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A volumetric comparison of the insular cortex and its subregions in primates

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ABSTRACT

The neuronal composition of the insula in primates displays a gradient, transitioning from granular neocortex in the posterior-dorsal insula to agranular neocortex in the anterior-ventral insula with an intermediate zone of dysgranularity. Additionally, apes and humans exhibit a distinctive subdomain in the agranular insula, the frontoinsular cortex (FI), defined by the presence of clusters of von Economo neurons (VENs). Studies in humans indicate that the ventral anterior insula, including agranular insular cortex and FI, is involved in social awareness, and that the posterodorsal insula, including granular and dysgranular cortices, produces an internal representation of the body's homeostatic state. We examined the volumes of these cytoarchitectural areas of insular cortex in 30 primate species, including the volume of FI in apes and humans. Results indicate that the whole insula scales hyperallometrically (exponent = 1.13) relative to total brain mass, and the agranular insula (including FI) scales against total brain mass with even greater positive allometry (exponent = 1.23), providing a potential neural basis for enhancement of social cognition in association with increased brain size. The relative volumes of the subdivisions of the insular cortex, after controlling for total brain volume, are not correlated with species typical social group size. Although its size is predicted by primate-wide allometric scaling patterns, we found that the absolute volume of the left and right agranular insula and left FI are among the most differentially expanded of the human cerebral cortex compared to our closest living relative, the chimpanzee.

Introduction

The insular cortex is located on the lateral wall of the cerebral hemispheres of mammals, overlying the claustrum, and interposed between the piriform, orbital, motor, sensory, and higher-order auditory cortices (Türe et al., 1999). Most primates have enlarged parietal and temporal opercula, and the insular cortex is hidden from view within the depths of the Sylvian fissure. In other primates where the Sylvian fissure is not as well developed (e.g., *Perodicticus*, *Galagoides*, *Loris*), the insula may be exposed on the brain's lateral surface (Preuss and Goldman-Rakic, 1991). The insula is interconnected with anterior cingulate cortex, rostral and dorsolateral prefrontal cortex, regions of the parietal and temporal lobes, as well as entorhinal cortex, amygdala, hypothalamus, and dorsal thalamus, and it is involved in viscerosensory, visceromotor, somatosensory, and interoceptive functions (Price, 1999; Critchley, 2005). Human functional neuroimaging studies show activation of

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Abbreviations: ALS, anterior limiting sulcus; AQ, asymmetry quotient; FI, frontoinsular cortex; fMRI, functional magnetic resonance imaging; ILS, inferior limiting sulcus; MRI, magnetic resonance imaging; SLS, superior limiting sulcus; VENs, von Economo neurons.

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the insula in association with an individual's emotional state that seems to reflect an internal representation of the body, providing a potential neurobiological basis for subjective awareness useful in the guidance of social interactions (Craig, 2002, 2009; Singer et al., 2009). Specifically, the human insular cortex is important for self-recognition, awareness of emotions, time perception, empathy, and decision-making under uncertainty, as well as the processing of music and language. It has been hypothesized that human cognitive evolution was accompanied by changes in capacities that rely on insula function, such as intersubjective perspective-taking, cooperation, and empathy (Singer et al., 2004; Craig, 2009). However, the neural structures that subserve such psychological specializations in our lineage remain unclear. Given the importance of the insular cortex for sociocognitive processing, the purpose of the current study was to examine the relative size of the insula and its constituent cytoarchitectural subdivisions in humans and other primates.

The primate insular cortex may be divided into three cytoarchitectural subregions based on the distinctiveness of granularity in cortical layer IV, defined by the presence of small, densely packed neurons (Rose, 1928; Mesulam and Mufson, 1982; Carmichael and Price, 1994; Öngür et al., 2003; Kurth et al., 2010a; Gallay et al., 2011). Accordingly, the cellular composition of the insula displays a gradient, transitioning from granular neocortex in the posterior and dorsal insula to agranular neocortex in the anterior and ventral insula, with an extensive intermediate zone of dysgranularity. In addition to the three sectors of insula that can be recognized in all primates, great apes and humans exhibit a distinctive subdivision of agranular insular cortex, frontoinsular cortex (FI), located within the most ventral anterior part of the agranular insular cortex adjacent to the orbital cortex. The FI is defined by the presence of clusters of von Economo neurons (VENs) in cortical layer Vb (von Economo, 1926; Allman et al., 2010). The VENs, which can also be found in the anterior cingulate and dorsolateral prefrontal cortex of humans and great apes, are large spindle-shaped projection neurons with a single basal dendrite (Nimchinsky et al., 1995, 1999; Fajardo et al., 2008).

