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Chapter 9

The Insular Cortex and the Amygdala: Shared Functions and Interactions

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1. Introduction

The Insular Cortex (IC) is a portion of the cerebral cortex folded deep within the lateral sulcus – in rodents surrounding the rhinal fissure - between the temporal and frontal lobes. The IC was first described by J.C. Reil in 1809 [1], after whom it received the name "the island of Reil". Historically, the IC has been mentioned with several names, including "the central lobe", "the fifth lobe", "intersylvian convolutions" and "intralobular gyri" (reviewed in [2]).

The most accepted subdivisions of the IC are the three regions described by Cecheto and Saper (1987) [3], based on the cytoarchitecture of its layers within the ventrodorsal plane. These include (1) the agranular insular cortex (AI) which surrounds the rhinal fissure and lacks a granular layer, (2) the dysgranular insular cortex (DI) which is located just dorsal to the rhinal fissure and contains a diffuse granular layer, and (3) the granular insular cortex (GI), situated just ventral to the secondary somatosensory cortex with a clear granular layer [3]. Each subdivision is believed to process particular sensory information. For example, the AI is believed to participate in nociceptive [4-6] and autonomic processing [3], the DI plays a role in gustatory processing [7, 8] and the GI has an important role in modulating visceral function [3].

In the rostrocaudal plane, subdivisions of the IC are still controversial. Several studies suggest at least two regions - one posterior and the other rostral. Within the rostral, two more subdivisions are usually described: the posterior rostral (sometimes called "central") and the anterior rostral.

In rodents, particularly in the rat, the IC runs along the rostral half of the rhinal fissure. There is, to date, no consensus on the exact location of the border between the IC and the perirhinal cortex, which runs along the caudal half of the rhinal fissure. The rostral end of the IC corresponds to 2 mm of the anterior rostral portion, which runs roughly anterior to the bregma – anterior to the genu of the corpus callosum. It is mostly agranular and usually subdivided into 2 strips: dorsal and ventral [9].

This anterior area is connected with the lateral frontal cortices and the motor thalamic nuclei [10] and receives projections mainly from the ventral part of the medial mediodorsal (MD), the parafascicular and central medial (CM) nuclei of the thalamus [11, 12], as well as with the motor-related amygdala regions [10], the locus coeruleus and the nucleus raphe magnus [4].

Posterior to this rostral agranular area is the central or posterior rostral portion, which includes the 3 main dorsoventral subdivisions described above [3].

The rat granular area is connected to the paraventricular [13], the visceral thalamic nucleus (the parvicellular division of the ventroposterior lateral nucleus of the thalamus, VPLpc; [3, 11]), the gustatory thalamic nucleus (the parvicellular part of the ventroposterior medial nucleus of the thalamus, VPMpc;[10]), the reticular nucleus [14], the sustantia innominata [15], the ventromedial parts of somatosensory thalamic nucleus (the ventroposterior medial thalamic nucleus; VPM, [10]), the posterior thalamic complex (Po), and the central medial nucleus (CM) of the thalamus [10, 16] as well as the medial parabrachial nucleus of the mesencephalon (PBN) and the nucleus of the solitary tract (NTS) [17-19]. Connections with the lateral hypothalamic area and the visceromotor regions in the brainstem including the vago-solitary complex have also been reported [17, 20, 21]. Cortically, it is connected with the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII), the infralimbic cortex [22], the caudate-putamen, the amygdala [23-27] and the bed nucleus of the stria terminalis (BNST, [19]).

The dysgranular area is connected to the paraventricular [13] and the gustatory thalamus (VPMpc; [3, 10, 28, 29]), the medial PBN, the rostral NTS [19, 21] reticular nucleus of the thalamus [30], the somatosensory secondary (SII; [23]), the basolateral and central nuclei of the amygdala [23, 29, 31], the BST [20] and the lateral hypothalamic area [29].

The more posterior part, which extends caudally from roughly 2 mm posterior to bregma [23], has been suggested to be involved in somatosensory functions, including pain [16, 32]. For a simplified scheme of IC connections, see **Fig. 1**.

