INTRODUCTION

The claustrum offers functionality of a higher order, enabling the organism to rapidly adapt to the subtleties and nuances of its ever-changing environment. In humans, a loss of any of these multisensory and heterotopic attributes may yet be demonstrated to be involved in some aspects of dementia, attention and other perturbations or disturbances of higher-order functions.

Edelstein and Denaro, 2004

The quotation above anticipates that loss of the proposed integrative functions of the claustrum might cause distinctive cognitive dysfunctions. Disconnection and degeneration of this structure might then contribute to cognitive and neuropsychiatric symptoms including those appearing in Alzheimer’s disease (AD). That the claustrum is important for at least some elements of the neuropsychological and neuropsychiatric syndromes of AD, and probably other dementias, is supported not only by its connections but also by neuropathological and in vivo neuroimaging correlative studies. Reported changes in claustral activity in neuroimaging studies are frequent, but largely little remarked upon and discussed. In this chapter the very limited literature about the claustrum in AD will be reviewed, and some speculative inferences about claustral dysfunction made in the context of the neuropathological progression of AD, and what is known about the wider relationship of regional and network brain dysfunction to the neuropsychological and neuropsychiatric manifestations of the disease.
CLAUSTRAL CONNECTIONS AND ALZHEIMER’S DISEASE

In AD there is early degeneration of the hippocampal/entorhinal complex followed by progressive degeneration of associative neocortex, with widespread disruption to intrahemispheric cortico-cortical, commissural and subcortical connections (Braak and Braak, 1991). In a recent high-resolution diffusion tensor imaging (DTI) study of normal primate brain the complex sheet of neurones and neuropil which constitutes the claustrum had the strongest probabilistic connections with the entorhinal cortex, but was also connected with most other cortical regions and some subcortical structures (Park et al., 2012). A tractography study of the human brain with fiber dissection showed that the claustrum had topographically organized connections with superior frontal, precentral, post-central and posterior parietal cortices (Fernández-Miranda et al., 2008). Traditional neuroanatomical tracing methods, which can more precisely determine the direction, origin, and termination of fibers in other primate species and in the cat, broadly align with these data and found topically ordered reciprocal connections (mainly ipsilateral) with all areas of the neocortex and, again important in the present context, with the entorhinal cortex (Insausti et al., 1987; Witter et al., 1988). Such techniques of course are not possible with the human brain, but it seems unlikely, given the enhanced development of both the claustrum and the cerebral cortex in man (see Chapter 7), that claustral connectivity is any less complex and neocortically pervasive in our own species. It follows that both hippocampal/entorhinal and progressive neocortical degeneration in AD can have anterograde and retrograde effects on regional claustral neuron populations in addition to any intrinsic participation in the neurodegenerative process. Studies of immunoreactive terminal species in the claustrum suggest extensive connectivity within the claustrum itself (Rahman and Baizer, 2007).

CHOLINERGIC PATHWAYS AND THE CLAUSTRUM

Cholinergic innervations extend to all parts of the human cerebral cortex. Cholinergic projections from the nucleus basalis of Meynert extend to the cortex via two pathways, one passing medially and another laterally within each hemisphere. In the human brain there is a strong cholinergic innervation into the claustrum (Mesulam M, personal communication) and the perisylvian division of the lateral cholinergic pathway originating in the nucleus basalis passes through the claustrum and supplies neurons in the frontoparietal operculum, insula and superior temporal gyrus (Selden et al., 1998). There is no direct evidence
of claustral/entorhinal connectivity in man but this may be strongly inferred from primate studies (Insausti et al., 1987).

Studies in different species provide evidence of widespread connectivity between the entorhinal cortex and subcortical structures, including basal ganglia, thalamus, hypothalamus, and amygdala as well as strong reciprocal connections with the claustrum (Canto et al., 2008). Extensive links with other structures in the limbic system and indirect connectivity via other limbic structures must also be present in humans (Price, 2007; Smythies et al., 2012), and there is histological evidence of anatomical contiguity between the intermediate part of the entorhinal area and the preamygdalar part of the claustrum (Heinsen et al., 1994).