Data from functional magnetic resonance imaging (fMRI) studies in humans suggest that anatomical variation in the cytoarchitecture of insular cortex may correspond to functionally distinct areas. Specifically, the posterior insula displays activation in the processing of thermosensory information, pain, hunger, thirst, and touch in a somatotopically organized posterior-to-anterior (foot to mouth) gradient (Ostrowsky et al., 2002; Craig, 2003, 2010). The more anterior regions of the insula, likely including agranular insular cortex and FI, complement the posterior insula's representation of one's body state with the ability to process subjective feelings and social awareness. For example, the sensation of pain in one's own body activates posterior insula, whereas feeling empathy for another's pain activates the anterior insula (Singer et al., 2004). Although imaging studies cannot provide direct correspondence between function and cytoarchitecture, different functions have been ascribed to the posterodorsal insular cortex, consisting of mostly granular and dysgranular cortices, versus the ventral anterior insular cortex, which is composed of agranular cortex and FI (Wager and Barrett, 2004; Mutschler et al., 2009; Kurth et al., 2010b). Further supporting the notion that the anterior insular cortex is important for social awareness, it is notable that a severe loss of VENs and widespread degeneration of this region are observed in human patients with the behavioral variant of frontotemporal dementia, a disease that impairs the individual's ability to recognize the impact of his or her actions on other's emotions (Seeley et al., 2006; Kim et al., 2012). A reduction of VENs within ACC and FI also occurs in human patients with agenesis of the corpus callosum, a condition that is linked to impoverished understanding of one's emotions and difficulty understanding the emotional states of others (Kaufman et al., 2008). Additionally, a greater number of VENs are present in the FI of autistic children, a finding that may relate to the enhanced interoception reported in these individuals (Santos et al., 2011).

It is also notable that left and right anterior insula display functional differences. Several studies have shown predominant activation of right anterior insula during arousing feelings with negative emotional valence and sympathetic activation, while approach behavior, positive affect, and parasympathetic function may associate predominantly with left anterior insula activation (Craig et al., 2000; Critchley et al., 2004; Craig, 2005). These opponent processes are thought to work in concert to provide a homeostatic balance and unified sense of awareness.

In the current study, we examined phylogenetic variation in the volume of insular cortex subdivisions. Such an approach is rooted in Jerison's (1973) principle of proper mass, which states that the volume of a particular cortical area is proportional, 'to the amount of information processing involved in performing the function'. As the volume of a region expands, the number of neurons and local connections within the region increases (Kaas, 2000), enhancing the fine-tuned processing of the functional output. The capacity for information processing of this nature might be particularly critical for regions underlying social interaction (Dunbar, 1998; Barton, 2006), including the anterior insular cortex (Lamm and Singer, 2010).

Although the volume of insular cortex has previously been measured in humans and apes using structural MRI (Semendeferi and Damasio, 2000), the volumetric extent of the cytoarchitectural subregions that comprise the insular cortex have not yet been examined. Moreover, quantitative data on the insular cortex are lacking from other species of primates beyond hominoids. In this study, we present new volumetric measurements of the insular cortex based on cytoarchitectural analysis from 30 primate species. We examined the allometric scaling of insular cortex and its subdivisions relative to brain size to determine whether the volume of agranular insula, including that containing FI in hominids, has increased in humans or any other primate clade. Additionally, we investigated whether the volume of insular cortex or any of its subdivisions are relatively expanded in species that live in larger social groups. Lastly, because the insula displays functional lateralization, we explored whether hemispheric asymmetry in the volume of the insular cortex is present among humans and great apes. In studying the relative size of these insular subregions across primates, we aimed to provide insight into the neural basis of specialized functions in social cognition.

Methods

Specimens

The sample used in this study consisted of 43 brain specimens from 30 different primate species (Fig. 1). The sample included representatives of strepsirrhines ($n = 6$), platyrrhines ($n = 8$), cercopithecoids ($n = 7$), and hylobatids ($n = 3$). The hominid sample included specimens from *Homo sapiens* ($n = 5$), *Pan troglodytes* ($n = 3$), *Pan paniscus* ($n = 3$), *Gorilla gorilla* ($n = 4$), *Pongo pygmaeus* ($n = 2$), and *Pongo abelii* ($n = 2$). The mass of the whole brain following initial fixation was available from every specimen and was a prerequisite for inclusion in this study. A complete list of specimens, including sex and age, is shown in Table 1.

Volumetric measurement methodology

To collect measurements in the greatest possible range of primate species, our sample consisted of specimens from several