DE GRUYTER Neuroforum 2018; 24(4): A151–A158

Gundela Meyer*

From the lateral edge to the center of the cortex: The development of the human insula

https://doi.org/10.1515/nf-2018-A008

Abstract: The human insula is a key node in a neuronal network which integrates interoceptive stimuli from the own body, and exteroceptive stimuli from the environment, and thus maintains the autonomic, emotional and socio-cognitive homeostasis of the body. In the last years, the insula has come into the focus of attention. Comparative anatomical studies showed that in many species the insula forms the lateral edge of the cortex. Very little is known about the prenatal development of the human insula, which is the first cortical region to mature. The origin of the pyramidal neurons for the insula is a small sector of the proliferating ventricular/subventricular zone at the cortico-striatal boundary (CSB). The CSB contains the radial glia cells, which are stem cells and give rise to a dense fascicle of radial glia processes. This fascicle traverses the external capsule and serves as a migration substrate for the neuroblasts on their way from the CSB into the insula. Around the 10/11th week of gestation, the lateral ventricle and its adjacent structures including the CSB bend in a C-shaped fashion. The insula now develops between a dorsal, fronto-parietal and a ventral, temporal CSB, which provide descending and ascending streams of neuroblasts, respectively, migrating along the radial glia fascicle. As a consequence of the ventricular rotation during ontogenesis, the human insula changes its initial position at the lateral edge of the cortex to its final central location, which reflects its integrative functions in brain activity.

Keywords: Radial glia; neuronal migration; lateral ventricle; cortical layers; ontogenesis.

Introduction

The insular cortex (insula, insular lobe, island of Reil) was first described by Reil in 1809 in the depth of the Sylvian fissure (lateral sulcus). In the last two decades, the insula has come into the focus of research because of its involvement in an unexpectedly wide array of activities related to of human cognition and emotions, to which novel imaging techniques provide access. A short list of the functions attributed to the insula may give a glimpse of its importance: Autonomic perception (interoception), viscero-sensitive, viscero-motor and vestibular functions, motor association, somatosensation, chemosensation, hearing, language, emotion awareness, pain perception, empathy, empathy for the pain of others, perception of time, attention, motivation, subjective music perception, aesthetic valoration of objective and subjective beauty, social consciousness, decision-making, craving and addiction, lust, disgust, smell and taste (summarized in 1,2). These many and varied activities are attributed to distinct subregions of the insular cortex, with the flow of information being directed from posterior to anterior. The posterior insula may serve as an example: it is activated by coldness, warmth, hunger and thirst, sensory stimulation and pain (3,4). In turn, the anterior insula complements the representation of one´s own body with subjective feelings and social interactions. While the own pain activates the posterior insula, empathy with another´s pain is processed in the anterior insula (5). In this, right and left insula show different activation patterns: the right anterior insula is under orthosympathetic control and activated by feelings of negative emotional value; by contrast, the left anterior insula is associated with positive emotions and parasympathetic stimulation. Both insulae work in concert also in other functional activities, complementing each other (4,6). The insula calibrates cardiorespiratory and cardiovascular activations in response to exteroceptive and interoceptive stimuli, with the right anterior insula playing the dominant role in an interoceptive network. As a whole, the insula integrates all the influences from the external world and from the own body in order to develop survival strategies and maintain at the same time an emotional and physiological homeostasis (7). Craig defined the human insula as part of the "sentient self" (3). The insula does, however, not represent the site of specific functions, but should rather be considered as an important hub in a functionally dynamic network, which involves many other cortical areas.

***Corresponding author: Gundela Meyer,** Facultad de Medicina, Universidad de La Laguna, Tenerife, Spain, gundelam@aol.com

Where is the location of the human insula?

