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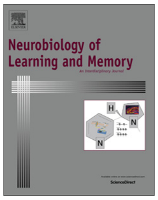

Review

The forgotten insular cortex: Its role on recognition memory formation

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ABSTRACT

For a long time, the insular cortex (IC) has been related with taste physiology and taste memory processes in animal studies. Recently, the role of the IC has been highlighted by findings involving the IC in non-taste memory formation in both human and animal studies. Recognition memory is based on the ability to assess the familiarity of a previously encountered stimulus, and it is considered a form of declarative memory. In this work, I am proposing that the IC and its related circuitry are highly involved in the conversion of novel to familiar stimulus for both object and taste recognition memory. In addition, I will review some of the molecular mechanisms involved in the modification of novelty to familiarity memory processes, including the role of epigenetic mechanisms on the consolidation of recognition memory within the IC. In the second part of the paper, I will review some of the possible mechanisms to transform a novel taste into a familiar aversive taste by a functional interaction between the IC and the amygdala. In summary, the IC is an important area that will open a new avenue for the study of the mechanisms involved in the neurobiology of learning and memory in the near future.

1. Introduction

Memory is one of the best strategies that animals have to cope with the environment. Remembering adequate shelter and places to find safe food for the offspring exemplifies the use of cognitive maps with a high adaptive value. Recognition memory is one of the survival skills developed by animals through evolution, and the impairment of this feature is one of the main characteristics of some amnesic syndromes such as Alzheimer's disease, i.e., the inability to discriminate between novel/familiar events. After the description of the amnesic syndrome in the HM case, in which most of the temporal lobe was ablated bilaterally, several memory processes have been linked to a network of cortical and subcortical regions in this lobe, including the perirhinal, parahippocampal, entorhinal cortices, amygdala and hippocampus (Ennaceur, Neave, & Aggleton, 1996; Mishkin, 1978; Winters & Bussey, 2005; Yonelinas et al., 2002). The insular cortex (IC) is part of the neocortex located in the lateral temporal lobe and has been highly correlated with taste function; however, it has also been correlated with other sensory modalities like vision, hearing, touch and odor (Augustine, 1996). Recently, the IC has been specially highlighted in human imaging literature and outcomes from brain surgery findings that have demonstrated its importance in several complex cognitive functions like emotion, perceptual functions, sensory-motor integration and body awareness [for a review in human literature see (Jones, Ward, & Critchley, 2010; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010)].

The term agnosia is defined as the clinical manifestation of impaired recognition without loss of basic sensory ability. The NIH states: "People with agnosia may have difficulty recognizing the geometric features of an object or face or may be able to perceive the geometric features but not know what the object is used for or whether a face is familiar or not." (See: http://www.ninds.nih.gov/disorders/agnosia/agnosia.htm). Although, agnosia for faces or tastes has been related with cognitive impairments involving the judgment of familiarity, it remains to be determined whether these pathologies would involve the IC function. Recognition memory is based on the ability to assess the familiarity of a stimulus previously encountered, and has at least two memory components: one is the judgment of familiarity of the items and the other is the recollection of contextual information where the memory for those stimuli was acquired (Eichenbaum, 2010; Yonelinas et al., 2002).

In the first part of the paper, I will propose how the IC could be involved in switching novel to familiar recognition memory processes for taste and visual stimuli. To do so, I will review the possible IC molecular mechanisms involved in the switching processes of recognition memory formation. In the second part, I am proposing that in order to transform a novel flavor to a familiar aversive taste a functional communication is necessary between the amygdala and the IC during conditioned taste aversion memory formation.

1.1. Anatomical summary

The anatomical connectivity of the IC (or Island of Reil) in primates and rodents has been extensively described in several revisions; nonetheless, the functional role of the IC in rodents on

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cognitive processes remains poorly studied [see (Benjamin & Golden, 1985; Jones et al., 2010)]. In the first human anatomical numerical cortical maps made by Brodman, the insula did not receive a number [(Craig, 2010; Kurth et al., 2010)]. However, during the last decades of the 20th century a better anatomical and functional description of the IC came along [see (Mesulam & Mufson, 1982)]. The IC is located in the lateral temporal lobe in primates and humans and has been regarded as the "hidden fifth lobe" located deep within the Sylvian fissure (Jones et al., 2010); see Fig. 1A). In rodents the IC (Krieg's areas 13 and 14) is located along the confluence of the rhinal sulcus and the medial cerebral artery. The anatomical boundaries of the IC span from the lateral frontal cortex to the perirhinal cortex in the rostrocaudal direction and from the ventral edge of somatomotor cortex to the pyriform cortex in the dorso-ventral directions (Cechetto & Saper, 1987; Kurth et al., 2010; Shi & Cassell, 1998).