**NEUROPATHOLOGY**

The claustrum, in common with other cortical and subcortical structures (e.g. nucleus basalis of Meynert, entorhinal cortex) does show degenerative changes in ageing and AD. A study of age-related changes of the claustrum in older dogs showed amyloid deposition and loss of neurons (Moryś et al., 1994). In the human brain there is evidence of age-related changes in the claustrum of non-demented people with neuronal loss and decreased volume in all subfields (Moryś et al., 1996). A small number of amyloid deposits in the para-amygdalar zone of the claustrum were found in the oldest people in the sample. No evidence of neurofibrillary tangles was reported. Neurofibrillary tangles, however, are said to accumulate and develop in the claustrum as well as in the amygdala and the thalamus at a later stage of AD and are found at Braak and Braak stage IV (Serrano-Pozo et al., 2011). The limited neuropathological studies in AD found the most severe changes in the ventral part of the claustrum, inferred from primate studies to have reciprocal connections with the entorhinal cortex. Claustral areas reciprocally connected to the neocortex were reported to show less cell loss and pathological change (Moryś et al., 1996). In a study of amyloid deposition in the human brain, amyloid deposits were found in the claustrum in all 14 cases of AD studied. The deposits were numerous type 2 plaques with some type 1 and type 3 plaques (Ogomori et al., 1989). Occasional but rare plaques were found in normal controls. The clinical heterogeneity of AD syndromes and issues of staging qualify interpretation of this evidence, however. Claustral degeneration was particularly marked in familial cases of AD caused by a presenilin mutation (Gustafson et al., 1998). In a neuropathological study of other neurodegenerative syndromes, amyloid and alpha-synuclein pathology in the claustrum was strongly related to dementia diagnosis in both Parkinson’s disease and dementia with Lewy bodies (Kalaitzakis et al., 2009). There is evidence of increased muscarinic M4
receptor activity in the claustrum and the cortex of patients with Lewy body dementia and AD (Piggott et al., 2003), possibly reflecting cholinergic dysfunction.

**THE CLAUSTRUM AND NETWORK CONNECTIVITY IN AD**

The march of neuronal degeneration in AD is paralleled by an increasing disruption of structural and functional connectivity. Intra- and interregional integrity is compromised, and in turn larger scale neurocognitive networks are affected (Sporns, 2011; Xie and He, 2011). Assessment of resting-state brain connectivity together with measures of gray matter volume and diffusion tensor imaging (DTI) has already begun to delineate these anatomically and functionally correlated networks in healthy brains (e.g. Greicius et al., 2009). For example, a network that is important for binding posterior cingulate, precuneal and medial temporal cortices, and which is activated during episodic memory tasks, is pathologically and functionally degraded early in AD and in mild cognitive impairment (e.g. Buckner et al., 2008; Greicius et al., 2004). Evidence of structural connectivity change in early AD has been obtained by DTI, and impairments in the medial prefrontal, posterior parietal, and insular cortex best differentiate between AD and healthy ageing (Shao et al., 2012). Disruption of structural connectivity in these regions has wider consequences for functional networks involved in memory processes, attention, awareness of self and the wider environment. Degradation of these primarily cholinergic connections can promote neuropsychiatric symptoms in AD as well as in dementia with Lewy bodies (Piggott et al., 2003), and abnormalities of the claustrum and the insula have been associated with the presence of positive symptoms in both neurodegenerative and psychiatric conditions (Bruen et al., 2008; Cascella et al., 2011).