The insula lies in the depth of the Sylvian fissure, totally hidden by the opercula (operculum: little lid) of the frontal, parietal and temporal lobes, and is therefore not visible at the surface of the hemispheres. Its rostral end borders the prefrontal areas, while its caudal end is defined by Heschl´s gyri in the auditory temporal lobe (Fg. 1A). Anterior, dorsal and posterior parts of the insula are surrounded by the circular sulcus (anterior, superior and inferior circular sulci) and thus delimited from the adjacent cortical areas. At its free rostal and basal surface, the *limen insulae,* the insula is transitional with the paleocortex of the primary olfactory cortex, which in turn represents the lateral boundary of the anterior perforated substance. Deep to the gray matter of the insular cortex is its white matter, known as the extreme capsule, which connects the insula with its afferent and efferent projection centers. The claustrum is medial to the extreme capsule, and almost co-extensive with the insula. Similarly co-extensive is the putamen that represents the external part of the lenticular nucleus, and is separated from the claustrum through the external capsule. These topographical relationships are important for surgical access to deep brain structures through the Sylvian fissure, in particular due to the large number of important blood vessels in this region (specifically, the middle cerebral artery and its main branches in the Sylvian fissure). This explains the many exhaustive descriptions of the anatomy of the human insula (8,9).

The claustrum lies between the external and the extreme capsules. A controversial question is whether the claustrum belongs to a claustro-insular complex. In many mammals, the topographical relationships between insula and claustrum are quite diverse, and even in human the dorso-caudal insula has no underlying claustrum. In this review we will not mention the claustrum again, since we believe that insula and claustrum are both dependent on their close topographic relationship with the olfactory cortex, without being strongly interconnected functionally or ontogenetically (10).

Macroscopical anatomy, cytoarchitecture and connectivity of the human insula

The insula can be divided into a larger anterior and a smaller posterior region, which are separated by the central sulcus of the insula (Fig. 1A). The anterior insula usually displays 3 short gyri, sometimes also an accessory gyrus, although their number can vary across brains and even between hemispheres (Fig. 1B).

The posterior insula is formed by two long gyri. All gyri converge radially toward the rostral and ventral insular pole. In human, an additional fronto-insular transition field has been described, which is densely populated by large spindle neurons in layer V, the “von Economo neurons”. Von Economo neurons are also found in the anterior cingulate cortex; they have extensive long-reaching axonal projections (12).

The cellular architecture (cytoarchitecture) of the primate and human insula has attracted the attention of many classical and recent researchers. Economo and Koskinas (11) divided the insula into an anterior agranular part, and a posterior granular part, with transitional forms in the intermediate insula. The term “granular” refers to the presence (or absence), width and cell density of granular layers II and IV, with particular emphasis on layer IV. Many other authors provided detailed studies of the cytoarchitectonic insular subfields. Since the resulting classifications of the insular fields are quite variable, we refer here to extensive reviews and meta-analyses (1,2). Mesulam and Mufson (13) provided a commonly accepted parcellation of the insula of the macaque moneky and human; additional subdivisions are possible, and have in fact been proposed. Mesulam and Mufson distinguish an anterior agranular insula, which lacks a layer IV, a middle dysgranular insula, where layer IV is irregularly formed, and a posterior granular insula, where layer IV is prominent. An important feature is the almost concentric arrangement of the agranular, dysgranular and granular fields from rostroventral to caudorostral around a reference point in the rostrobasal insular pole, where the insula is continuous with the paleocortex. This concentric arrangement of the insular fields according to the presence and prominence of layer IV was reported in other species (cat,14; rat, 15), but cannot be generalized (16, see below).

The connectivity of the insula is extremely complex. Many subcortial and cortical connections were described in non-human mammals (16; summarized by1, 18), and now modern techniques of neuroimaging allow a precise determination of axonal connections also in the human