2. Functions of the insular cortex

Following the reports on intraoperative recordings made by Penfield and colleagues showing that the IC is a viscerosensory and visceromotor region [33, 34], the old James–Lange theory of emotions was revived. The James–Lange theory of emotions states that "bodily changes follow directly the perception of the exciting fact… our feeling of the same changes as they occur is the emotion… we feel sorry because we cry… afraid because we tremble" [35]. In other words, our nervous system responds to emotional experiences with physiological changes (e.g., a rise in the heart rate and dryness of the mouth), primarily mediated by the autonomic system (e.g., sympathetic responses) and the hypothalamus-pituitary-adrenal axis. Emotions are the feelings that result from these physiological changes. Thus, the insula appears as a possible site where such autonomic responses and general bodily states are represented cortically at any given time.

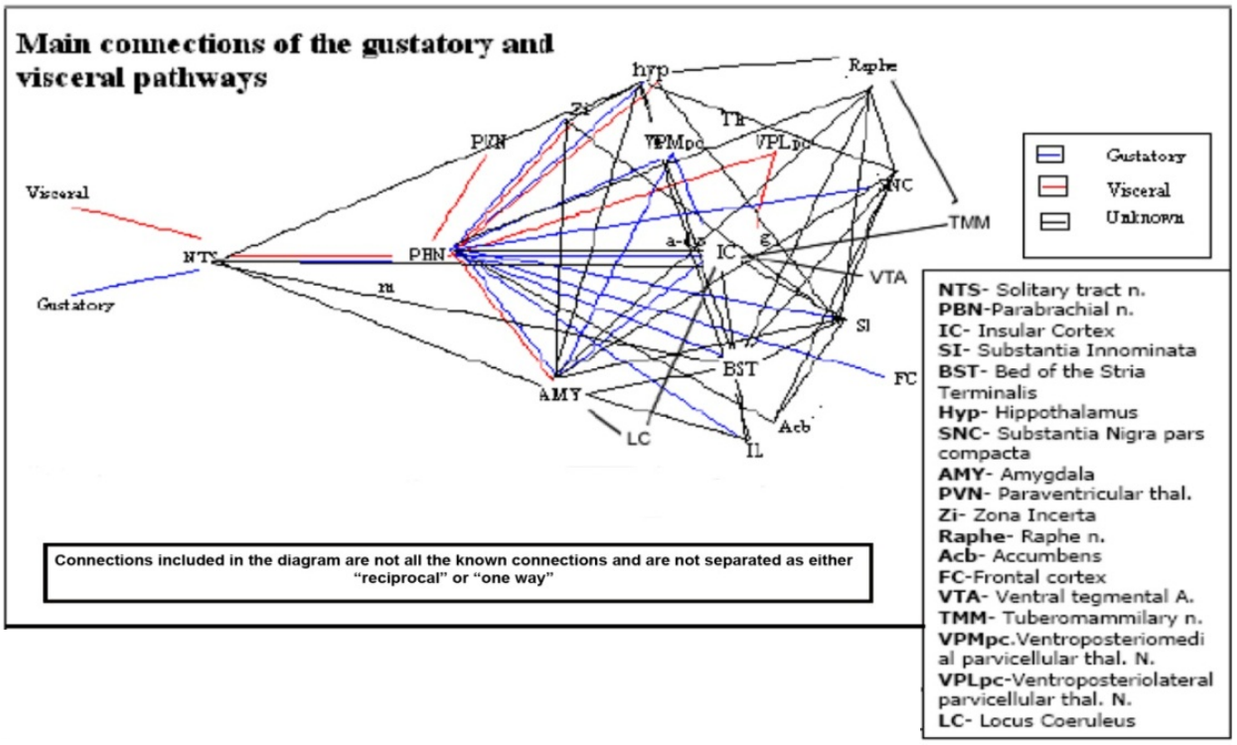

Figure 1. Anatomical connections of taste and visceral areas of the insular corex

Damasio´s somatic marker hypothesis suggests that such ever changing representations of bodily states are required for decision making [36], stored in the insula and other somatosensitive areas [36-39] and triggered by the amygdala or prefrontal cortex (as primary or secondary inducers, [39]). Thus, congruent with both the James-Lange theory of emotions and Damasio's somatic marker hypothesis, the IC is believed to be the brain site where the representations of bodily states are created in response to emotional stimuli and which mediates interoceptive awareness and the subjective experience of feelings [38].

