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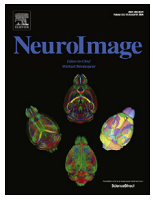

The pathoconnectivity network analysis of the insular cortex: A morphometric fingerprinting

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ABSTRACT

Brain disorders tend to impact on many different regions in a typical way: alterations do not spread randomly; rather, they seem to follow specific patterns of propagation that show a strong overlap between different pathologies. The insular cortex is one of the brain areas more involved in this phenomenon, as it seems to be altered by a wide range of brain diseases. On these grounds we thoroughly investigated the impact of brain disorders on the insular cortices analyzing the patterns of their structural co-alteration. We therefore investigated, applying a network analysis approach to meta-analytic data, 1) what pattern of gray matter alteration is associated with each of the insular cortex parcels; 2) whether or not this pattern correlates and overlaps with its functional meta-analytic connectivity; and, 3) the behavioral profile related to each insular co-alteration pattern. All the analyses were repeated considering two solutions: one with two clusters and another with three. Our study confirmed that the insular cortex is one of the most altered cerebral regions among the cortical areas, and exhibits a dense network of co-alteration including a prevalence of cortical rather than sub-cortical brain regions. Regions of the frontal lobe are the most involved, while occipital lobe is the less affected. Furthermore, the co-alteration and co-activation patterns greatly overlap each other. These findings provide significant evidence that alterations caused by brain disorders are likely to be distributed according to the logic of network architecture, in which brain hubs lie at the center of networks composed of co-altered areas. For the first time, we shed light on existing differences between insula sub-regions even in the pathoconnectivity domain.

1. Introduction

Connectomics is "a comprehensive structural description of the network of elements and connections forming the human brain" (Sporns et al., 2005). This approach has led to a picture of cerebral functioning in terms of networks and has emphasized the great need for an overarching mapping of the whole structure of connections that shapes the human brain (the so-called *connectome*).

Recent studies provide evidence that brain disorders cause rarely alterations on a single cerebral site; rather, they tend to impact on many different regions. Moreover, converging findings suggest that pathological alterations of neuronal assemblies do not occur randomly but follow specific patterns of propagation based on anatomical and functional pathways (Cauda et al., 2017, 2018b; Crossley et al., 2014; Fornito et al., 2015; Manuello et al., 2018b; McTeague et al., 2016; Menon, 2013).

A certain set of co-altered brain areas, which can subserve several cognitive processes, has been suggested to overlap in different diseases (Crossley et al., 2014). With regard to mental illness, for instance, it has been proposed that abnormalities in a certain set of brain areas might be frequently associated with a wide spectrum of psychiatric conditions (Crossley et al., 2016b; Goodkind et al., 2015). Another recent meta-analysis provides further evidence for overlapping patterns of brain alterations in certain neuropsychiatric disorders – i.e., autism spectrum disorder, schizophrenia, and obsessive spectrum disorder (Cauda et al., 2017, 2012b).

Abbreviations: ACC, anterior cingulate cortex; ALE, anatomical likelihood estimation; CEN, central executive network; DACC, dorsal anterior cingulate cortex; DMN, default mode network; FDR, false discovery rate; GM, gray matter; MNI, montreal neurological institute; VBM, voxel-based morphometry; VENs, Von Economo's neurons.

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These findings may be counterintuitive, as we are inclined to think that each brain disorder should exhibit a specific pattern of brain alterations, related to both its pathogenesis and development. Indeed, intriguing results from animal models indicate that degenerative pathologies principally impact on the network hubs that are more vulnerable to disruption by virtue of their extensive connections and activity (Crossley et al., 2014; Raj et al., 2012; Seeley et al., 2009). As a result, a small set of brain regions may be more likely to be frequently affected by a large number of brain disorders (F. Cauda et al., 2019; Ellison-Wright and Bullmore, 2010; Goodkind et al., 2015; Liloia et al., 2018; Menon, 2013; Saxena and Caroni, 2011).

The propagation of neuronal alterations within brain areas might form recognizable networks that depend on the structure of brain connectivity (Cauda et al., 2018b; Manuello et al., 2018b; Raj et al., 2012; Tatu et al., 2018; Yates, 2012; Zhou et al., 2012). This aspect is so important that it could generate a new perspective as to how clinicians are used to consider brain disorders (Buckholtz and Meyer-Lindenberg, 2012; Caspi et al., 2014; Cole et al., 2014). Finding out what kind of patterns are associated to the alteration of different brain sites is the first fundamental step in order to reach a comprehensive understanding of how brain disorders impact on the connectome.

The *co-alteration network analysis*, which can be considered as a fascinating new subfield of pathoconnectomics, can be defined as *the description of networks formed by co-altered brain areas*. This type of analysis can describe the undirected (non-causal) propagation patterns of alterations produced by brain disorders. If certain brain areas – typically those playing a functional central role (brain hubs) – are thought to be frequently affected in brain deterioration (Cole et al., 2014; Crossley et al., 2016a, 2014), then it can also be hypothesized that each hub may form typical connecting patterns with other altered cerebral areas.

In principle, the method we are proposing could be equally applied to the study of any brain region, whether a hub or not. However, several elements made us identify the insular cortex as a particularly suitable candidate. Among the brain hubs, the insula has vast and extensive connections to many regions of the cortex and limbic system (Cauda et al., 2011, 2013; Cauda and Vercelli, 2013; Chang et al., 2013; Kelly et al., 2012; Stephani et al., 2011; Uddin, 2015; Vercelli et al., 2016). The insular cortex has been associated with a variety of important functions, ranging from pain perception and speech production to social emotions (Cauda et al., 2012b), including the conscious monitoring of the body's condition via the integration of different unconscious stimuli (both external and internal) with emotional processes, as well as the conscious detection of error (Cauda et al., 2012a, 2011; Klein et al., 2013; Nieuwenhuys, 2012; Vercelli et al., 2016; Wylie and Tregellas, 2010). The integration of external sensory stimuli with inputs coming from the limbic system has led to suggest that the insula may play a fundamental role in the generation and maintenance of a state of awareness related to the body's condition (Cauda et al., 2011; Manuello et al., 2018a). These relevant roles put the insula at the interface between the inner and the external worlds, thus making it a pivotal center within the brain functional architecture (Ahmed et al., 2016; Douaud et al., 2014; Fjell et al., 2015; Jagust, 2013; Jones et al., 2016; Klein et al., 2013; Voytek and Knight, 2015).