The IC has been divided into three main areas: the dorsal granular zone, the dysgranular area in the middle, and the ventral agranular area (see, Fig. 1B and C). The dysgranular IC has been related with gustatory modalities, whereas the granular region is related with viscerosensory cortical areas, and the posterior agranular area has been related with multimodal and limbic-autonomic integration (Kosar, Grill, & Norgren, 1986; Saper, 1982; Shi & Cassell, 1998). Interestingly, despite the IC being known as the gustatory neocortex, the taste-related functions area occupies around 20% of the total IC area. Thus, the taste area in the rat is primarily located in the dysgranular insular cortex (Cechetto & Saper, 1987; Ogawa, Ito, Murayama, & Hasegawa, 1990; Yamamoto, 1984), 1 mm wide and 3 mm long, with boundaries that do not extend beyond AP +3.0 mm rostrally from Bregma (Benjamin & Akert, 1959; Kosar et al., 1986; Yamamoto, Matsuo, & Kawamura, 1980). The anatomical connections of the IC suggest that this region plays an important role in the mediation of visceral reactions with inputs from several information modalities. Thus, the viscerosensory cortex resides in the granular insular cortex, caudo-dorsal to gustatory neocortex (Cechetto & Saper, 1987; Ito, 1992). A possible reason why the IC is involved in several cognitive functions could be that limbic inputs from amygdala, dorsomedial nucleus of the thalamus, and the prefrontal cortex converge with primary sensory inputs that are not seen within any other sensory area of the cortex (Krushel & Van der Kooy, 1988; Selemon & Goldman-Rakic, 1988; Shi & Cassell, 1998).

2. Recognition memory

This section summarizes some experiments that show putative biochemical and molecular mechanisms involved in the mnemonic process of transforming stimuli from novel to familiar in the IC. The ability to form and store memory in the central nervous system depends on the plasticity that may occur in the patterns of neural activity at the synapse. Different forms of synaptic plasticity that persist over time require a rapid intracellular signaling that triggers the expression of new genes that contribute to the functional and structural modifications of synapses. It has been known for decades that protein synthesis and changes in transcriptional factors are involved in memory consolidation (McGaugh, 1966, 2000; Swank & Sweatt, 2001). Recently, a novel approach studying epigenetic mechanisms involved on memory formation has been

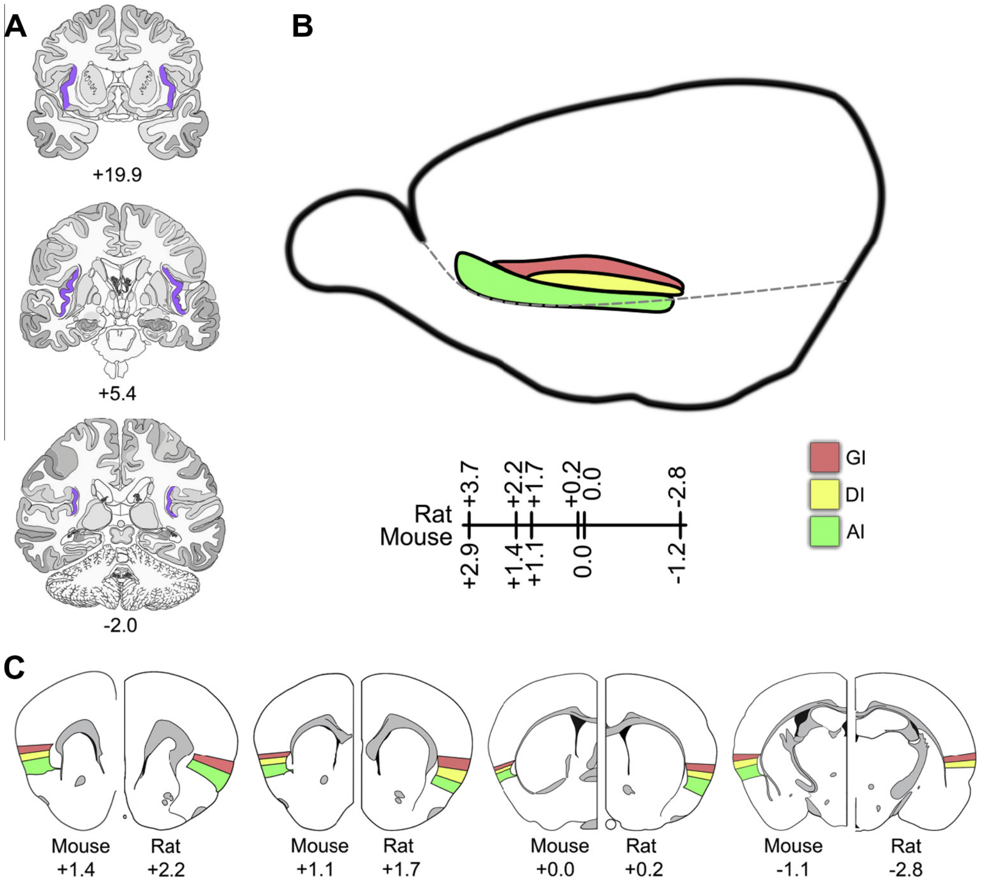

Fig. 1. (A) Schematic representation of the IC in humans, the coordinates are from the anterior commissure. (B) Schematic representation of the IC in mice and rats along the rhinal sulcus showing the granular, disgranular and agranular IC. (C) Schematic representations of coronal sections of mice (left) and rats (right) at various AP sections from bregma as zero.