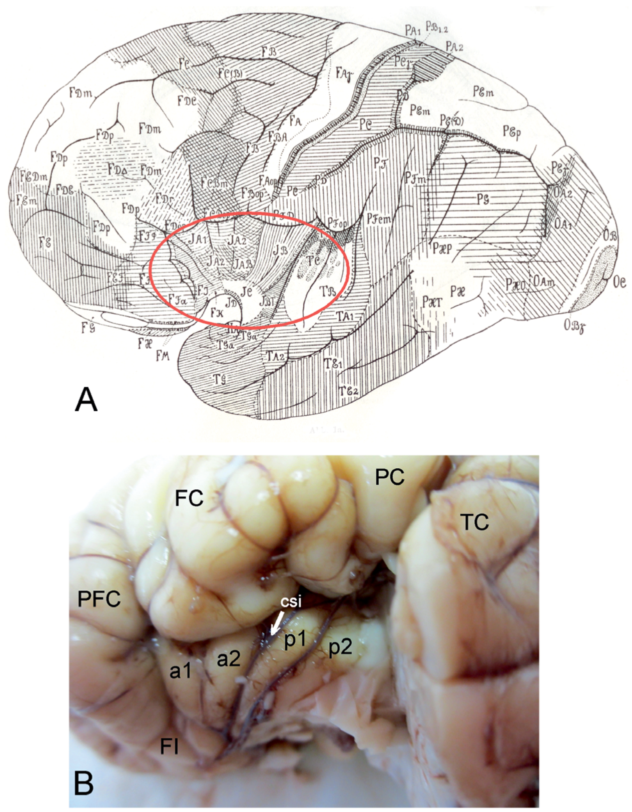

Fig.1: A: Cytoarchitecture of the lateral hemisphere according to von Economo and Koskinas (1925). The Sylvian fissure is opened and the insular region surrounded with a red circle, to show the central position of the insula, and its boundaries with the adjacent cortical areas. B. The insula in a newborn infant, already displaying the adult gyration pattern. The rostral pole of the temporal lobe (TC) was dissected out to show the gyri in the insular region. In this case there were only 2 short gyri (a1 and a2), and two posterior gyri (p1 and p2). The white arrow points to the central sulcus of the insula (csi), while the red asterisk indicates the position of the *limen insulae*. FC: frontal cortex; FI: fronto-insular cortex, PC: parietal cortex; PFC: prefrontal cortex.

insula (19, 20). We can summarize that the insula is connected through wide-range cortico-cortical fiber projections with practically all lobes, even with distant regions in the occipital and entorhinal cortex. The reciprocal functional and structural connections with the anterior cingulate cortex are particularly important, because both the anterior cingulate and insular cortices are activated by many cognitive and affective stimuli (6). Furthermore, connections with the insula are established with the hippocampus, amygdala, hypothalamus, thalamus (ventral posterior lateral parvicellular nucleus, ventral posterior medial parvicellular nucleus, and dorsomedial nucleus), and also with putamen, globus pallidus, nucleus caudatus and nucleus accumbens (18,20).

Comparative developmental history of the insula

The insula is commonly regarded as a phylogenetically "old" structure, in close relationship with the olfactory paleocortex and the claustrum. An influential theory postulated the existence of a general bauplan of the pallium or cortex valid for all amniotes, and based on the common expression of specific transcription factors during development (21). This bauplan has 4 main divisions: 1: A medial pallium as the origin of the hippocampus, 2: a dorsal pallium that would give rise to the neocortex, 3: a lateral pallium representing the future insula, olfactory cortex and claustrum, and a ventral pallium as the origin of the cortical parts of the amygdala. In rat and mouse, the insula forms a longitudinal strip of cortex along the upper bank of the rhinal sulcus, while its ventral border is bordering with the paleocortex. As in primates, the rodent insula displays agranular, dysgranular and granular fields, which extend in parallel from rostral to caudal (22). Also in the cat there are agranular, dysgranular and granular insular fields, located in parts of the sulcus rhinalis and the gyrus orbitalis (14).

With the appearance of the Sylvian fissure and the formation of the temporal lobe ***ventral*** to the insula in primates, the basic topographical relationships between the insula and its adjacent lobes have changed: opposed to its previous position at the lateral edge of the cortex, the insula now lies at its very center.

Are size and structure of the human insula particularly prominent? This question was addressed by Bauernfeind et al. (23) by measuring the volumes of the agranular, dysgranular and granular fields of the insula in 30 different primates including man.

The absolute allometric size difference between human and chimpanzee is in fact significant for the left and right anterior insula, and the left frontoinsular cortex; this difference is even larger than that observed in the prefrontal cortex. These data indicate that the anterior insula is important for social consciousness and complex social interactions; in the case of humans, this is possibly related to an increased capacity for empathy and the understanding of the emotional state of others.

A completely different aspect of the comparative anatomy of the insula was addressed by Butti and Hof (16). They looked at insular cytoarchitecture in a large variety of species, which are usually not examined in the laboratory, such as the Beluga whale, Florida Manatee, various artiodactyls, and the Altlantic walrus as a carnivore. Among these species, the structure of the insula was quite diverse, but in no case was the organisation into agranular, dygranular and granular subfields recognizable, in contrast to the typical situation of primates, rodents and cat. The authors point out that many species do not have any granular layer IV at all, not only in the insula, but in no other cortical area. A comprehensive understanding of cortex evolution, including evolution of the insula, should thus not be limited to studies of common laboratory species, but take into account different, alternative models of cortex formation.