It has been shown by several researches that the insula is among the most anatomically and functionally altered regions of the brain across psychiatric and neurological disorders (Crossley et al., 2014, 2015; Goodkind et al., 2015; McTeague et al., 2016, 2017; Namkung et al., 2017; Sprooten et al., 2017). Critically, previous work from our group has highlighted that the insula is not only one of the areas that are more affected across the literature, but also one of those involved by the majority of brain disorders (F. Cauda et al., 2019; Liloia et al., 2018). This suggests that the insular cortex may have as yet an unknown role in the development of alterations caused by brain disorders. Moreover, this heterogeneity with respect of disease affection, made the insula the perfect focus for a transdiagnostic approach, allowing in principle to account for different pathological processes behind the development of the co-alteration network. As a further element, and coherently with all this, as pointed out by Behrens et al., 2013, the insula is among the most often investigated brain regions. Based on this, and considering the equal suitability of any brain region to our approach, we therefore decided to direct our attention to a structure of potential interest for a wide part of neuroscience researchers. Finally, given the importance of the insula as a brain hub, we thought it to be ideal in order to also test the hypothesis that, when a crucial brain hub is affected by pathology, the associated co-alteration network may largely reflect its functional connectivity.

It is well known that the insular cortex exhibits a marked heterogeneity both in functional and cytoarchitectonical aspects (Cauda et al., 2012a, 2011). For this reason, this brain area can be better described adopting some kind of parcellation. However, no consensus has been reached on the number of parcels to be used (Cauda and Vercelli, 2013), nor on the modalities better capturing differences between sub-regions. We decided to follow the solution proposed by Kelly et al. (2012), based on multi-modal convergence criterion and non-hierarchical clustering. Among the various dimensionality options (i.e., from 2 to 15 clusters), we selected those showing the best cross-model agreement for both the hemispheres (i.e., 2, 3 and 9 clusters), as highlighted by Cauda and Vercelli (2013). Since a number of clusters over 3 was not sufficient to guarantee reliable amount of data for statistical results (for an explanation of this aspect see (Cauda et al., 2018a), we focused on the bipartite (labeled as K2 throughout the text) and tripartite (labeled as K3 throughout the text) solutions (Fig. S2). The bipartite option follows the anterior-posterior distinction (Cauda et al., 2011; Cauda and Vercelli, 2013; Tian and Zalesky, 2018). Following the behavioral domain analysis described in the original work by Kelly et al. (2012), the anterior parcel is associated with language and memory functions, while the posterior one is associated with action execution, somesthesis and sexuality. The tripartite option consists, coherently between hemispheres, of an anterior dorsal parcel, a middle parcel covering both ventral and dorsal insula, and a dorsal posterior parcel. According to literature, the dorsal portion of the anterior insula is mainly involved in salience evaluation (Menon and Uddin, 2010; Xue et al., 2018), while the dorsal posterior region is classically described as the seat of interoceptive representation (Craig, 2003). The ventral insula is described as associated with emotion and empathy processing, especially in its anterior part, while the central insula is mainly involved in interoception and somatosensation (Kurth et al., 2010). The related regions of interest (ROIs) where available on http://fcon_1000.projects.nitrc.org.

The aim of this study was to investigate: 1) what pattern of neuronal alterations' distribution is associated with different portions of the insula; 2) whether or not the insula meta-analytic co-activation patterns can provide meaningful elements to interpret the co-alteration patterns; and 3) the behavioral profile associated with the areas of the insular co-alteration patterns. To do so, we used the voxel-based morphometry (VBM) data of the BrainMap database.

Studies of brain morphometry with the help of the VBM technique have been performed by many researchers as structural magnetic resonance imaging-based measures of decreased values are considered as valid markers of atrophy which can describe disease state and development (Frisoni et al., 2010). Furthermore, the VBM approach is such that it is not biased to one specific brain structure but gives a comprehensive evaluation of anatomical differences throughout the brain (Ashburner and Friston, 2001). A number of studies show that gray matter abnormalities are associated with many psychiatric diseases. For instance, cortical thickness has been found to be variously reduced in patients with major depressive disorder and bipolar disorder (Niu et al., 2017), schizophrenia (Kuperberg et al., 2003; van Haren et al., 2011), borderline personality disorder (Soloff et al., 2008), autism spectrum disorder (Pereira et al., 2018), obsessive-compulsive spectrum disorder (van den Heuvel et al., 2008), and neurodegenerative diseases such as Alzheimer's (Manuello et al., 2018; Matsuda, 2013), frontotemporal dementia (Muñoz-Ruiz et al., 2012), Parkinson's disease (Lee et al., 2018),

dementia with Lewy bodies (Burton et al., 2002), Huntington's disease (Mühlau et al., 2009). As VBM can be applied regardless of the type of neuropathological condition in a transdiagnostic approach (Cauda et al., 2019; McTeague et al., 2016), we decided to use the data obtained from all brain disorders that were present in the BrainMap VBM database, with the aim to achieve the most overarching analysis of how pathological processes affect the insular cortex.

2. Materials and methods

2.1. Selection of studies

We conducted an extensive meta-analytic search using the software *Sleuth* to query the VBM database of BrainMap (Fox et al., 2005; Fox and Lancaster, 2002; Laird et al., 2005b). BrainMap is one of the largest international repositories of neuroimaging data (Vanasse et al., 2018). It comprises a database of thousands of brain imaging studies (functional and structural MRI data), from which data on regional effects can be retrieved (in our case, regions of altered gray matter density, volume or concentration). Data are reported in MNI/Talairach coordinates and are ideal to conduct meta-analyses from a large subject pool, by making meta-analytic morphologic queries. At the moment of the search (February 2018), the BrainMap VBM database contained 994 articles, for a total of 3151 experiments, 75,727 subjects, and 21,827 locations.

In order to assess the impact of brain disorders on the insular cortex, we performed a first search capable of retrieving all the VBM studies that matched the following query:

Search 1:

[Experiments Contrast is Gray Matter] AND [Experiment Context is Disease Effects] AND [Observed Changes is Controls>Patients] AND [Locations TD Label is Gyrus Insula].

