Claustrum

COMMENTARY

Claustral Delusions

The claustrum, a thin strip of neurons located medially to the insula, is as intriguing as it is understudied. With a particularly dense reciprocal connectivity with large swaths of cortex (1), and a plethora of neuromodulatory inputs, the claustrum has been the object of a number of hypotheses regarding its functions. These hypotheses include a role for the claustrum in integration of sensory information to create a unified conscious experience (2), cortical synchronization (3), modulation of cortical functional networks (4), saliency detection (5, 6), active sensing (7), and segregation of attention (8, 9). Interestingly, all these hypotheses revolve around a common theme, that of enabling the formation of an accurate and cohesive representation of the world around us.

In their article 'A new perspective on delusional states – evidence for claustrum involvement', Patru and Reser (10) hypothesize that disruption of claustral function may contribute to the pathogenesis of psychotic symptoms, delusions in particular. The authors' suggestion is intriguing and should spark interest in an understudied and potentially relevant brain region. Importantly, direct evidence supporting the hypothesis is lacking, and a more cautious approach would be to broaden the discussion to psychoses rather than only delusions. The authors review the anatomy and functional connectivity of the claustrum, as well as hypotheses regarding its function, and place it in the context of the broad, yet sometimes confusing, clinical literature regarding claustral lesions in patients with delusions or psychotic behavior. A major confound of these studies is the extent of the lesions, which in most cases extended well beyond the claustrum. They then provide a number of intriguing hypotheses for how the claustrum may be responsible for the formation of delusions. Interestingly, it has recently been proposed that salvinorin A, a hallucinogenic kappa opioid agonist, may be acting on the claustrum, causing a disruption of the conscious binding of information to form an accurate representation of the surrounding world (11). This hypothesis is compatible with the proposal of Patru and Reser, and both are cohesive with the evolving notion of a potential role for the claustrum in selective allocation of attention, potentially through prioritizing salience to selected objects, reducing the salience of non-prioritized objects.

Delusions are profoundly debilitating psychotic symptoms. Although conceptual models for these symptoms are still highly speculative, it is plausible, as suggested by Patru and Reser, that a common feature is impairment of the ability to accurately assess the 'validity' of the interpretation of reality. Breakdown of the assessment process may lead patients to adopt constructs of reality that contain implausible characterizations. Altered sensory gating and perception, reported in patients with major psychoses, may represent components of such breakdown and resonate with growing evidence on claustral functions. Several authors have suggested that aberrant salience, involving complex neural circuits including the striatum, amygdala, and several cortical regions, may represent a key element underlying psychoses (12–16). In a classic treatise, Kapur (17) proposed that psychosis is a state of aberrant salience, causing delusions to evolve gradually in schizophrenic patients. Initially, patients develop heightened sensory receptiveness and increased awareness of the environment, in which many individual elements, which were previously ignored, now gain significant salience. This subtly altered perception of the world leaves the patients overwhelmed and confused, and therefore delusions are suggested to be a 'top–down' cognitive explanation that the individual imposes on experiences of aberrant salience, in an effort to make sense of them. This explanation ties together the proposed role of the claustrum in mediating selective attention (8) with the notion proposed by Patru and Reser (and previously by Cascella (18, 19)) that disruption of the claustrum could lead to the development of delusions in schizophrenia. With this perspective, disturbance of claustral function, either through direct disruption of the claustrum, or by a circuit-level effect on inputs to the claustrum, would disrupt the appropriate segregation of salience to distinct objects in the world, overwhelming the individual with inputs. Interestingly, the most significant inputs to the claustrum arise from the orbitofrontal cortex and anterior cingulate (1, 4, 20). Potentially, in the context of the hypothesis raised by Patru and Reser, these prefrontal inputs could be defining the 'attentional strategy' implemented by the claustrum. Thus, disruption of the prefrontal inputs to the claustrum may lead to acceptance of non-conventional and implausible constructs emerging from the integration of sensory inputs. With this perspective in mind, similar arguments could be made regarding expected disruptions of the claustrum in other situations of attention deficits, such as attention deficit disorder (21–23). Kapur suggests that dopamine is a major component defining salience (16). As expression of Drd1dopamine receptors appears to extend within the mouse claustrum (www.mouse.brain-map.org), it will be interesting to test

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the prediction that dopamine may modulate transmission within claustral circuits.