The ontogenesis of the human insula

In view of the vast amount of macroscopical, microscopical, hodological and functional studies on the insula, it is surprising how little we know about the prenatal development of the human insula. A first shallow Sylvian groove appears at 13 gestational weeks (GW), concurrent with the emergence of the middle cerebral artery. The central sulcus of the insula appears at 18–21 GW, the other insular sulci form at 27–28 GW. The right insula develops earlier than the left one (24). Importantly, cortical maturation and vascularization of the lateral hemisphere initially start in the insular region, which thus represents the ontogenetically oldest cortex. In this context it is interesting to note that the insula is the source of neural (EEG) and hemodynamic (fMRI) spontaneous activity, the “delta bursts”, which were detected in preterm infants at 32–36 GW (25). These are transient slow delta waves with superimposed fast frequency alpha-beta spindles, which appear in the right and left insula plus the right temporal pole, progress to other cortical locations, and disappear around birth. Their incidence and morphology indicate the degree of cortical maturation in preterm infants. The localization of delta bursts in the insula shows that this brain region plays a key role in the maturation of the human cortex.

The possible mechanisms that contribute to the formation of the complex, heterogeneous human insula were analyzed by our group (Gonzalez-Arnay et al. 2017) (26). In general, each cortical region has a proliferating ventricular and subventricular zone. From here, postmitotic pyramidal cells migrate along the basal processes of radial glia cells toward the surface, to settle down in their final layer of the growing cortex. According to the “protomap”-hypothesis (27), a primordial map in the ventricular zone provides positional information regarding regional specificity that is maintained in the future cortex. In contrast to its adjacent cortical lobi, the insula has a spatially restricted ventricular zone, which is localized at the cortico-striatal boundary (CSB). Immunohistochemistry using specific antibodies against radial glia (anti-vimentin, anti-nestin) provided us with a clear histological demonstration of radial glia processes, which extend in a fan-like manner from their origin in the ventricular/subventricular zone to their end feet at the pìal surface. This radial glia-architecture, combined with immunostaining using pallium-specific antibodies (anti-Tbr1), shows the migration pathway of the future, Tbr1-positive insular neurons from the CSB to their destination (Fig. 2A). Their migration substrate is a dense fascicle formed by the basal processes of the radial glia (Fig. 2B, Fig.3), which courses through the external capsule and then gradually ramifies within the insular cortex (26).

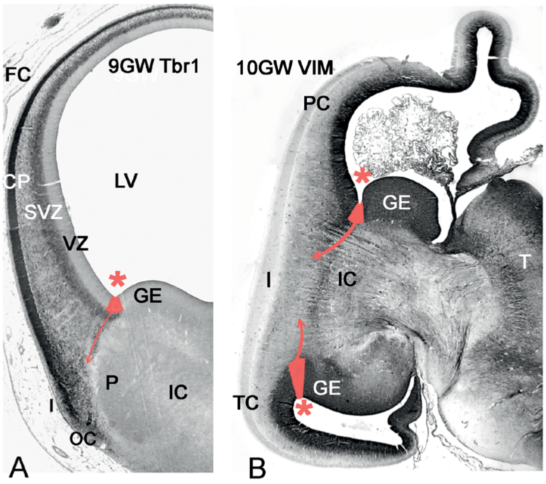

Fig. 2: A: Coronal section through a fetal brain at 9 GW. The cortical part of the telencephalon is immunostained with an anti-Tbr1 antibody and shows the cortico-striatal boundary (its ventricular zone is in red and marked with a red asterisk). The red arrow indicates the direction of the lateral cortical migration stream into the insula and the adjacent paleocortex.. CP: cortical plate, FC: frontal cortex, I: insula, IC: internal capsule, GE: ganglionic eminences, LV: Lateral ventricle, OC: olfactory cortex, P: putamen, SVZ: subventricular zone, V: ventricular zone. B: Coronal section at a slightly more posterior level in a 10 GW fetus, immunostained with an anti-vimentin antibody. With the growth of the temporal lobe, the cortico-striatal boundary is visible both dorsally and ventrally. The insula is limited by the fronto/parietal lobes dorsally, and the temporal lobe ventrally. The migration streams into the insula (red arrows) follow the radial glia fascicle originating in the cortico-striatal boundary.

