Cerebral Cortex Advance Access published August 14, 2012

Cerebral Cortex
doi:10.1093/cercor/bhs249

To the Editor,

In their recent paper, Chang et al. (2012) explained some inconsistencies in the results for the number of insular cortex clusters. They reported three insular clusters, one anterior dorsal, one posterior dorsal, and one middle-anterior ventral. In a previous paper (Cauda et al. 2011) on the same subject, we parcellated the insula into two clusters, one anterior ventral and one posterior dorsal. We confirmed these results in a recent meta-analytic paper (Cauda, Costa et al. 2012).

To explain the divergences between the two studies, Chang et al. claimed that we "employed a very coarse resolution (only 10 insular region of interest (ROIs) compared with our 1252) and a priori fixed the number of clusters to 2." This is incorrect, as we actually performed two different analyses: an ROI-based analysis employing 10 ROIs and a voxelwise analysis employing a number of ROIs equal to the number of voxels in the brain. Furthermore, the optimal number of clusters was not fixed but was determined using an appropriate procedure [see Supplementary Materials of (Cauda et al. 2011)].

We would like to suggest a simple explanation for the discrepancies between the studies that parcellated the insular surface into 2 (Jakab et al. 2011; Cloutman et al. 2012) (Taylor et al. 2009; Cauda et al. 2011; Cauda, Costa et al. 2012) versus 3 (Deen et al. 2011; Chang et al. 2012) or more clusters (Kurth et al. 2010; Power et al. 2011; Yeo et al. 2011). As introduced by Chang et al., the hierarchical clustering performed on the ROI-wise analysis of our 2011 paper moderately supports a tripartite subdivision of the insula. Given a dataset, the determination of the optimal number of parcels is not a trivial task. Several methods for calculating the optimal number of clusters have been proposed; however, none is faultless (Bowman et al. 2004). Differences between the datasets in terms of data acquisition, technical and numerical aspects may lead to a different determination of the correct number of parcels. This point corroborates the results of those papers that employ methods that do not assume an a priori number of critical components, such as the one developed by Cohen et al. (2008) and used in Nelson et al. (2010). Here, the whole-brain connectivity map of each node is examined for large-scale differences between the nodes. The nodes obtained by resting state functional connectivity magnetic resonance imaging (MRI)are compared with task-evoked data in functional magnetic resonance imaging (fMRI) to corroborate the findings from the functional connectivity analyses. Using this method, the authors suggested a pentapartite subdivision of the anterior insular cortex (AI) where 3 clusters are present in the anteriormost AI and 2 in the posteriormost AI. Other papers suggested an insular clusterization involving more than the common bipartite or tripartite scheme (Cohen et al. 2008; Kurth et al. 2010; Power et al. 2011; Yeo et al. 2011; Kelly et al. 2012). It must be noted, however, that the histological and electrophysiological data on humans and monkeys support the bipartite (see, e.g. Rivier and Clarke 1997; Jezzini et al. 2012) as well as the tripartite insular parcellations (see, e.g. Mesulam and Mufson 1982).

A recent and inspiring paper by Kelly et al. (2012) clearly demonstrated this phenomenon; rather than choosing a fixed number of clusters, they reported a number of insular cortex clusters with K between 2 and 15 (cf. Fig. 4). With $K = 2$ the parcels are very similar to our clusters, with $K = 3$ then a middle-anterior ventral cluster appears. The coexistence of different parcellation schemes is understandable in the light of the intrinsically hierarchical nature of the resting state brain networks that have been evidenced in neuroimaging studies (Power et al. 2011; Yeo et al. 2011; Doucet et al. 2011), and hypothesized in the theories of Damasio (1994) and Craig (2002, 2009) that posited a hierarchical organization within the insula representing information about the body's homeostatic state. Indeed, in this view, different levels of complexity may be nested in a hierarchical structure that starts from a bipartite insular subdivision and move to more complex parcellation schemes where each of the two previous clusters is further subdivided. That hypothesis finds a partial support in several recent studies such as Nelson et al. (2010), Yeo et al. (2011), Cauda, Torta et al. (2012), Kelly et al. (2012), and Touroutoglou et al. (2012). However, Kelly et al. point out that not all numbers of parcels lead to a high cross-modal agreement and mean consensus. We have summarized these results in Table 1. The cross-modal agreement, the first criterion chosen by Kelly et al. to find the optimal number of clusters, indicates whether a certain parcellation scheme gained the agreement of all the three parcellation modalities employed (resting state fMRI, task-based fMRI, structural covariance); the second criterion is the mean consensus, which is a measure of "the stability with which pairs of voxels were placed in the same cluster, across the 20 data collection sites": it is evident in Table 1 that in this analysis the only two solutions that have a high cross-modal agreement and mean consensus for the right and left insulae are $K = 2$ and 9. Given the suggested hierarchical structure of the brain networks (Leech et al. 2012), it can be hypothesized that these two solutions may constitute two different parcellation steps in the same hierarchical structure. Nonetheless, the present knowledge of the insular parcellation may be further improved or modified using higher-resolution imaging data, improved signal-to-noise ratios (Gonzalez-Castillo et al. 2012), alternative imaging modalities, and refined techniques such as the analysis of temporal functional modes described by Smith et al. (2012), which takes into account temporally dynamic relationships among regions.