A key objective of Patru and Reser is to provide a primer, enhancing awareness on the part of clinicians and researchers regarding the possibility that the claustrum may play a role in the pathophysiology of psychoses. Their hope, which we support, is that in the design of future experiments studying psychiatric conditions, particular attention will be devoted to the claustrum. The connectivity of the claustrum positions it as a potential hub in the vast circuitry controlling sensory processing, salience, and attention. From a systems-level perspective, there appears to be good cause to incorporate the claustrum in brainwide functional and connectivity analyses in normal sensory processing, as well as in disease. Thus, we may expect to gain crucial information regarding this intriguing brain region, as well as hopefully identify underlying causes of debilitating symptoms of major neuropsychiatric disorders.

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Ami Citri
The Edmond and Lily Safra Center for Brain Sciences
Jerusalem, Israel
Email: ami.citri@mail.huji.ac.il

Department of Biological Chemistry
Institute of Life Sciences
The Hebrew University of Jerusalem
Jerusalem, Israel

Sabina Berretta
Translational Neuroscience Laboratory
Mclean Hospital
Belmont, MA, USA

Department of Psychiatry
Harvard Medical School
Boston, MA, USA

Program in Neuroscience
Harvard Medical School, Boston
MA, USA

References

1. Torgerson CM, Irimia A, Goh SY, Van Horn JD. The DTI connectivity of the human claustrum. Hum Brain Mapp 2015; 36: 827–38.
2. Crick FC, Koch C. What is the function of the claustrum? Philos Trans R Soc Lond B Biol Sci 2005; 360: 1271–9.
3. Smythies J, Edelstein L, Ramachandran V. Hypotheses relating to the function of the claustrum. Front Integr Neurosci 2012; 6: 53.
4. Reser DH, Richardson KE, Montibeller MO, Zhao S, Chan JM, Soares JG, et al. Claustrum projections to prefrontal cortex in the capuchin monkey (*Cebus apella*). Front Syst Neurosci 2014; 8: 123.
5. Remedios R, Logothetis NK, Kayser C. Unimodal responses prevail within the multisensory claustrum. J Neurosci 2010; 30: 12902–7.
6. Remedios R, Logothetis NK, Kayser C. A role of the claustrum in auditory scene analysis by reflecting sensory change. Front Syst Neurosci 2014; 8: 44.
7. Smith JB, Alloway KD. Interhemispheric claustral circuits coordinate sensory and motor cortical areas that regulate exploratory behaviors. Front Syst Neurosci 2014; 8: 93.
8. Goll Y, Atlan G, Citri A. Attention: the claustrum. Trends Neurosci 2015; 38: 486–95.
9. Mathur BN. The claustrum in review. Front Syst Neurosci 2014; 8: 48.
10. Patru MC, Reser DH. A new perspective on delusional states – evidence for claustrum involvement. Front Psychiatry 2015; 6: 158. doi: http://dx.doi.org/10.3389/fpsyt.2015.00158
11. Stiefel KM, Merrifield A, Holcombe AO. The claustrum's proposed role in consciousness is supported by the effect and target localization of Salvia divinorum. Frontin Integr Neurosci 2014; 8: 20.
12. Aleman A, Kahn RS. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog Neurobiol 2005; 77: 283–98.
13. Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, et al. Expected value and prediction error abnormalities in depression and schizophrenia. Brain 2011; 134: 1751–64.
14. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophr Bull 2010; 36: 472–85.
15. Meisenzahl EM, Schmitt GJ, Scheuerecker J, Moller HJ. The role of dopamine for the pathophysiology of schizophrenia. Int Rev Psychiatry 2007; 19: 337–45.
16. Pankow A, Knobel A, Voss M, Heinz A. Neurobiological correlates of delusion: beyond the salience attribution hypothesis. Neuropsychobiology 2012; 66: 33–43.
17. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003; 160: 13–23.
18. Cascella NG, Gerner GJ, Fieldstone SC, Sawa A, Schretlen DJ. The insula-claustrum region and delusions in schizophrenia. Schizophr Res 2011; 133: 77–81.
19. Cascella NG, Sawa A. The claustrum in schizophrenia. In: Smythies JR, Edelstein LR, Ramachandran VS, eds. The claustrum. San Diego, CA: Academic Press; 2014, pp. 237–43.
20. Zingg B, Hintiryan H, Gou L, Song MY, Bay M, Bienkowski MS, et al. Neural networks of the mouse neocortex. Cell 2014; 156: 1096–111.
21. Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2008; 63: 332–7.
22. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry 2006; 47: 1051–62.
23. Fassbender C, Schweitzer JB, Cortes CR, Tagamets MA, Windsor TA, Reeves GM, et al. Working memory in attention deficit/hyperactivity disorder is characterized by a lack of specialization of brain function. PLoS One 2011; 6: e27240.