Support for this notion comes from a large number of recent studies in humans, monkeys and rodents, recently reviewed in [40]. Such studies include anatomical, electrophysiological, lesion, pharmacological and imaging studies, as well as operatory stimulation techniques which have yielded plausible roles for the IC in dozens of different functions. Several studies indicate that the IC is involved in taste processing [7, 8, 28, 41], viscerosensory information processing [3, 20, 26, 38, 42, 43], temperature and pain perception [44, 45], olfaction [46] auditory processing [47-49], somatosensory perception [49, 50], drug craving [51], motor tasks [52] and post-stroke motor-recovery functions [53].

Studies in humans have suggested a role for the IC in the ability to feel our own heartbeat [54, 55], negative emotional states including pain [56], social exclusion [57] positive emotional states [58, 59], empathy [60, 61], cognitive control tasks [62] and speech [62, 63-66]. All the above functions may have as a common denominator the IC as a possible correlate of awareness [66], while others have suggested that the role of the IC may be to respond to the perceived salience, novelty or unexpectedness of sensory events mediated by the representation of bodily reactions [67].

In spite of the fact that complex cognitive functions, speech and self awareness are associated with humans and non-measurable in rodents, when IC functional maps of rats and humans are compared, the similarities are striking. In fact, the rat and human insular cortices have common functional areas - as shown in Figure 2 - which suggests a degree of convergence in overall IC functions (compiled from: Rat IC [7, 16, 23, 32, 45, 46, 68-70]; Human IC [71-75]).

Insular dysfunction or hypofunction has also been associated with neurological disorders, such as frontotemporal dementia [76] and spatial neglect [77, 78], as well as with common neuropsychiatric disorders [79] such as schizophrenia [80, 81], depression [82, 83], autism [54, 84], eating disorders [85], anxiety [86, 87], Parkinson´s disease [88, 89] and addiction [90].

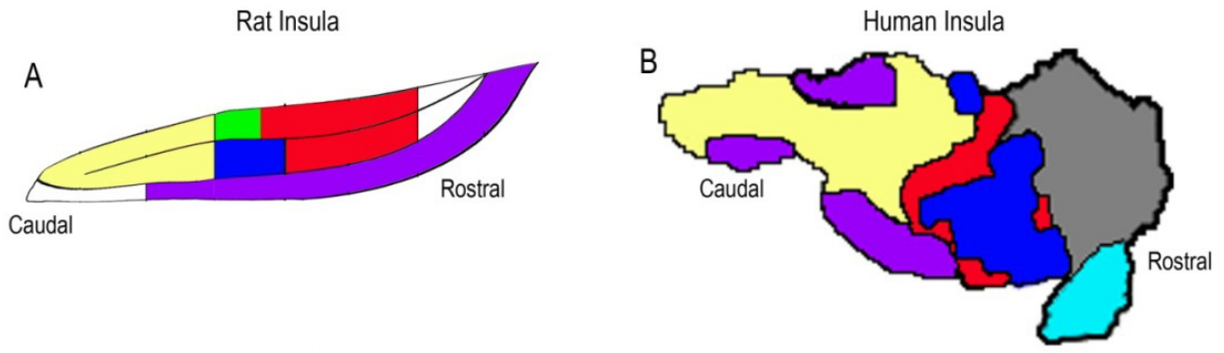

Figure 2. Functional organization of the rat (a) and the human (b) Insular Cortex. Green represents auditory related functions. Yellow represents somatosensory related functions. Purple represents pain associated functions. Red represents cardiac related functions. Blue represents taste related functions. Grey represents cognitive functions and Cyan represents social related functions.
Auditory (green), somatosensory (yellow), pain (purple), cardiovascular (red), taste (blue), cognitive (grey) and social (cyan) representations are shown within the insula.

3. The primary viscerosensory cortex within the insular cortex

Visceral sensory information reaches the IC from the lateral parabrachial nucleus, the nucleus of the solitary tract [18, 19, 21, 91] and the visceral thalamus (VPLpc) [68]. Although a clear map of the viscerosensory area of the IC is still missing, areas within both the dysgranular and granular cortices have been identified as viscerosensory responsive [3, 10, 19, 92-94]. In Cechetto and Saper (1987) [3], a viscerosensory area within the Insular cortex was reported while exploring from 2.0 mm anterior to 0.5 mm posterior to the crossing of the anterior commissure (around the bregma) in rats. They found the majority of the baroreceptor-responsive units between +1.00 and -0.5 mm. Yasui and colleagues [27] explored the rat left insula between 3 mm anterior to 1 mm posterior to bregma and found viscerosensory responsive neurons to aggregate 0.5 mm around the anterior commissure. Zhang and Oppenheimer [94] found responsive cells throughout the rat insular cortex, as far rostral as +2.0 mm and as posterior as -1.5 mm from the bregma, with rightward predominance. In contrast, Shi and Casell (1998) found responsive cells throughout the rat insular cortex, but with leftward predominance [10, 23].