(see Section 1 of Supplementary methods for details of the literature search process). We decided to focus on decreased values only. From a theoretical point of view, there is general agreement in the neuroscientific literature that decreased values can be seen as density reduction or atrophy of GM.

Additionally, we performed a second search using the following criteria:

Search 2:

[Experiments Contrast is Gray Matter] AND [Experiment Context is Disease Effects] AND [Observed Changes is Controls>Patients] AND [Locations MNI image is *] where the MNI images represent each of the parcels selected from the work of Kelly et al. (2012). The two searches were designed to retrieve foci of alteration from both the hemispheres, although every extracted experiment could report an effect either in both hemispheres or in only one of the two. Search 2 was repeated twice to retrieve the data related to the $K = 2$ segmentation (i.e. K2_ant and K2_post) and 3 times for what concerns the $K = 3$ segmentation (i.e. K3_ant, K3_mid, K3_post) (See Section 3 in the Supplementary methods for details of the alteration density analysis).

2.2. Anatomical likelihood estimation on co-alteration and co-activation data

The VBM data retrieved were statistically elaborated with the method of the anatomical likelihood estimation (ALE) (Eickhoff et al., 2012, 2009; Turkeltaub et al., 2012), so as to obtain modeled anatomical effect maps representing the overall distribution of gray matter co-alterations with the insula. ALE is a quantitative method that can be used for estimating consistent morphological alterations across several neuroimaging studies (Laird et al., 2005a, 2009; Turkeltaub et al., 2002) (See Section 4 of the Supplementary methods and Fig.S3 for the estimation of possible selection bias).

ALE maps showed the brain areas in which multiple studies reported statistically significant alteration peaks (i.e., foci of interest) Since we analyzed locations with morphologic alterations, ALE maps revealed the brain regions that were likely to be altered together (Cauda et al., 2018a; Manuello et al., 2018b; Tatu et al., 2018).The ALE map derived from the analysis of the whole insula (obtained through Search 1) was thresholded at a voxel-level (FWE $p < 0.05$) (Eickhoff et al., 2017, 2016), while the maps related to Search 2 were thresholded at a cluster-level (FWE $p < 0.01$).

In order to provide a further element to improve the interpretation of the co-alteration networks, we finally performed an ALE analysis on data derived from the BrainMap functional repository in order to construct the meta-analytic co-activation pattern of each of the five bilateral parcels of the insula (Robinson et al., 2010). A third search was performed based on the following criteria:

Search 3:

[Experiments Context is Normal Mapping] AND [Experiment Activation is Activations Only] AND [Locations MNI image is *] where the MNI images represent each of the bilateral parcels selected from the work of Kelly et al. (2012), as it was in Search 2. Search 3 was thus repeated 5 times.

According to ALE literature, brain areas exhibiting common activation patterns are considered to be connected.

2.3. Comparison between co-alteration and co-activation patterns

In order to inspect the similarities and divergences between the couples of co-alteration and co-activation patterns originating from a same bilateral parcel (i.e. results of Search 2 and Search 3), the following analyses were performed. First, we ran Pearson's correlation between each couple of maps. Second, we computed the extension of the co-alteration map being in overlap with the corresponding co-activation map. In this second analysis the insula was excluded from the maps.

2.4. Analysis of behavioral profile

To associate specific psychological functions with the areas forming the co-alteration patterns related to the five bilateral parcels, we performed on the VBM ALE maps only (data from Search 2) an analysis of behavioral profile using the behavioral analysis plug-in for the software Mango (Lancaster et al., 2012). This tool is based on the BrainMap functional database and provides a quantitative association between a user defined ROI (i.e., each of the ALE maps) and 51 behavioral subdomains, organized in 5 classes: action, cognition, emotion, interoception, and perception. In accordance with Lancaster et al. (2012), only sub-domains with a z-score ≥ 3 were maintained. An average value was obtained for each of the 5 classes, by computing the mean of the related sub-domains with above threshold z-score.

2.5. Construction of the morphometric co-alteration networks

In order to describe in detail the statistical relationship between the insula and the co-altered regions, we constructed the anatomical co-alteration networks of the bilateral insulae, applying a methodology recently developed by our group to the data obtained through Search 1. This kind of analysis can determine whether or not the alteration of the insula is statistically related to the alteration of other brain areas. In the output produced, nodes represent altered regions, whereas edges link couples of nodes which are more likely to be altered together rather than one independently from the other. This particular dependency was computed using the Patels' κ index (Patel et al., 2006) (for a