During fetal development, the CSB defines the border between the cortex and the ganglionic eminences. The latter are subcortical structures that give rise to the basal ganglia, but are also the origin of GABAergic interneurons for the cortex. The CSB was also termed the "anti-hem", a putative signaling center enriched with certain developmental control genes, such as Pax 6. The anti-hem was suggested to instruct the regionalization of the neocortex, working in concert with the cortical hem, located at the medial edge of the telencephalon (28). An evolutionary significance of the CSB was attributed to the fact that the lateral edge of the cortex is the source of the "lateral cortical stream" leading neuroblasts into those centers which derive from the lateral and ventral pallium. These are the olfactory cortex, endopiriform nucleus, claustrum and cortical parts of the amygdala (29). Furthermore, the CSB contributes to the sequential development of thalamocortical and corticothalamic fibers in the internal capsule (26,29). Since the definitions of the anti-hem and the CSB were established in mammals (rodents) and sauropsides (birds and reptiles), it is not surprising that the insula did not attract much attention in these models. In fact, the insula of mice is quite inconspicuous and rather appears as a ventral appendage of the lateral neocortex.

Our study (González-Arnay et al. 2017) (26) proposed a different interpretation of the CSB: it is the main source of the human insula. It is known that the human ventricular system is very different from that of rodents. In the small smooth rodent brain, the lateral ventricle displays a slight ventral and caudal curve. By contrast, the human lateral ventricle is C-shaped, with an inferior horn in the temporal lobe appearing early in development. While the cortex at 9 GW is still smooth and rodent-like (Fig. 2A), at 10/11 GW the lateral ventricle extends into the developing temporal lobe (Fig. 2B). In a coronal section at 10 GW, the dorsal, fronto/parietal CSB appears almost like a mirror image of the ventral, temporal CSB, with both enclosing the insula and providing it with neuroblasts through the glia fascicle in the external capsule (Fig. 3). The radial glia fascicle is most prominent at15–18 GW (Fig.3). With the emergence of the temporal lobe, the insula is no longer the most lateral part of the cortex, but acquires a central position. This new, central position reflects the integrative functions of the human insula, a phylogenetically ancient structure that becomes an important hub in a neuronal network implicated in homeostatic, emotional and cognitive activities.

A further aspect of the CSB as a clearly defined part of the ventricular zone is its longitudinal course traversing several lobes. The CSB follows the border between the future basal ganglia and the adjacent cortical areas from rostral to caudal, and thus extends from prefrontal, frontal and parietal levels into the temporal lobe, where the ganglionic eminences are less prominent. The degree of granularity of each insular subregion may correlate with the rostro-caudal position of its source in the CSB.