Unlike the visceromotor infralimbic cortex, the IC is usually considered viscerosensory [42, 95, 96]. However, extensive evidence suggests that the IC may have direct motor functions. This idea is supported by major efferent projections from the IC to autonomic brain centres, including the lateral hypothalamic area, the parabrachial nucleus [20], the vago-solitary complex, the nucleus of the solitary tract [17, 21] and the central nucleus of the amygdala [24-27, 97, 98]. Yasui and colleagues [27] reported that intrainsular microstimulation of the rostral part of the DI-GI induced increased arterial pressure and tachycardia, while stimulation of the caudal part produced a reduction of arterial pressure and bradycardia. Other studies have reported that electrical stimulation of the IC in mammals (including humans, non-human primates, cats, dogs and rodents) elicits changes in blood pressure, heart rate and respiratory frequency, respiratory arrest, gastric and bowel motility, gastric and abdominal sensations, nausea and vomiting [34, 49, 98-105]. There is evidence suggesting that this effect is direct where identified visceral insular efferents are linked to the autonomic effects of insular electrical stimulation [106], while it has also been reported that the IC is the main projection site of the cardiovascular depressor sites of the lateral hypothalamic area [107].

The lateralization seen in electrophysiological studies has also been described after stroke models using middle cerebral artery occlusion (MCAO). Right MCAO-damage to the insula and adjacent frontoparietal cortex in rats, significantly increased blood pressure, renal sympathetic nerve activity and plasma norepinephrine levels was compared with left MCAO and controls [69, 108].

4. Taste–related behaviours

The rat, like all other mammals, displays an innate fear for novel tastes (neophobia, [109]). This spontaneous behaviour limits the consumption of novel food until the rat's brain assesses its gastrointestinal effects. Provided that the tastant does not become associated with toxicosis, the consumption will increase on subsequent exposures to that same taste (attenuation of neophobia, i.e., familiarity). If, however, the consumption of the novel tastant results in visceral malaise, robust aversion specific to that tastant develops (conditioned taste aversion - CTA). This is one of the most robust paradigms used to study learning and is called conditioned taste aversion (CTA) [110, 111]. In the laboratory, a malaise-inducing agent - usually LiCl i.p. - is used to induce transient malaise in controlled CTA training. After a single exposure to a novel taste (conditioned stimulus - CS) and the subsequent injection of LiCl (unconditioned stimulus - US), the animal associates the malaise with the taste and acquires an aversion to it.

In the case that the malaise follows the consumption of a familiar taste, the animal has to relearn that the familiar harmless taste is now associated with a malaise. This involves a process known as latent inhibition (LI - the decreased potency of a pre-exposed CS to be associated with an US) and produces, behaviourally, a lower aversion on a subsequent CTA to that taste [112-114].

A CTA memory can last for months if un-retrieved [115], but after repetitive exposures of the taste in the absence of the negative reinforcer, the animal relearns rapidly that the taste is not noxious and the memory is extinguished (experimental extinction [115-117]).

5. The gustatory system in the rat

Gustatory information arrives from taste buds to the rostral pole of the nucleus of the solitary tract (NTS) from cranial nerves VII, IX and X [118]. From the NTS, both taste and viscerosensory neurons project to the parabrachial nucleus in the pons (PBN) [118, 119]. Gustatory neurons arrive mainly to the medial PBN (mPBN) [120-122] and visceral neurons to the lateral part (latPBN) [3, 18, 118], with some overlap [123].

The PBN has been shown to be essential for the perception and learning of tastes (reviewed in [123]). Lesions on either the medial or lateral parts of the nucleus disrupt taste preference [120, 124], selective neophobia [125, 126], sodium appetite [127, 128] and CTA [121, 126-130].