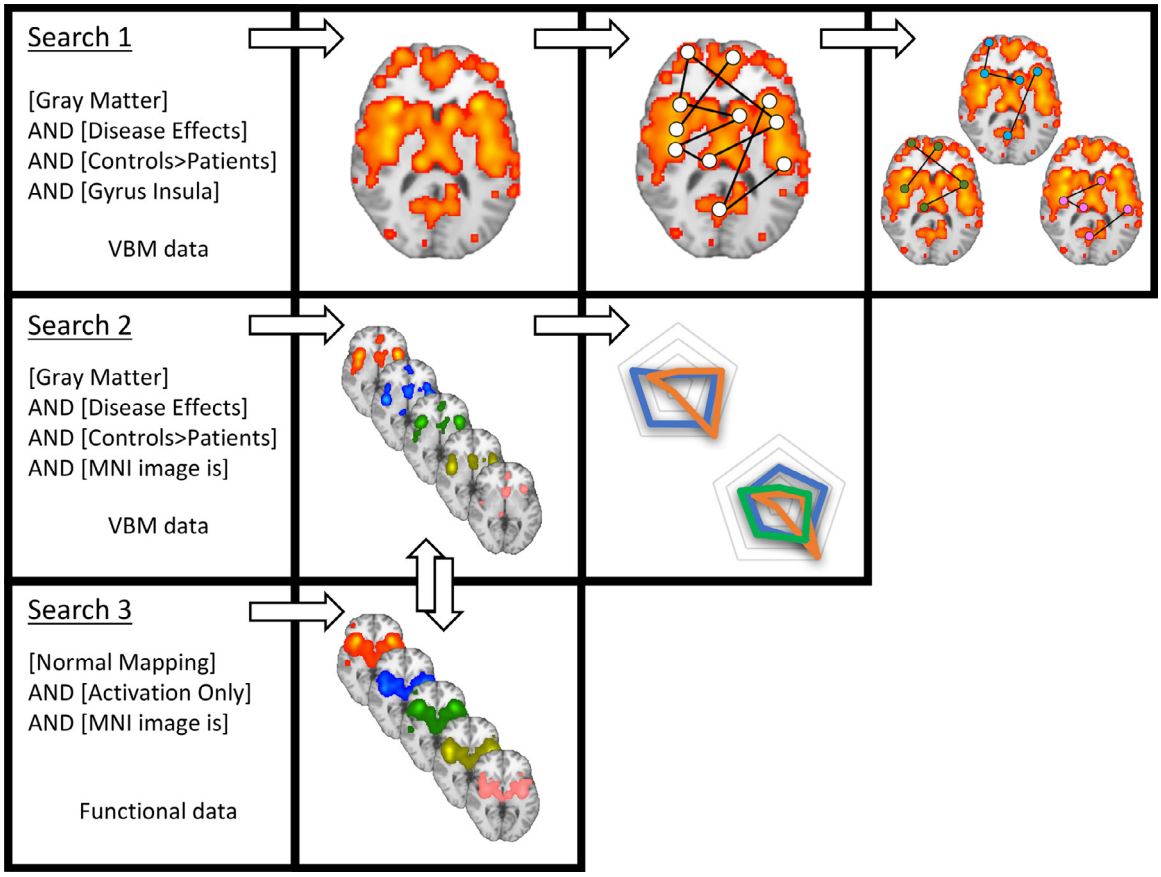

Fig. 1. A graphic summary of the analyses performed. Top row: from Search 1 on VBM data, the co-alteration pattern was obtained. Based on this, we generated the whole brain co-alteration network, that was then broken up into one unilateral sub-network for each unilateral insula parcel (networks shown in this figure were built for visualization purpose only). Middle row: from Search 2 on VBM data we obtained five bilateral co-alteration patterns, one for each insula sub-parcel. On each co-alteration pattern the behavioral analysis was performed. Bottom row: from Search 3 on functional data we obtained five bilateral co-activation patterns, one for each insula sub-parcel. The corresponding co-alteration and co-activation patterns where then compared.

more detailed description of this approach, see Cauda et al. (2018a) and Manuello et al. (2018b)). From this complete whole brain network we extracted one sub-network for each of the selected Kelly's unilateral parcels (a total of 4 sub-networks for the K2 solution, and 6 sub-networks for the K3 solution). This was achieved with a three-steps procedure. First, the nodes anatomically located inside the given parcel of interest were identified and considered as roots. Second, only the first neighbors of the root nodes (i.e., nodes directly linked with at least one node located in the parcel) were preserved. Third, all the edges between non-roots nodes were eliminated (See Fig. 1 for a graphic summary of this procedure, as well as of the other analyses performed). For each of the obtained sub-networks, we calculated the total number of nodes and edges. In order to describe the spatial pattern of co-alteration of each parcel at macro-level, we distinguished the location of the non-root nodes in 7 groups: frontal lobe, parietal lobe, temporal lobe, occipital lobe, midbrain, subcortical areas and insula. Of note, non-root nodes located in the insulae were counted separately from the other lobes, in order to highlight the co-alteration between them. The repartition of the nodes was based on the Talairach Client tool (Lancaster et al., 2000) and refined by two expert researchers. To estimate the strength of co-alteration of each insula parcel with every lobe, for every sub-network the values of the edges connecting the root nodes with the nodes in a same lobe were summed, and then divided for the summed values of all the edges of the sub-network. Values were then expressed as percentages. We interpreted this measure as the strength of the co-alteration of each insula parcel with each lobe.

2.6. Data and code availability

Both VBM and functional meta-analytic data are freely available as part of the BrainMap database.

Kelly's insula ROIs can be freely downloaded from http://fcon_1000.projects.nitrc.org.

No specific tools where developed to perform the analyses described.

3. Results

3.1. Results from the queries

Our first search retrieved a total of 207 papers, 277 experiments, 4213 foci, for a total of 14,916 subjects (7218 pathological subjects) (see also Figure S1 and Table S1). This means that the 8.8% of VBM experiments included in the BrainMap database report a decrease effect in the insula. Only five brain regions obtained a slightly higher value (see Section 2 in the Supplementary methods and Tab S4 for a comparison with the rest of the brain). Experiments were distributed across 23 disorders, the most represented being schizophrenia (with 48 experiments). 51 experiments were classified as "Other" since they investigated more than one brain disorder, or because less than 3 experiments retrieved in the data set investigated that same neuropathology (see Tab. S2 for the complete breakdown, and Section 5 of the Supplementary methods for the analysis of potential representation bias across disorders). Based on

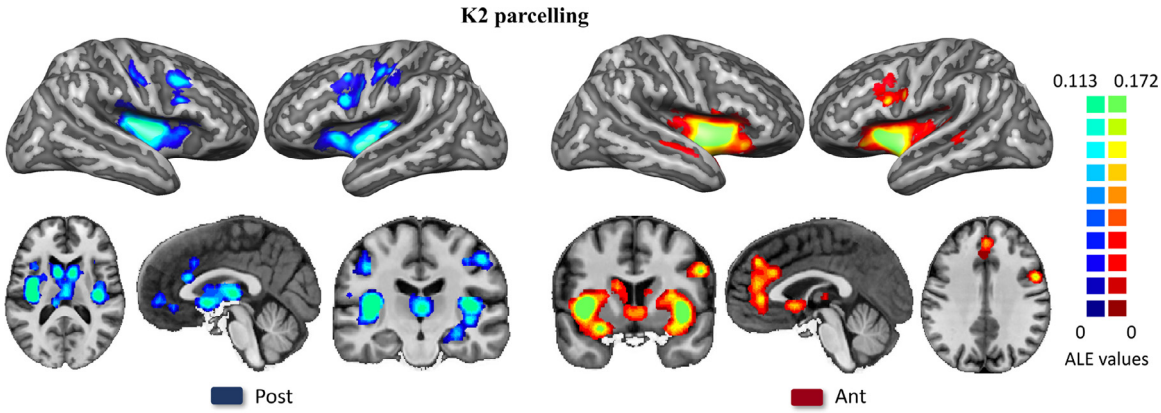

Fig. 2. The co-alteration patterns of the anterior (red) and posterior (blue) bilateral parcels of the K2 solution. The color scale represents ALE values.

the spatial distribution of the foci, the alteration density of the insula was found to be almost three times greater than the rest of the brain.