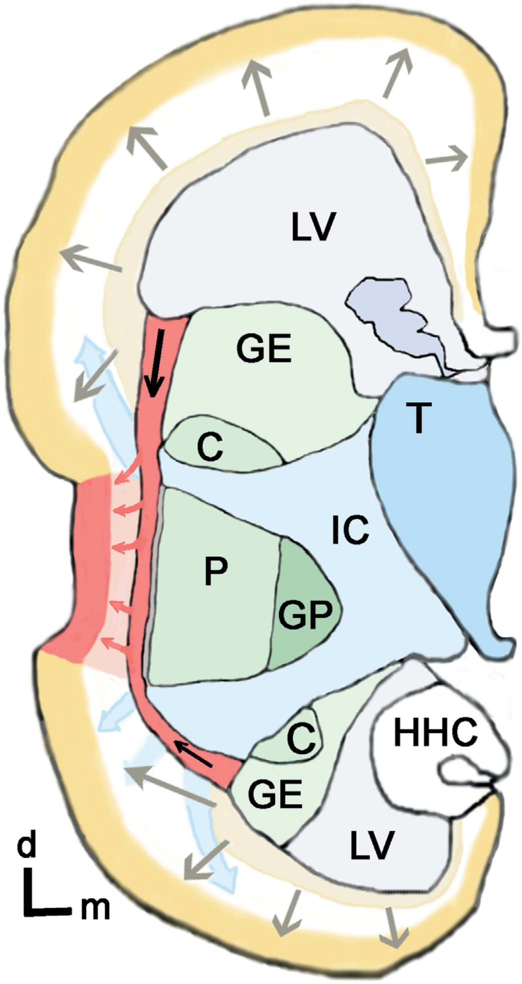

Fig.3: Diagram of the migration pathways from the CSB of the frontal, parietal and temporal lobes into the insula (in red), drawn from a coronal section of a 16 GW fetus. The direction of the descending and ascending parts of the radial glia fascicle (also in red) is indicated by arrows. The dominant orientation of the radial glia in the main lobes is marked with gray arrows. The internal capsule (CI) is represented in clear blue; it traverses the CSB on its way into the cortical white matter. In pink, the subplate of the insula. C: caudate, GE: ganglionic eminence, GP: globus pallidus, HHC: head of the hippocampus, LV: lateral ventricle, P: putamen, T: thalamus. D: dorsal, m: medial.

This suggests a relationship between the agranular character of the anterior insula and the agranular character of the frontal areas adjacent to the frontal CSB. In turn, the parietal CSB is continuous with a proliferating ventricular zone, which is the origin of the somatosensory cortex, an extremely granular isocortex (11). The posterior and dorsal insular region deriving from this part of the CSB is granular and in some parts even hypergranular (2).

Interestingly, the glia fascicle ascending from the temporal CSB into the ventral insula is less prominent, which might be related to the fiber tracts (anterior commissure) and cell groups (claustrum) interposed between insula and temporal CSB. This topographical relationship might result in an impaired radial migration which in turn could explain the dysgranular character of the middle and ventral insula. Dysgranularity may be the result of an intermixture of migration streams of neuroblasts, which derive predominantly from the parietal, and to a lesser degree, from the temporal CSB.

The migration and fiber streams of the human insula were recently studied with high-angular resolution diffusion magnetic resonance imaging tractography (30). The course of the migration streams described in this study at 15 GW is compatible with our description of the origin of projection neurons from the CSB and their migration along the radial glia fascicle (26) (Fig. 3).

The limited growth of the insula is in accordance with the limited sector of the ventricular zone at the CSB, which is the source of insular neurogenesis and migrations. However, the poorly developed subventricular zone (SVZ) of the insula is equally important; its spatial extension at the CSB is limited by the internal capsule (26). The SVZ is identified immunohistochemically using specific antibodies against the transcription factor Tbr2 (31); it is subdivided into an inner and outer SVZ; the latter is considered the origin of many neurons in the supragranular layers II and III. Unfortunately, the origin of the granular layer IV in the human cortex is not yet well known, and layer IV may derive from progenitor cells in the inner and/or outer SVZ. Furthermore, the insula does not have an own intermediate zone, and also the subplate between insula and the extreme capsule is narrower than in the adjacent cortices. It is thus remarkable that the insula is able to form gyri and sulci. However, gyration of the insula takes place in a different time window, during the last months of pregnancy, when neuronal migrations are basically finished (26).

Final comments

The identification of the mechanisms leading to the architectonic differentiation and central position of the human insula is only just beginning. Experimental strategies in laboratory animals (e. g. genetic modifications in the mouse) do not appear very promising taking into account the evolutionary peculiarities of the human insula. An additional difficulty is the fact that many developmental events occur during the second half of pregnancy, and are therefore difficult to replicate in the laboratory (e. g. by using the so-called “brain organoids”. Technical improvement of existing methods, and the development of novel imaging strategies may help to further investigate the prenatal developmental processes, which is important for a better understanding of developmental and neurodegenerative pathologies.

Examples are Alzheimer´s disease, where the agranular insular fields are more affected by neurofibrillary tangles than the granular fields (32). The number of von Economo-neurons in the frontoinsular cortex is dramatically reduced in the frontotemporal dementia (33). Schizophrenia patients have a volume decrease especially of the anterior insula (34). Also in patients affected by autism spectrum disorder, there are complex alterations in the activity of the insula, with differences between subfields in the right and left hemispheres (35). As we would expect from a cortical region so closely related to the perception of emotions and affective control, the insula of patients with bipolar affective disorder displays a variety of functional and structural alterations. For instance, a reduced volume of the gray matter of the right posterior, and the left anterior and ventral insula was described together with an increased volume of the gray matter in the left anterior and dorsal insula (36).