From the mPBN the gustatory responsive neurons project to the gustatory thalamus (the VPMpc [3, 131]) and later reach the IC [3, 67, 132]. However, in contrast to other sensory systems (except olfaction) where sensory input reaches the thalamus before getting to the cortex, the gustatory system shows a direct connection between the mPBN and the IC that bypasses the thalamus [21]. The role of each of these connections remains unknown. Besides the PBN and the IC, the VPMpc sends and receives projections from the reticular nucleus of the thalamus [30] and from the amygdala [133], although the cells from the VPMpc that project to the amygdala are different to those that project to the IC [31]. There is still no consensus to date over the role of the VPMpc-IC or the VPMpc-amygdala pathways.

Lesion studies have not been able to shed light into the functions of the VPMpc. Some studies have reported that VPMpc-lesioned animals retain a normal concentration response to preferred and non-preferred tastes [134-137] but may have disrupted [137], impaired [127, 130] or else have no effects on CTA [134, 135, 138, 139]. Current views suggest a role in comparing novel and familiar tastes [140] in more complex gustatory learning tasks or in attention to gustatory function [135, 136, 141].

6. The primary taste cortex within the insular cortex

The gustatory area within the IC is localized in the dysgranular insular cortex [21, 29], roughly between the rhinal fissure and the medial cerebral artery (MCA) - an area that has also been identified in the rat as taste-responsive using intrinsic signal imaging [141] and electrophysiological recordings [7, 28, 69, 140, 142-144].

7. Role of the IC in taste function

Lesions of the IC produce no perceptual deficits [145, 146] or effects on taste discrimination to preferred tastes [146, 147]. Moreover, recent evidence suggests that IC lesions after CTA lead to the original preference of the taste [148], which implies that IC may not have a role in modulating the original taste preference.

Taste neophobia corresponds to the reluctance to try a novel food. IC lesions induce a consistent decrease in taste neophobia when the novel taste is presented in a familiar environment [146, 148-152]. As most studies so far have focused on taste memory,

pharmacological interventions into the IC are performed only after taste presentation and very few - if any - pharmacological studies have investigated the neurotransmitters involved in taste neophobia per se.

When it comes to the role of the IC in taste familiarity, reports show an interesting duality. IC lesions appear to produce no effects on animals' capacity to attain taste familiarity [151], but several reports document a role for the IC in taste familiarity learning as a result of pharmacological manipulations [153, 154], showing that taste familiarity requires cholinergic activity in the IC [155, 156] but that it is independent of NMDA and AMPA channel activity [157-160]. Perhaps this dichotomy can be explained either by compensation from other areas after IC lesions or, given the role of neophobia discussed above, it is possible that IC output per se may modulate familiarity. In the last case, lacking a neophobic/novelty output may not affect familiarity, but altering such output pharmacologically may affect a familiarity trace processed elsewhere, possibly at the PBN.

8. Conditioned taste aversion

A large number of studies using transient pharmacological manipulations of the gustatory IC have shown that the IC has a role in CTA to novel tastes [117, 161], familiar tastes (also known as latent inhibition) [155, 162] and the extinction of CTA [115, 117]. Interestingly, IC lesions only partially affect CTA acquisition [145, 146, 148, 149, 163] but, when performed after CTA learning, IC lesions completely disrupt CTA memory retention [143, 145, 146, 164, 165] leading to the original preference for the taste [148]. This suggests that when an intact IC is present, it is not only involved in CTA acquisition and consolidation, but it may even be the site where CTA memories are stored (or else the capacity to retrieve them). The partial impairments seen when IC lesions are performed before CTA, on the other hand, suggest that such a seemingly crucial role for the IC in CTA can be compensated for when lacking IC. The area that can compensate for the lack of IC remains unidentified, although subcortical structures - including the PBN - have been proposed [166]. How can the IC be the site of memory acquisition and retention and yet be compensated almost completely? It is possible that the IC is part of a complex network of areas involved in aversive taste learning. A role for the amygdala in CTA acquisition (as will be discussed below), the redundancy seen in the direct PBN-IC, the PBN-VPMpc-IC and the PBN-amygdala-IC connections explained above, the possibility of attaining compensation from the olfactory system for the lack of taste proper and the possibility that IC lesions may induce unspecific taste aversion responses such as generalization, are some of the various possible hypotheses that have not been tested to date but which may explain this compensation.