3.2. The insula co-alteration pattern

3.2.1. K2 solution

3.2.1.1. Anterior bilateral cluster. The related search retrieved 122 experiments and 2080 foci. Along with the insula, alterations affect preferentially the superior and inferior frontal gyri, anterior cingulate gyrus, superior temporal gyrus, caudate, thalamus, and claustrum (Fig. 2).

3.3. Posterior bilateral cluster

The related search retrieved 80 experiments and 1330 foci. Along with the insula, alterations affect mainly the precentral and postcentral gyri, inferior frontal gyrus, anterior cingulate gyrus, left hippocampus, caudate, and thalamus (Fig. 2).

3.3.1. K3 solution

3.3.1.2. Anterior bilateral cluster. The related search retrieved 76 experiments and 1433 foci. Along with the insula, alterations are mainly located in the medial frontal gyrus, middle frontal gyrus, anterior cingulate gyrus, right precuneus, left hippocampus, claustrum, amygdala, thalamus, and caudate (Fig. 3).

3.3.1.3. Middle bilateral cluster. The related search retrieved 87 experiments and 1317 foci. Along with the insula, alteration are mainly located in the left middle and inferior frontal gyri, right hippocampus, right claustrum, left amygdala, thalamus, and caudate (Fig. 3).

3.3.1.4. Posterior bilateral cluster. The related search retrieved 40 experiments and 664 foci. Along with the insula, alterations are mainly located in the left inferior frontal gyrus, right middle frontal gyrus, left anterior cingulate cortex, thalamus, and caudate (Fig. 3).

3.4. Comparison between co-alteration and co-activation patterns of the insula

3.4.1. K2 solution

The degree of correlation between the co-alteration and the co-activation patterns of the anterior bilateral parcel of the insula was $r = 0.56$. The 54% of the co-alteration map was in overlap with the corresponding co-activation map. In the posterior bilateral cluster, the correlation between the 2 conditions was $r = 0.61$, and the 57% of the co-alteration map was in overlap with the corresponding co-activation map (Fig. 4 and Fig. S4) (See Tab.S3 for details of the fMRI paradigms included in the functional data behind the co-activation patterns).

3.4.2. K3 solution

The degree of correlation between the co-alteration and the co-activation patterns of the anterior bilateral parcel of the insula was $r = 0.53$. The 52% of the co-alteration map was in overlap with the corresponding co-activation map. In the middle bilateral cluster, the correlation between the 2 conditions was $r = 0.62$, and the 60% of the co-alteration map was in overlap with the corresponding co-activation map. Finally, the degree of correlation between the co-alteration and the co-activation patterns of the posterior bilateral parcel of the insula was $r = 0.56$. The 60% of the co-alteration map was in overlap with the corresponding co-activation map. (Fig. 4 and Fig. S4) (See Tab.S3 for details of the fMRI paradigms included in the functional data behind the co-activation patterns).

3.5. Analysis of behavioral profile

3.5.1. K2 solution

The behavioral profile of the co-alteration pattern related to the anterior parcel had peak score for "Emotion ($z = 7.1$), "Interoception" ($z = 7$) and "Perception" ($z = 7$). In turn, the co-alteration pattern related to the posterior parcel had peak score for "Emotion" ($z = 8$) (Fig. 5).

3.5.2. K3 solution

The behavioral profile of the co-alteration pattern related to the anterior parcel had peak score for "Cognition" ($z = 6.5$) and "Emotion" ($z = 6.4$). Scores of the co-alteration pattern related to the middle parcel had the highest peak for "Emotion" ($z = 6.2$). Lastly, the behavioral decoding of the co-alteration pattern related to the posterior parcel had the peak score for "Emotion" ($z = 7.7$) (Fig. 5).

3.6. The insula co-alteration network

The complete bilateral network counts 14 nodes in the right insula and 6 in the left insula. Of note, none of the nodes is localized in the middle parcel of left insula when using the tripartite subdivision (i.e. K3 solution). Therefore, it was not possible to create the co-alteration network for the middle parcel of the left insula (K3_mid_L). Coherently, the co-alteration networks for the anterior and posterior parcel of the left insula in the bipartite subdivision (K2_ant_L and K2_post_L) are identical to the co-alteration networks for the anterior and posterior parcel of the left insula in the tripartite subdivision (K3_ant_L and K3_post_L) respectively. When moving from the bipartite partition to the tripartite one, all but one of the nodes becoming part of the right middle partition where previously in the posterior one (for the Talairach coordinates of the nodes as well as their membership to Kelly's parcels, please see Table 1).

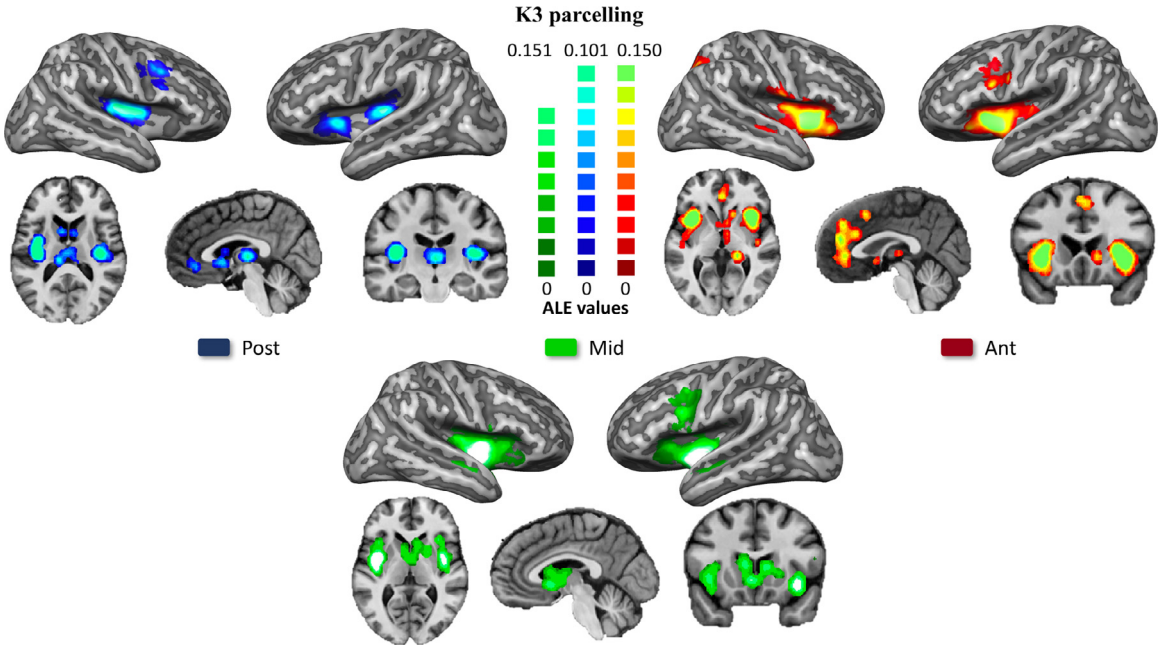

Fig. 3. The co-alteration patterns of the anterior (red), mid (green), and posterior (blue) bilateral parcels of the K3 solution. The color scale represents ALE values.