Altogether, these examples show that the insula is affected in many diverse ways in practically all cases of mental dysfunctions and psychiatric diseases. Particularly striking is the variable behavior of the different subfields of the insula, which raises the question of whether the functional areas are correlated with the cytoarchitectonic areas. The insula thus remains a poorly understood cortical region, and future research should take into account its complex structure, connectivity and developmental history.

Article note: German version available at https://doi.org/10.1515/nf-2018-0008

Literature

Nieuwenhuys, R. (2012) The insular cortex: a review. Prog. Brain Res. *195*, 123–163.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., Eickhoff, S.B. (2010) A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct. Funct. *214*, 519–534.

Craig, A.D. (2010) The sentient self. Brain Struct. Funct. *214*, 563–577.

Craig, A.D. (2011) Significance of the insula for the evolution of human awareness of feelings from the body. Ann. N. Y. Acad. Sci. *1225*, 72–82.

Singer, T., Seymour, B, O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D. (2004) Empathy for pain involves the affective but not sensory components of pain. Science *303*, 1157–1162.

Medford, N., Critchley, H.D. (2010) Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct. Funct. *214*, 535–549.

Oppenheimer, S., Cechetto, D. (2016) The Insular Cortex and the Regulation of Cardiac Function. Compr. Physiol. *6*, 1081–133.

Naidich, T.P., Kang, E., Fatterpekar, G.M., Delman, B.N., Gultekin, S.H., Wolfe, D., Ortiz, O., Yousry, I., Weismann, M., Yousry, T.A. (2004) The insula: anatomic study and MR imaging display at 1.5 T. Am. J. Neuroradiol. *25*, 222–232.

Tanriover, N., Rhoton, A.L, Jr, Kawashima, M., Ulm, A.J., Yasuda, A. (2004) Microsurgical anatomy of the insula and the sylvian fissure. J. Neurosur. *100*, 891–922.

Buchanan, K.J., Johnson, J.I. (2011) Diversity of spatial relationships of the claustrum and insula in branches of the mammalian radiation. Ann. N. Y. Acad. Sci. *1225* Suppl.1, E30–63.

Von Economo, C., Koskinas, G.N. Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen. J. Springer Berlin (1925).

Allman, J.M., Tetreault, N.A., Hakeem, A.Y., Manaye, K.F., Semendeferi, K., Erwin, J.M., et al. (2011) The von Economo neurons in the frontoinsular and anterior cingulate cortex. Ann. N. Y. Acad. Sci. *1225*, 59–71.

Mesulam, M.M., Mufson, E.J. (1985) The insula of Reil in man and monkey. Architectonics, connectivity, and function. In: Peters, A., Jones, E., editors. Cerebral cortex. New York, USA and London, UK: Plenum Publishing Corporation: p 179–224.

Clascá, F., Llamas, A., Reinoso-Suárez, F. (1997) Insular cortex and neighboring fields in the cat: a redefinition based on cortical microarchitecture and connections with the thalamus. J.Comp. Neurol.*384*, 456–82

Zilles, K., Zilles,B., Schleicher, A. (1980) A quantitative approach to cytoarchitectonics. VI. The areal pattern of the cortex of the albino rat. Anat. Embryol. (Berl)*159*, 335–360

Butti, C., Hof, P.R. (2010) The insular cortex: a comparative perspective. Brain Struct. Funct. *214*, 477–493.

Allen, G.V., Saper, C.B., Hurley, K.M., Cechetto, D.F.(1991) Organization of visceral and limbic connections in the insular cortex of the rat. J. Comp. Neurol. *311*,1–16.

Augustine, J.R. (1996) Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Brain Res. Rev. *22,* 229–244

Ghaziri, J., Tucholka, A., Girard, G., Houde, J.C., Boucher, O., Gilbert, G., Descoteaux, M., Lippé, S., Rainville, P., Nguyen, D.K. (2017) The Corticocortical Structural Connectivity of the Human Insula. Cereb. Cortex. *27*, 1216–1228.

Ghaziri, J., Tucholka, A., Girard, G., Boucher, O., Houde, J.C., Descoteaux, M., Obaid, S., Gilbert, G., Rouleau, I., Nguyen, D.K. (2018) Subcortical structural connectivity of insular subregions. Sci. Rep.*8*, 8596.

