions (Cotard delusion)	5(2) (13%)
	Sleep disturbances	6 (16%)
Seizure type (patients may fit >1 severities)	1) Partial	7 (18%)
	2) Generalised	15 (39%)
	3) Status epilepticus	13 (34%)
	4) Refractory status epilepticus	10 (26%)

When examining these terms, it becomes quickly clear that human claustral lesions do not selectively impair a singular domain. Consequently, the wide range of symptoms observed following claustral lesions do not provide compelling evidence to support prominent current theories of claustrum function derived mostly from animal work, which include spatial navigation, attentional allocation, cognition, multisensory integration and salience computation.

So how might we explain these findings?

One interpretation of our results is that the absence of specific deficit fits with the increasingly popular hypothesis that the 'one region one function' approach to the brain is reductive. In network approaches to function there may be an element of redundancy as processes are distributed in several areas.

Alternatively, these results may suggest that human claustrum may have a more general function not picked up in the case reports. Supporting this conclusion, we analysed fMRI data from 14,000 studies using software from Neurosynth to find that our claustrum mask was similarly associated with general rather than domain-specific activation.

One clue as to what this general role may be comes from the disproportionately high incidence of seizures following claustral lesions. This may be in keeping with a general role for the claustrum in maintaining excitation-inhibition balance.

Conclusion

The wide range of symptoms observed following claustral lesions do not provide compelling evidence to support prominent current theories of claustrum function.

The lesions studies can be taken as support for the hypothesis that the claustrum regulates cortical excitability. These findings will help guide our work on claustral function at the Department of Anatomy, Physiology and Genetics at the University of Oxford and also forms the backbone of our recent paper in Brain (Atilgan et al., 2022).

Acknowledgements

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

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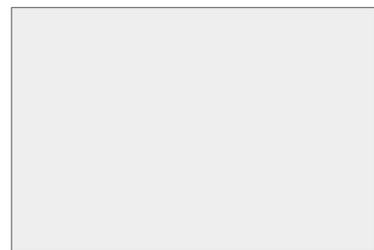
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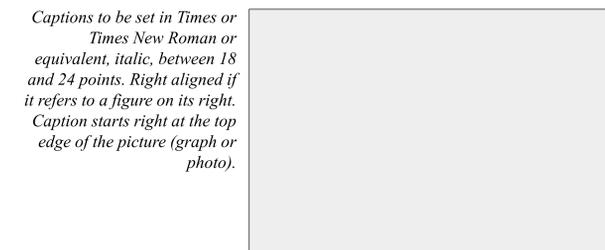
Method

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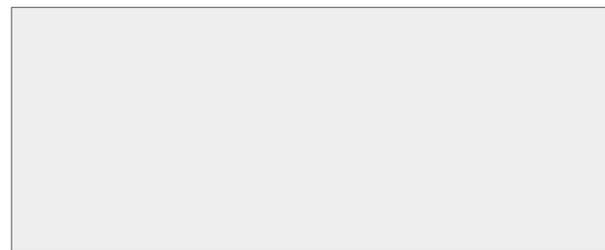
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Results

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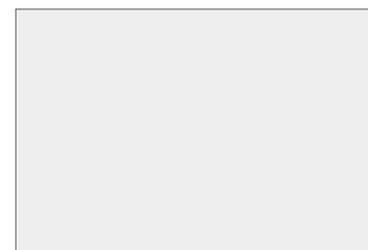
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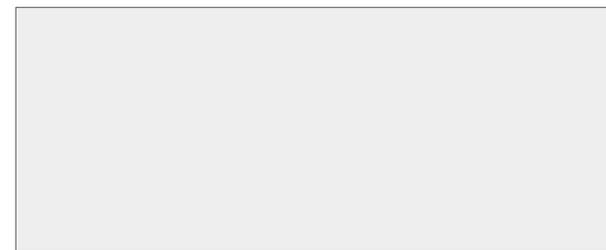
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Conclusion

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