Table 1
Talairach coordinates of the nodes and their membership to Kelly's parcels for both K2 and K3 solutions.

Node (Name)	TAL coordinates x	Y	z	Kelly's parcels $K = 2$	$K = 3$
Insula_R	28	12	−20	K2_ant_R	K3_mid_R
Insula_R_1	40	2	−14	K2_ant_R	K3_mid_R
Insula_R_2	42	−6	−10	K2_ant_R	K3_mid_R
Insula_R_3	40	0	−10	K2_ant_R	K3_mid_R
Insula_R_4	48	14	−6	K2_ant_R	K3_ant_R
Insula_R_5	44	4	−4	K2_ant_R	K3_mid_R
Insula_R_6	44	14	−4	K2_ant_R	K3_ant_R
Insula_R_7	38	22	−2	K2_ant_R	K3_ant_R
Insula_R_8	38	12	2	K2_ant_R	K3_ant_R
Insula_R_9	40	14	2	K2_ant_R	K3_ant_R
Insula_R_10	42	14	2	K2_ant_R	K3_ant_R
Insula_R_11	44	−8	4	K2_post_R	K3_post_R
Insula_R_12	34	−24	10	K2_post_R	K3_post_R
Insula_R_13	42	−24	−2	K2_post_R	K3_mid_R
Insula_L	−36	16	−12	K2_ant_L	K3_ant_L
Insula_L_1	−34	16	−12	K2_ant_L	K3_ant_L
Insula_L_2	−46	−14	−10	K2_post_L	K3_post_L
Insula_L_3	−42	−14	−10	K2_post_L	K3_post_L
Insula_L_4	−32	−12	−10	K2_post_L	K3_post_L
Insula_L_5	−50	4	−4	K2_post_L	K3_post_L

Table 2
Details of the number of nodes and edges composing the co-alteration network of each insula parcel.

	Sub-network	n of root nodes	n of nodes	n of edges
K2 solution	left anterior	2	268	449
	left posterior	4	259	871
	right anterior	11	312	2084
	right posterior	3	218	437
K3 solution	right anterior	6	235	1041
	right middle	6	312	1184
	right posterior	2	177	296

Details of the number of nodes and edges in each sub-network are provided in Table 2, while the distribution of the nodes across lobes is described in Figs. 6 and 7.

4. Discussion

4.1. The insula co-alteration pattern

Our analysis confirms what previously evidenced in Cauda et al. (2020; 2019; 2014): the insular cortex is frequently and differently altered by a wide variety of brain disorders (Alcauter et al., 2015; Fathy et al., 2019; Igata et al., 2017; Seok and Cheong, 2020; Torres et al., 2016; Wang et al., 2019). Interestingly, the insula, together with some subcortical nuclei, appears to be one of the most altered areas of the brain (Cauda et al., 2019), as confirmed by the high fraction of BrainMap experiments reporting at least one focus of alteration in this brain region. Coherently, we found the insula to exhibit a density of alteration that is approximately three times the alteration of the whole brain. Moreover, the range of diseases that produce alterations in the insular cortex is highly diversified, including neurological and psychiatric conditions.

Each of the obtained co-alterations patterns of the insula comprises cortical and subcortical areas. In particular, frontal areas (especially the inferior frontal gyrus) and subcortical regions (such as the thalamus and the caudate) are present in co-alteration patterns based on either bipartite or tripartite parceling. On the contrary, the amygdala and parietal sites show to be co-altered with the insula only in patterns based on the tripartite parceling, which might indicate more specificity compared with the bipartite parceling.

Overall, the results reflect the extensive anatomical connections of the insula with many brain sites (Cauda et al., 2012a, 2011; Dosenbach et al., 2007; Mesulam and Mufson, 1982; Taylor et al., 2009; van den Heuvel et al., 2009). Parts of these pathways are long-range projections, as the insula has been found to be rich of Von Economo's neurons (VENs), large spindle-shaped cells that appear to be involved in processes capable of monitoring the state of the body, such as interoception and proprioception (Allman et al., 2005; Cauda et al., 2014, 2013; Medford and Critchley, 2010; Seeley et al., 2007). In particular, the anterior cingulate cortex (ACC) appears to be frequently co-altered with the insula. It is well known that these two areas are central parts of the salience network (SN), a disruption of which could account for