Puelles, L., Kuwana, E., Puelles, E., Bulfone, A., Shimamura, K., Keleher, J., et al. (2000) Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6, and Tbr-1. J. Comp. Neurol. *424,* 409–438.

Fujita, S., Adachi, K., Koshikawa, N., Kobayashi, M. (2010) Spatiotemporal dynamics of excitation in rat insular cortex: intrinsic corticocortical circuit regulates caudal-rostro excitatory propagation from the insular to frontal cortex. Neuroscience *165*, 278–292.

Bauernfeind, A.L., de Sousa, A.A., Avasthi, T., Dobson, S.D., Raghanti, M.A., Lewandowski, A.H.,et al. (2013) A volumetric comparison of the insular cortex and its subregions in primates. J. Hum. Evol. *6,* 263–279.

Afif, A., Bouvier, R., Buenerd, A., Trouillas, J., Mertens, P. (2007) Development of the human fetal insular cortex: study of the gyration from 13 to 28 gestational weeks. Brain Struct. Funct. *212*, 335–346

Arichi, T., Whitehead, K., Barone, G., Pressler, R., Padormo, F., Edwards, A.D., Fabrizi, L. (2017) Localization of spontaneous bursting neuronal activity in the preterm human brain with simultaneous EEG-fMRI. Elife *6*, pii e27814.

González-Arnay, E., González-Gómez, M., Meyer, G. (2017) A Radial Glia Fascicle Leads Principal Neurons from the Pallial-Subpallial Boundary into the Developing Human Insula. Front. Neuroanat. *11*, 111.

Rakic, P. (1974) Neurons in rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science *183*, 425–427.

Assimacopoulos, S., Grove, E.A., Ragsdale, C.W.(2003) Identification of a Pax6-dependent epidermal growth factor family signaling source at the lateral edge of the embryonic cerebral cortex. J. Neurosci. *23*, 6399–6403

Molnár, Z., Butler, A.B. (2002) The corticostriatal junction: a crucial region for forebrain development and evolution. *Bioessays*. *24(6),* 530–541.

Das, A., Takahashi, E. (2017) Neuronal Migration and Axonal Pathways Linked to Human Fetal Insular Development Revealed by Diffusion MR Tractography. Cereb. Cortex. *31*, 1–9.

Betizeau, M., Cortay, V., Patti, D., Pfister, S., Gautier, E., et al. (2013) Precursor diversity and complexity of lineage relationships in the outer subventricular zone of the primate. Neuron *80*, 442–457.

Bonthius, D. J., Solodkin, A., Van Hoesen, G. W. (2005). Pathology of the insular cortex in Alzheimer disease depends on cortical architecture. J. Neuropathol. Exp. Neurol. 64, 910–922.

Santillo, A.F., Nilsson, C., Englund, E. (2013). von Economo neurones are selectively targeted in frontotemporal dementia. Neuropathol. Appl. Neurobiol. *39(5*), 572–9.

Shepherd, A. M., Matheson, S. L., Laurens, K. R., Carr, V. J., and Green, M. J. (2012). Systematic meta-analysis of insula volume in schizophrenia. Biol. Psychiatry *72*, 775–784.

Yamada, T., Itahashi, T., Nakamura, M., Watanabe, H., Kuroda, M., Ohta, H., Kanai, C., Kato, N., Hashimoto, R.I (2016) Altered functional organization within the insular cortex in adult males with high-functioning autism spectrum disorder: evidence from connectivity-based parcellation. Mol. Autism *5*; 41.

Tang, L.R., Liu, C.H., Jing, B., Ma, X., Li, H.Y., Zhang, Y., Li, F., Wang, Y.P., Yang, Z., Wang, C.Y. (2014) Voxel-based morphometry study of the insular cortex in bipolar depression. Psychiatry Res. *224(2*), 89–95.

Bionotes

Gundela Meyer
Facultad de Medicina, Universidad de La Laguna
Tenerife
Spain
E-Mail: gundelam@aol.com

Prof. Dr. med. em. Gundela Meyer studied Medicine at the Universities of Göttingen and Valencia (Spain). She received her doctoral degree at the University of La Laguna (Spain). After completing the specialist training in Psychiatry she received the Professorship for Neuroanatomy at the University of La Laguna. The main focus of her research is the development of the cerebral cortex, in particular of the human.