When an animal with an intact IC is CTA trained, CTA memories (or the capacity to retrieve them) are stored in the IC. This role in storage appears to be non-time-dependent [146], unlike hippocampal-dependent learning systems where hippocampal involvement in memory retention lasts for a limited time only [167-171].

Determining whether IC lesions after CTA induce CTA retention deficits or a loss of the capacity to retrieve the memory is difficult to assess. Support for the idea that CTA

memories are stored in the IC come from a complete lack of spontaneous recovery in several pharmacological and lesion studies, whereas support for the idea that the IC is involved in retention but not the storage of CTA memory comes from studies by Bermudez-Rattoni and colleagues, showing that foetal implants into the IC can recover the capacity to retrieve previously acquired CTA [172-173].

It must be kept in mind that the perception of flavour requires an interaction between smell and taste [174]. IC lesions have also been shown to impair both CTA learning and taste-potentiated odour aversion (POA) learning, suggesting that the IC may also have a role in the integration of odours, tastes and illness [147].

Congruent with animal studies showing a role for the IC in taste function and taste-odour integration, reports from humans show that electrical microstimulation of the gustatory IC induces changes in gustatory function [175, 176] as well as different olfactory sensations [34].

In conclusion, the IC is not involved in taste perception or basic discrimination. The fact that IC lesions after CTA render complete amnesia implies that an intact IC is crucial for CTA memory retention or retrieval. Pharmacological manipulations affecting CTA memory consolidation, reconsolidation, extinction and latent inhibition, suggest that the IC is also involved in CTA acquisition.

The evidence that IC lesions disrupt taste neophobia leading to the original preference of the taste but have no effect on taste familiarity, together with the fact that pharmacological manipulations of the IC affect familiarity and memory extinction, suggest a role for the IC in novelty and novelty-induced taste rejection. In fact, the IC has been suggested to be involved in reactions to the novelty and associative salience exclusive to taste stimuli [149].

A role for the IC in taste saliency and novelty is congruent with the majority of human studies reported for different IC functions, where a common denominator could be a role in the perceived salience, novelty or unexpectedness of sensory events mediated by the representation of bodily reactions [67], which could lead to self-awareness. In this sense, assuming that the output of the IC will eventually be turned into emotion, it is possible that the visceral and gustatory areas within the IC - together with other IC regions - create a bodily representation of taste perception, odour, autonomic responses, pain and somatosensory activation, visual and auditory stimulation, all of which are integrated to determine the salience of a given combination of sensory inputs and autonomic responses relevant to creating an emotion. One must keep in mind that at any given time a huge amount of sensory information flows to the cortex (visual, auditory, tactile, pain, proprioception, taste and smell) together with a huge amount of information from autonomic functions, most of which change constantly to maintain body homeostasis. Thus, the bodily representation required for an emotion needs to be filtered out to only the most salient, novel and relevant information.

9. The insula-amygdala network

Anatomically, the IC and the amygdala are closely connected, both directly and through their main outputs and inputs (see figure 1). There are massive reciprocal connections

between the insular cortex and the amygdala [10, 23, 29, 177, 178] to all amygdalar subdivisions [179]. The ventral agranular insular area projects preferentially to the medial extended amygdala, while the viscerosensory and somatosensory portions of the insular cortex project preferentially to the central extended amygdala [180]. Furthermore, the amygdaloid projections from the posterior insular cortex appear to be organized in a feedforward parallel fashion targeting all levels of the intra-amygdaloid connections linking the lateral, basolateral and central nuclei [10, 23]. It must be noted that the PBN-insular cortex projections pass across the central nucleus of the amygdala [21]. Interestingly, Shi and Cassel (1998) [23] reported that cortical connections from the somatosensory secondary cortex to the IC may convey somatosensory information to the amygdala [23] and relay shock information to the BLA during fear conditioning [181].

All other main areas that are connected to the IC have reciprocal connections to the amygdala. The VPMpc projects to the amygdala [31, 132, 182] although the cells from the VPMpc that project to the amygdala are different from those that project to the IC [31]. The BNST also projects to the amygdala [20, 183], the LHA [20] and the PBN [18].