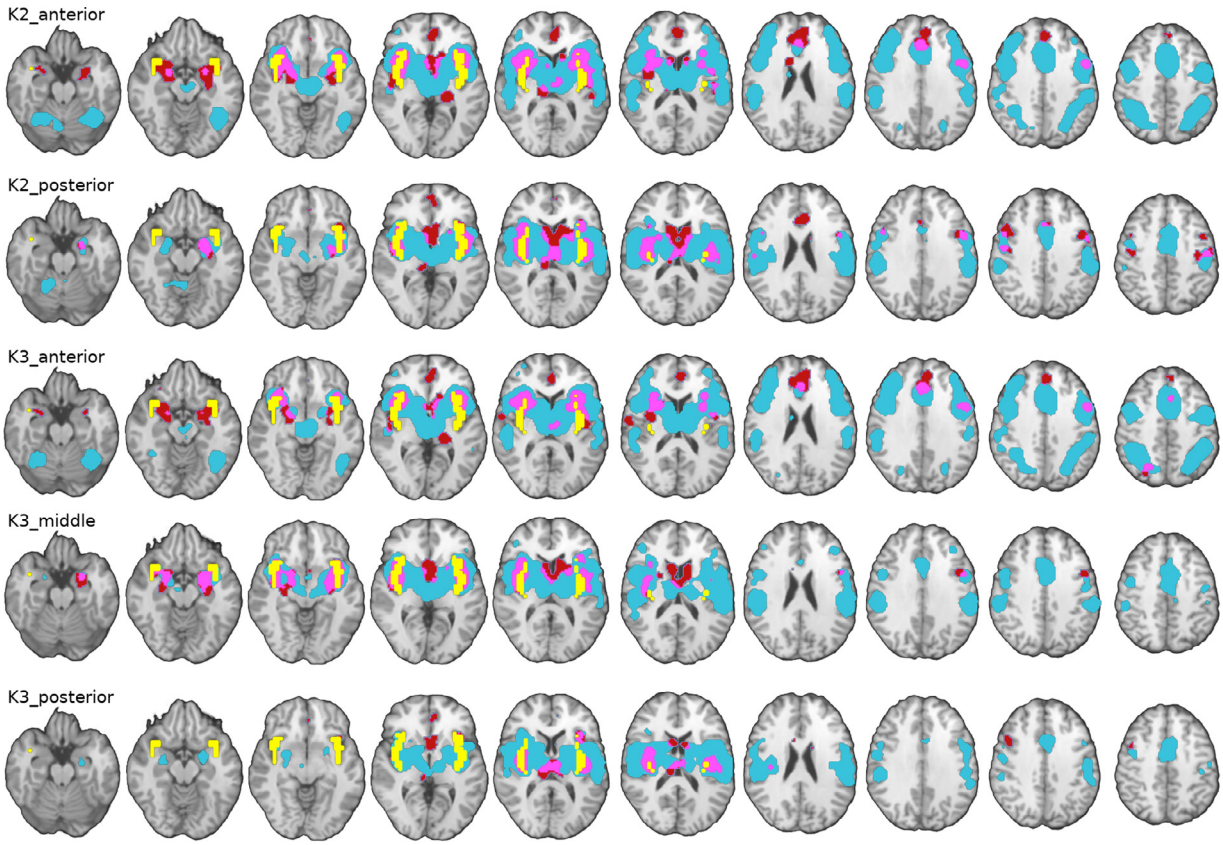

Fig. 4. Comparison between the co-alteration (red) and co-activation (light blue) patterns for each bilateral parcel (both K2 and K3 solutions). The overlap between the two condition is in magenta, while the insula is in yellow.

the symptoms of impairment of salience detection and self-monitoring that can be found transdiagnostically in a variety of neurological and psychiatric syndromes.

4.2. Analysis of edges distribution

It is interesting to observe that the edges connect the insula with regions tending to be not below the z coordinate of the insula node itself, with no co-alteration with the cerebellum and only few with the midbrain and subcortical regions. This observation suggests that the insula is co-altered by pathology only together with higher-order structures, especially with cortical areas. As the insula is associated with functions that integrate lower- and higher-order cognitive areas, evaluating sensory and limbic stimuli, monitoring the body and the environment to carry out error detection processes (Ahmed et al., 2016; Cauda et al., 2012a, 2011, 2012b; Douaud et al., 2014; Fjell et al., 2015; Jagust, 2013; Jones et al., 2016; Klein et al., 2013; Manuello et al., 2016; Nieuwenhuys, 2012; Vercelli et al., 2016; Voytek and Knight, 2015; Wylie and Tregellas, 2010), it should appear surprising that it is not greatly co-altered with limbic and subcortical regions. As the co-activation map shows that the insula can be functionally connected with many extracortical structures, for instance, the cerebellum (Figs. 4 and S4), the co-alteration patterns of each insular parcel seem to suggest that the insula has a bottom-up pathoconnectivity profile, in which it appears to be co-altered mostly with those cortical areas with which it is functionally connected so as to exert a bottom-up influence (e.g. error or salience detection), rather than with those lower-order regions whose information is thought to be subjected by an insular integration.

Each cluster is widely connected with all the cortices, but their co-alteration edges are not equally distributed between the lobes (Figs. 6 and 7). The most strongly co-altered lobe with each insular cluster is the frontal one, confirming that the insula tends to be altered together with higher-order and philogenetically recent areas. This might also be due to the anatomical proximity between the frontal cortices and the insula. In turn, the occipital lobe, which is far away from the insula and has chiefly a sensory nature, is one of the less co-altered areas with the insula.

The lobar distribution of the edges is also different between clusters. For instance, the left posterior cluster is the one which is the most co-altered with the frontal lobe. Also in the right insula, the posterior cluster for the bipartite solution (K2_R_post) is slightly more strongly co-altered than the anterior (K2_R_ant), and the posterior cluster for the tripartite solution (K3_R_ant), even if it has overall less edges than other cluster, exhibits a 40% of the strength of its co-alteration directed to the frontal cortices. Surprisingly, posterior clusters are less associated to the occipital lobe than the anterior ones. These findings are unexpected, as Kelly and colleagues (2012) have found that the posterior clusters are preeminently associated with motor and perceptual functions, while the anterior ones are more related to cognition. It should be observed, however, that all the insular clusters have been associated to some extent with cognition, both in our analysis and in that by Kelly and colleagues (2012). Still, our results point out that the co-alteration network of the posterior insula might be more associated with cortices characterized by higher-order functions.

Another interesting observation is that the right insula presents much more nodes and edges of co-alterations than the left one. This suggests that the right insula may be more susceptible than the left one to pathology. Finally, the distributions of the strength of co-alteration of each cluster for every lobe are clearly heavy-tailed (Figs. 6 and 7), with few edges characterized by high κ values and many weak edges with low κ values.