In the field of connectivity and memory, functional MRI (fMRI) studies of AD have shown deactivation of the claustrum as well as of the insula, posterior cingulate, temporal and lateral parietal cortex in patients and healthy older adults during a paired associates learning paradigm, both at encoding and at retrieval (Gould et al., 2006). Some of the regions that show task-induced deactivation are not part of the default mode network and their deactivation in memory encoding and retrieval may develop a broader understanding of memory deficits in AD. The claustrum is not part of the default mode system, but it does appear to be interconnected with a network of structures directly involved in memory retrieval. These structures include a distinctive neuronal type, the Von Economo neuron (VEN; Figure 11.1), which is abundant in humans
and richly represented in both the insula and the claustrum (Williamson, 2007). This author suggested that the activity of VEN in the claustrum would influence the function of a strongly interconnected and extensive network of heteromodal cortex. This activity might in turn facilitate the interactions between the default-mode network and task-related networks. Reduction of activity in the claustrum, therefore, could influence the functioning of task-related networks and, in particular, the efficiency of a memory-related network in AD.

Again, Park et al. (2012) suggested that the loss of spatial memory in AD (Didic et al., 2011) might be due not only to degeneration of the entorhinal cortex and the hippocampus but also to impairment of the related integrating function of the claustrum. They point to the claustrum’s extensive connections with cortical areas and the likely involvement in more global aspects of perception and consciousness.

COGNITION AND THE CLAUSTRUM IN AD

The advent of fMRI and other functional imaging techniques have increasingly provided evidence about the involvement of the claustrum (either directly or indirectly via its connections with key structures) in cognition. This issue is more comprehensively reviewed in other chapters, but as suggested above, changes in claustral activity in neuroimaging studies are frequently reported but draw little or no comment. The
broad picture emerging from the available literature from animal and human studies suggests a crucial involvement in tasks in which integration of information processed by the brain via different sensory modalities (Banati et al., 2000; Hadjikhani and Roland, 1998) or across modalities (Baugh et al., 2011; Olson and Graybiel, 1980) is needed. There is also evidence against this, with other studies suggesting that, although the claustrum processes multisensory information, there are no multisensory cells in this structure, hence the multisensory integration of information cannot be mediated by the claustrum (Remedios et al., 2010). Others have suggested that its role might be better defined in the sense of ascertaining multisensory conceptual congruency (Naghavi et al., 2007). In AD, volumetric changes in both right and left claustrum were found to be significantly correlated with performance on confrontation naming and visuoconstructive tasks (Venneri et al., 2008) (Figure 11.2).

Similar findings were reported by another recent voxel-based correlation study with patients in the mild cognitive impairment (MCI) preclinical stage of AD. In this study, volumetric changes in both right and left claustrum were found to correlate, as previously found, with confrontation naming, but also with scores on the category fluency test (Gardini et al., 2013). No correlation in the claustrum was found when a similar analysis was carried out in age-matched controls. This pattern of findings might indicate that neuronal loss in the claustrum is interfering with efficient performance on this task and that the claustrum may provide a supportive role in semantic/phonological retrieval. The most probable process would be mediating the integration of visual, conceptual and phonological information to ascertain congruency between these different modes, to achieve successful confrontation naming.

A link between variance in cholinergic function in the claustrum and verbal memory learning scores in MCI patients was detected in a study of nicotinic acetylcholine receptor binding in a preclinical stage patient.
group, providing additional evidence that early changes in this structure might modulate cognitive performance in patients with either established or prodromal AD (Terrière et al., 2010).