Table 1
Mean consensus and cross-modal agreement for different number of insular clusters (Kelly et al. 2012). The only two solutions that have a high cross-modal agreement and mean consensus for the right and left insulae are K = 2 and 9.

	Number of insular clusters	2	3	4	5	6	7	8	9	10	11	12
Right insula	Cross-modal agreement	x	x		x	x	x		x			
	Mean consensus	x							x			x
Left insula	Cross-modal agreement	x	x	x					x			
	Mean consensus	x		x					x		x	

An interesting future development would be the evaluation of the cross-modal agreement between all the different techniques used to parcellate the insular cortex, such as neurophysiology, histology, fMRI, diffusion tensor imaging, and anatomy.

Franco Cauda[1] and Alessandro Vercelli[2]
[1]Department of Psychology,
[2]Department of Anatomy, Pharmacology and Forensic Medicine, University of Turin, Torino, Italy
Address correspondence to Franco Cauda.
Email: franco.cauda@unito.it

References

Bowman FD, Patel R, Lu C. 2004. Methods for detecting functional classifications in neuroimaging data. Hum Brain Mapp. 23:109–119.

Cauda F, Costa T, Torta DM, Sacco K, D'Agata F, Duca S, Geminiani G, Fox PT, Vercelli A. 2012a. Meta-analytic clustering of the insular cortex: characterizing the meta-analytic connectivity of the insula when involved in active tasks. Neuroimage. 62:343–55.

Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. 2011. Functional connectivity of the insula in the resting brain. Neuroimage. 55:8–23.

Cauda F, Torta DM, Sacco K, D'Agata F, Geda E, Duca S, Geminiani G, Vercelli A. 2012b. Functional anatomy of cortical areas characterized by Von Economo neurons. Brain Struct Funct.

Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. 2012. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb Cortex. [Epub ahead of print] PubMed PMID: 22437053.

Cloutman LL, Binney RJ, Drakesmith M, Parker GJ, Lambon Ralph MA. 2012. The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography. Neuroimage. 59:3514–3521.

Cohen AL, Fair DA, Dosenbach NU, Miezin FM, Dierker D, Van Essen DC, Schlaggar BL, Petersen SE. 2008. Defining functional areas in individual human brains using resting functional connectivity MRI. Neuroimage. 41:45–57.

Craig AD. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 3:655–666.

Craig AD. 2009. How do you feel now? The anterior insula and human awareness. Nat Rev Neurosci. 10:59–70.

Damasio AR. 1994. Descartes' error: emotion, reason, and the human brain. New York: Putnam.

Deen B, Pitskel NB, Pelphrey KA. 2011. Three systems of insular functional connectivity identified with cluster analysis. Cereb Cortex. 21:1498–1506.

Doucet G, Naveau M, Petit L, Delcroix N, Zago L, Crivello F, Jobard G, Tzourio-Mazoyer N, Mazoyer B, Mellet E, et al. 2011. Brain activity at rest: a multiscale hierarchical functional organization. J Neurophysiol. 105:2753–2763.

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA. 2012. Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis. Proc Natl Acad Sci USA. 109:5487–5492.

Jakab A, Molnár PP, Bogner P, Béres M, Berényi EL. 2011. Connectivity-based parcellation reveals interhemispheric differences in the insula. Brain Topogr. 25:264–271.

Jezzini A, Caruana F, Stoianov I, Gallese V, Rizzolatti G. 2012. Functional organization of the insula and inner perisylvian regions. Proc Natl Acad Sci USA. 109:10077–10082.

Kelly C, Toro R, Di Martino A, Cox CL, Bellec P, Castellanos FX, Milham MP. 2012. A convergent functional architecture of the insula emerges across imaging modalities. Neuroimage. 61:1129–1142.

Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. 2010. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct. 214:519–534.

Leech R, Braga R, Sharp DJ. 2012. Echoes of the brain within the posterior cingulate cortex. J Neurosci. 32:215–222.

Mesulam MM, Mufson EJ. 1982. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol. 212:1–22.

Nelson SM, Dosenbach NU, Cohen AL, Wheeler ME, Schlaggar BL, Petersen SE. 2010. Role of the anterior insula in task-level control and focal attention. Brain Struct Funct. 214:669–680.

Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL,, et al. 2011. Functional network organization of the human brain. Neuron. 72:665–678.

Rivier F, Clarke S. 1997. Cytochrome oxidase, acetylcholinesterase, and NADPH-diaphorase staining in human supratemporal and insular cortex: evidence for multiple auditory areas. Neuroimage. 6:288–304.

Smith SM, Miller KL, Moeller S, Xu J, Auerbach EJ, Woolrich MW, Beckmann CF, Jenkinson M, Andersson J, Glasser MF, et al. 2012. Temporally-independent functional modes of spontaneous brain activity. Proc Natl Acad Sci USA. 109:3131–3136.

Taylor KS, Seminowicz DA, Davis KD. 2009. Two systems of resting state connectivity between the insula and cingulate cortex. Hum Brain Mapp. 30:2731–2745.

Touroutoglou A, Hollenbeck M, Dickerson BC, Feldman Barrett L. 2012. Dissociable large-scale networks anchored in the right anterior insula subserve affective experience and attention. Neuroimage. 60:1947–1958.

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR,, et al. 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 106: 1125–1165.