Within the PBN, the latPBN sends dense afferents to the central nucleus of the Amygdala (CeA) and more sparse afferents to the basolateral nucleus (BLA) and the lateral area (LAA), whilst the mPBN projects more densely to the BLA and LAA, but more scarcely to the CeA [18]. The lateral part of the BNST also receives inputs from the PBN and, from there, the BNST axons join those coming from the PBN and project together to the amygdala [18].

Other PBN subnuclei also project to both the IC and the amygdala. The externo-lateral PBN (elPBN) receives both gustatory and visceral inputs and projects with a calcitonin-gene related peptide (CGRP) into the insular cortex ([184] and to the amygdala ([27, 185]). CGRP microinjections into the amygdala induce fear-like behaviour in absence of aversive stimuli [186] as well as with increased heart rate and arterial pressure [187].

10. The role of the amygdala in taste function

The BLA has a crucial modulatory role in almost all memory tasks that include an emotion-arousing component. For Pavlovian fear conditioning, the BLA is not only the site where memory consolidation takes place but is also the site of long-term memory storage (for a review, see [188, 189]). As for other learning tasks, such as inhibitory avoidance or CTA, the BLA is not the site of memory storage but rather it modulates the memory consolidation of those memories stored in other brain regions (for reviews, see [190-192].

Dunn and Everitt (1988) [149] reported that BLA - but not CeA - lesions impair CTA. Furthermore, BLA lesions may impair taste neophobia [150] and arousal-induced taste neophobia, as well as passive avoidance [149]. Pharmacological BLA manipulations suggest a modulatory role in CTA after novel taste presentation, during visceral malaise and its association with the taste [193-197].

BLA stimulation affects IC neuronal responses [8] whereas BLA tetanic stimulation induces long-term potentiation in the ipsilateral IC [157, 158, 198]. Interestingly, induction of this

long-term potentiation in the BLA–IC projection before CTA training enhances memory retention [199].

Other studies have suggested that CTA memory acquisition in the IC requires an intact BLA [200] and combined IC and BLA reversible or permanent lesions induce stronger CTA impairment than IC or BLA lesions alone [130, 193, 201-203].

Lesions in the BLA and LAA impair CTA moderately, but the combination of lesions of the VPMpc and the amygdala completely disrupts CTA [130, 204] and neophobia and induces weight loss [204]. Lesions of the amygdala have also been shown to produce the faster extinction of odour-taste (saccharin) association learning [205]. Moreover, transient pharmacological manipulations of the amygdala have been shown to impair CTA [140, 192, 206-208] and suggest that CTA consolidation depends upon protein synthesis and requires CREB and cfos activation in the CeA [192, 206, 207], whereas extinction depends upon protein synthesis in the BLA [192]. Interestingly, neither amygdalar nucleus is involved in CTA memory reconsolidation [140, 208], which probably suggests that the amygdala is involved in CTA acquisition but not in CTA memory storage.

Interactions of the amygdala with other brain regions have also been shown to be necessary for CTA. One study reported that lesions in the basal forebrain that deplete the neocortical innervation of acetylcholine (ACh), paired with lesions of the BLA, completely disrupt CTA, while each by itself may only impair learning [203, 209].

The amygdala has been well established as subserving fear and other emotional responses (reviewed in [188]). Together with other frontal cortical areas, it constitutes a major part of the so-called limbic system. Thus, it is possible that the role of the amygdala in taste function could be linked to the emotional and hedonic valence of gustatory stimuli in response to the salient bodily representation provided by the IC.

11. Other amygdalar functions shared by the IC

Ample evidence suggests that the amygdala can modulate memory consolidation in different memory systems through its many efferent projections to other brain regions [210]. Several reports show that the amygdala is involved in hippocampus-dependent (spatial or contextual) learning paradigms [211]. The basolateral complex of the amygdala (BLA; consisting of the lateral, basal and accessory basal nuclei) is critical for mediating the effects of stress on memory in several types of learning [212]. BLA also interacts with the IC in regulating taste neophobia [151, 20, 213] and, as mentioned earlier, CTA.