The claustrum may also contribute to the neurological substrate of cognitive reserve in healthy elderly, and a negative correlation between claustrum activity during a visual memory task and an index of cognitive reserve was found by a neuroimaging study which investigated the biological underpinning of cognitive reserve in normal and abnormal ageing (Solé-Padullés et al., 2009). However, no correlation in the claustrum was found in mild AD patients in that study. The different correlation with healthy and with abnormal ageing, might be a disease effect. One explanation of the difference might be that progression of neuropathology would diminish or eliminate the claustrum’s supportive contribution to this aspect of cognitive reserve, as the integrative mechanisms involved degrade. Functional neuroimaging studies of episodic memory in healthy ageing and AD have also highlighted a claustral contribution to episodic memory retrieval. A recent quantitative meta-analysis showed that, during memory retrieval, healthy controls showed greater levels of activity in several brain regions, including the claustrum, than patients with AD (Schwindt and Black, 2009). This meta-analysis suggests that defective retrieval in AD is the product of dysfunction in a wide network of cortical and subcortical structures, including the claustrum. Of interest also are the findings of a recent study of deep brain stimulation (DBS) in AD. Following one year of stimulation, increases in regional brain metabolism were observed not only in temporal and parietal cortex but also in bilateral paracentral lobule and right precentral gyri, bilateral postcentral gyri, right lingual gyrus, and left claustrum, while decreased metabolism was detected in the left anterior cingulate, left middle frontal, and right inferior frontal gyri (Laxton et al., 2010). This increase in metabolism in areas of the default mode network, and decrease in areas of the salience network, suggested that treatment with DBS was contributing to a re-balancing of these networks, and this could have cognitive benefit for treated patients. These authors, however, were not able to detect any behavioral change because of lack of statistical power and small sample size. Based on the regional metabolic increases in structures such as the anterior cingulate and the claustrum, it might be a reasonable speculation that positive effects on cognitive executive control, memory retrieval, and also assessment of cognitive congruency might be expected.

Discrete and cross-modal neuropsychological dysfunctions involving episodic or semantic memory, visuospatial function or other cognitive domains are not the only or even the earliest symptoms which draw attention to, or develop, in the course of this neurodegenerative disease (Cummings, 1985, 2005). An important group of symptoms arises from
more fundamental changes in the nature of the AD patients’ experience of reality. These symptoms are arguably facilitated by the progressive degradation of personal episodic memories in the course of AD, so that a plausible (to the subject) and usually less threatening version of reality can emerge in consciousness. Patients may also demonstrate, however, a more systematic impairment of world representation with loss of the ability to distinguish the animate from the inanimate or to judge the plausibility of beliefs. This group of symptoms, which includes neglect, anosognosia, misidentification, fantastic confabulation, totemism and other forms of delusional awareness, indicate dysfunction in other brain networks supporting the normal structures of conscious awareness (Feinberg et al., 2010; Venneri and Shanks, 2010). These symptoms have been subject to only rudimentary phenomenological description and analysis so far, and this is one reason why related neural networks are less well explored and understood. Lesion studies as well as limited structural and functional studies in AD suggest an important component of these networks will involve right hemisphere dorsolateral frontal, orbitofrontal and parietal cortices (Bruen et al., 2008; Feinberg et al., 2010). In a morphometric study in AD, delusional misidentifications of place or of person with related confabulations or more persistent delusional memories correlated significantly with low gray-matter density values in the right inferior frontal gyrus and inferior parietal lobule. In the left hemisphere there was significant correlation in the inferior and medial frontal gyri, but there was also a significant cluster of correlation in the left claustrum (Bruen et al., 2008) (Figure 11.3). In discussion, the probable involvement of the claustrum in higher-order, integrative functions including facilitation of rapid transfer of information along its anteroposterior and ventrodorsal axes and the instantiation

of multimodal (cognitive, perceptual, motor) syntheses was cited (Crick and Koch, 2005). It was further speculated that claustral dysfunction might impair (directly or indirectly) the normal synchronization of perceptual and cognitive experiences in AD patients, contributing to delusional misinterpretation of percepts, memories or mental images.

Additional evidence bearing on a possible claustral contribution to normal awareness and disorders of awareness in AD comes from studies in frontotemporal dementia (FTD) and schizophrenia, as well as the arguments in other chapters about the claustrum’s special role in the emergence of self-reflective consciousness (see, for example, Chapters 9 and 14).

The importance of VEN in the insula and claustrum was discussed above in the context of task-related functions, but VEN are also phylogenetically increased in man, especially in fronto-insular cortex and in the right hemisphere. A histopathological study of VEN in FTD showed a highly significant and specific degeneration of VEN which was related to the early and nosologically distinctive impairment of self-awareness, empathy and reasoning in these patients (Seeley et al., 2006). The distinction from AD controls was emphasized, but these controls did not have frontal symptoms and had preservation of social awareness and empathy. This is true of many AD patients, but VEN do degenerate as AD progresses and the disease may present in some cases with early changes of environmental and social awareness. It seems reasonable to suggest that fronto-insular dysfunction, in which the claustrum will be implicated or will contribute, will be an important determinant of changes in self-awareness in both neurodegenerative disorders. There is convergent evidence from Lewy body dementia supporting the role of the claustrum and its connections in the correct interpretation of visual percepts. A recent study reported that Lewy body pathology in the claustrum, detected using alpha-synuclein immunohistochemistry, correlated highly with pathological changes in other regions of the visual association cortex, such as Brodmann areas (BA) 18 and 19, as well as in the insular and transentorhinal cortex (Yamamoto et al., 2007). These authors suggested that Lewy body pathology in the claustrum is more closely related to dysfunction in visual areas and that misidentification in Lewy body dementia might be the product of damage in the visuo-claustral pathway as well as the visuo-amygdaloid pathway. They also suggested that these two pathways might act as relay stations and that paralimbic structures, including insular and transentorhinal cortex, may mediate connections between visual areas and limbic areas. The relationship of claustral atrophy to misidentification delusions in AD reported by Bruen et al. (2008) might be interpreted in a similar way. Degeneration of claustral cholinergic pathways, resulting from interference with the claustrum’s critical mediating role, might impair the veridical interpretation of visual inputs and contribute to delusional misidentification.
More supportive evidence for a central role of claustral structural/functional damage in the genesis of psychotic symptoms derives from the appearance of psychoses following transient dysfunction of the claustrum in a case of severe transient encephalopathy (Sperner et al., 1996). In this case the symptoms cleared once dysfunction in gray matter in the claustrum had resolved. Again, morphometric findings similar to those observed in AD were reported in a voxel based correlational analysis of delusions in schizophrenia (Cascella et al., 2011). In this study, significant inverse correlations between the severity of delusions and gray matter volume values in the left claustrum and right insula were found in a large sample of adult patients with schizophrenia, corroborating the evidence from neurodegenerative diseases that integrity of the claustrum may be critical for the correct interpretation of visual percepts, mental images and memories.

**CONCLUSION AND FUTURE DIRECTIONS**

This review chapter has presented converging evidence from studies of cognitive and neuropsychiatric symptoms which flag up the emerging importance of degeneration of the claustrum in AD, and which suggests a critical role of the neuropil and connectivity of this structure in a range of functions which are essential for the maintenance of efficient cognition and a veridical interpretation of reality and the environment. The review, however, has also highlighted a fundamental and curious neglect of this structure in the neurodegenerative neuroscience literature. Claustrum involvement is often found in structural and functional neuroimaging studies of AD as well as in studies of ageing and of healthy young adults, but the reasons for claustrum deficits, dysfunction or differential activation are rarely analyzed, and even less frequently interpreted in terms of higher-order cognitive functions. This chapter, while inevitably to some degree speculative, has attempted to fill this gap and, while reviewing the available findings, has also tried to provide a preliminary theoretical rationale which might be used as a framework to make inferences about the physiological function of the claustrum in normal cognition and its possibly central role in some of the symptoms observed in neurodegenerative diseases like AD.

The evidence reviewed above helps corroborate theories that explore the importance of the disconnection between cortical and subcortical structures which follows the degeneration of cholinergic neurons (including those in the claustrum) and related cholinergic pathways, isolating mediotemporal structures from associative areas of the neocortex (Smith, 2002). In broad terms, efficient cognition would be disrupted with a breakdown of the normally aligned and synchronized computational processes in different brain circuits to which the claustrum seems
to make a central contribution. This distinctive kind of multimodal disruption may make a critical contribution to both the neuropsychological and neuropsychiatric symptoms in AD. This hypothesis would of course need prospective testing, and modern structural and functional connectivity techniques will be the essential methods for clarifying the role of the claustrum in healthy and pathological states.

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References