Interestingly, the IC has also been reported to be involved in the memory consolidation of inhibitory avoidance [214] and object recognition memory [215] - both learning systems that have been shown to be modulated by the amygdala [216, 217]. As stated at the beginning of this chapter, in humans insula activation has been correlated to processing threats and seeing emotional images in patients with anxiety disorders [218, 219], contextual fear conditioning [220], negative emotional states, including pain [56, 221], and positive emotions [58, 59]. Interestingly, all of the above conditions have also been reported to activate the

amygdala [220-224]. As such, does the IC have shared functions with the amygdala? Do they interact?

12. Insular cortex and amygdala interactions

For learning and memory, extensive evidence suggests that the amygdala interacts with other brain regions, including the BNST, the nucleus basalis, the hippocampus and the entorhinal cortex (reviewed in [190, 225]).

In CTA, studies have shown that learning is modulated by interactions between the amygdala and the IC. Ferreira and colleagues (2005) showed that the glutamatergic activation of the amygdala enhances CTA, an effect that can be blocked by the glutamatergic blockage of the IC [226].

Interactions between the insular cortex and the amygdala have been hinted at in some human studies [227]. In one of these, the over-activation of both areas was reported in patients with anxiety disorder [219], while in another study the ventral agranular frontoinsula was shown to co-activate with the amygdala in social–emotional paradigms [38, 45, 52, 228].

As we have discussed before, IC activity has been correlated with several functions that also recruit amygdala activity. The fact that IC stimulation elicits cardiovascular responses is also not unique for the IC. In fact, electrical stimulation of the amygdala induces stress-related responses, including tachycardia and elevated arterial pressure as well as renal, intestine and skin vasoconstriction [229], while the stimulation of the CeA produces bradycardia, dilation of the pupils and movements of the mouth and tongue [230]. Furthermore, a study using single cell recordings of the amygdala in the cat reported that 46% of cells responded to carotid sinus nerve stimulation and that half of them responded to selective baroreceptor or chemoreceptor activation [231].

Other electrophysiological recordings have also shown that amygdala neurons respond to cardiovascular challenges. Cechetto and colleagues reported that over 23% of all recorded amygdala neurons responded to chemoreceptor activation and 16% to baroreceptor activation in cats [232]. In a different study, a cardiovascular pressure stimulus elicited predominantly inhibitory responses in one-half of amygdalar neurons. Most neurons in the central and basal nuclei responded to carotid chemoreceptor activation with excitation. Moreover, when testing responses to external sensory stimulation, 33% of recorded neurons responded to visual stimulation, 55% to acoustic, 39% to tactile and 59% to olfactory stimuli. Two-thirds of the neurons responded to more than one external sensory stimulus, demonstrating a convergence of sensory processing on single amygdalar neurons. Also, and as expected, 86% of recoded neurons responded to behavioural arousal [233].

So far, evidence seems to indicate that the IC and the amygdala share an enormous number of functions and properties. Although the idea that the IC is involved in creating bodily representations that are used by the amygdala to produce the correct emotional response is attractive, there is to date no real evidence that can distinguish the roles of either area.

Nevertheless, if we were to accept this model, where the role of the IC is to create and convey a bodily representation to the amygdala, which would be used to modulate and coordinate an emotional response to the stimulus, both the IC and the amygdala would be expected to receive direct autonomic and sensory information and to elicit cardiovascular responses. As such, the IC projections to the amygdala, together with the cortical connections from the somatosensory secondary cortex to the IC that convey somatosensory information to the amygdala [23], would relay the salient autonomic and sensory information needed to create an emotional response.

The mode and timing of the IC-amygdala interaction remains elusive and has not been the subject of much research. In an fMRI study in cats, depressor cardiovascular challenges produced a decline of signal-intensity in the right insula and increased signal intensity in the amygdala [234]. By way of contrast, Williams and colleagues reported using fMRI in humans such that the initial perception of fearful faces induced, first, increased activity in the insula, then a greater engagement of the medial prefrontal cortex and, finally, activity in the left amygdala [235]. Does the IC-Amygdala interaction imply synergic activation? Or does it imply inhibition? Is the IC expected to be activated before the amygdala? According to the data so far, the presence of massive feedforward excitatory projections and the electrophysiological studies commented on throughout this chapter suggest reciprocal excitatory connections. Furthermore, according to the IC´s bodily representation-amygdala´s emotional response model, IC activation should precede that of the amygdala. To date, there is no conclusive evidence as to how this interaction takes place. Nevertheless, it is clear that in order to understand emotions we need to comprehend how the two of its major participants interact.

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