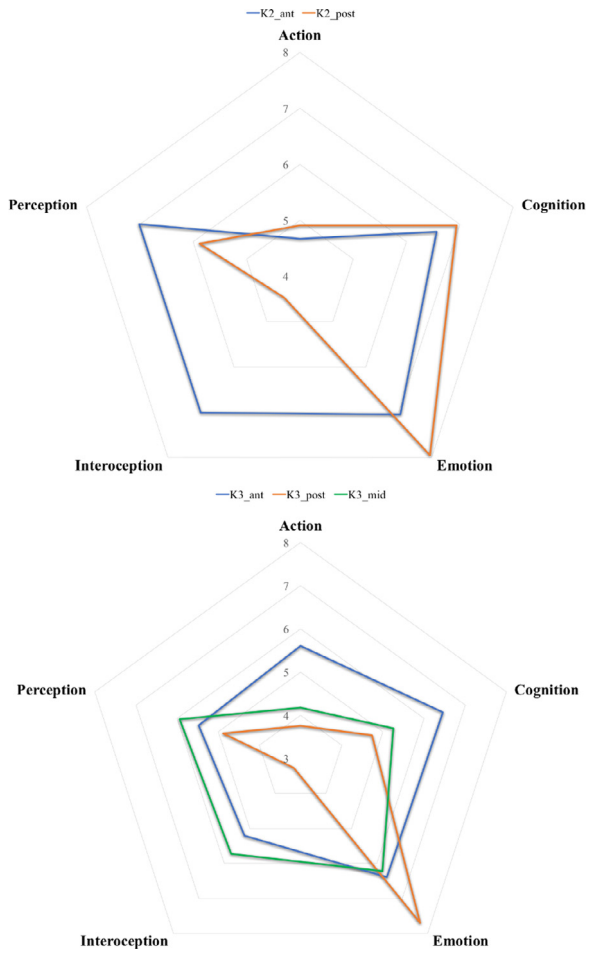

Fig. 5. Results of the behavioral analysis computed on the co-alteration bilateral patterns for both the K2 (top), and the K3 (bottom) solutions. Blue = anterior; orange = posterior; green = middle.

4.3. Relationship between co-alteration and co-activation with the insula

With the exception of the subcortical structures (such as the cerebellum) that are co-activated but not co-altered with the insula, overall the insula co-alteration patterns correlate well with the corresponding co-activation ones, with the former widely being in overlap with the latter. This finding provides evidence that the brain areas that are altered along with the insula are not randomly affected; rather, they tend to be altered in terms of their functional connectivity. This is also a significant result that confirms the strict relationship between anatomical and functional connectivity profiles (Abdelnour et al., 2014) and accords well with the line of research suggesting that brain connectivity might play a role in the development and distribution of neuronal alterations (Cauda et al., 2018b; Iturria-Medina and Evans, 2015; Raj et al., 2012; Zhou et al., 2012). In particular, distinct structural and functional connectivity patterns have been associated with the spatial distribution of brain disorders, for instance in amyotrophic lateral sclerosis, Alzheimer's disease and the behavioral variant of frontotemporal dementia (Buckner et al., 2009; Du et al., 2007; Ravits, 2014; Zhou et al., 2010). A relationship between dementia and intrinsic connectivity network has been strongly put forward (Seeley et al., 2009), and functional abnormal patterns related to deficits of semantic memory have been found in the default mode network (DMN) of patients with mild cognitive impairment (Gardini et al., 2015).

All these findings support the conjecture that large functional networks involved in synchronous neural activity may be selectively more vulnerable and, thereby, may enhance the development of alterations more quickly than region-specific functional systems. In addition, abnormalities in functional connectivity hubs and pathways might couple to neurophysiological, metabolic, and genetic aspects of brain cell biology to increase the impact and the distribution of the alteration process (Iturria-Medina and Evans, 2015; Saxena and Caroni, 2011). Both anatomical and functional connectivity seem therefore to be correlated not only in the normal and healthy brain (Cauda et al., 2011; Honey et al., 2009) but also in the brain that is pathologically affected (Crossley et al., 2016b; Gardini et al., 2015; Iturria-Medina and Evans, 2015; Iturria-Medina et al., 2014; Seeley et al., 2009).

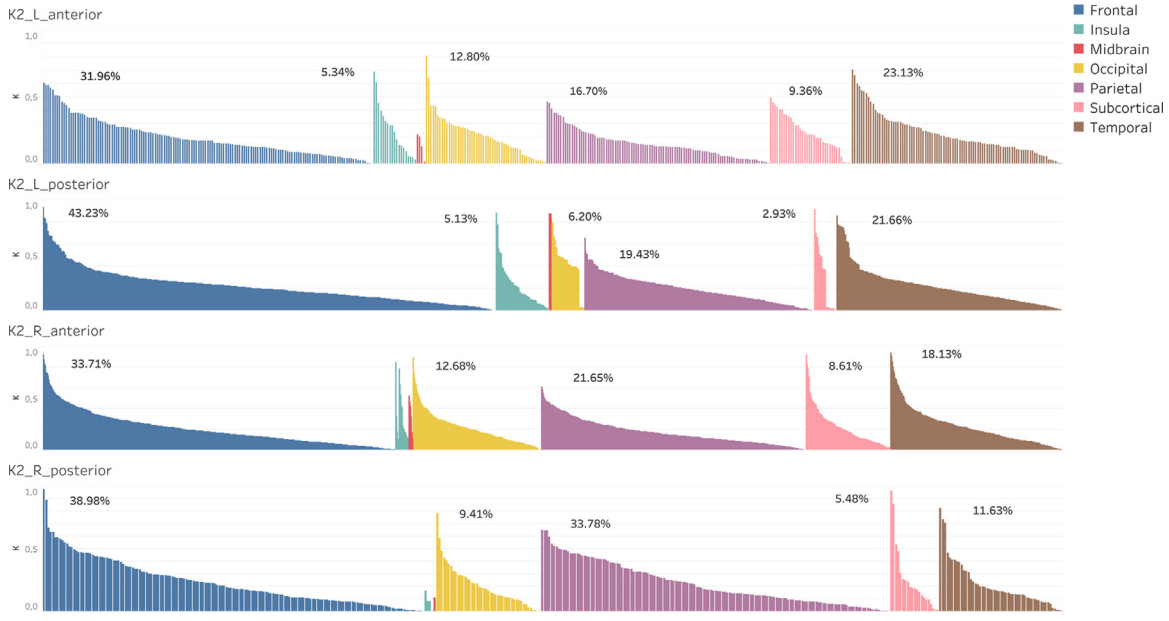

Fig. 6. Distribution of the edges' values for each lobe/group, for the K2 solution. Only lobes/groups accounting at least for the 2% of the total Patel's κ were visualized. Blue = frontal lobe, green = insula (non-root), red = midbrain, yellow = occipital lobe, purple = parietal lobe, pink = subcortical regions, brown = temporal lobe.

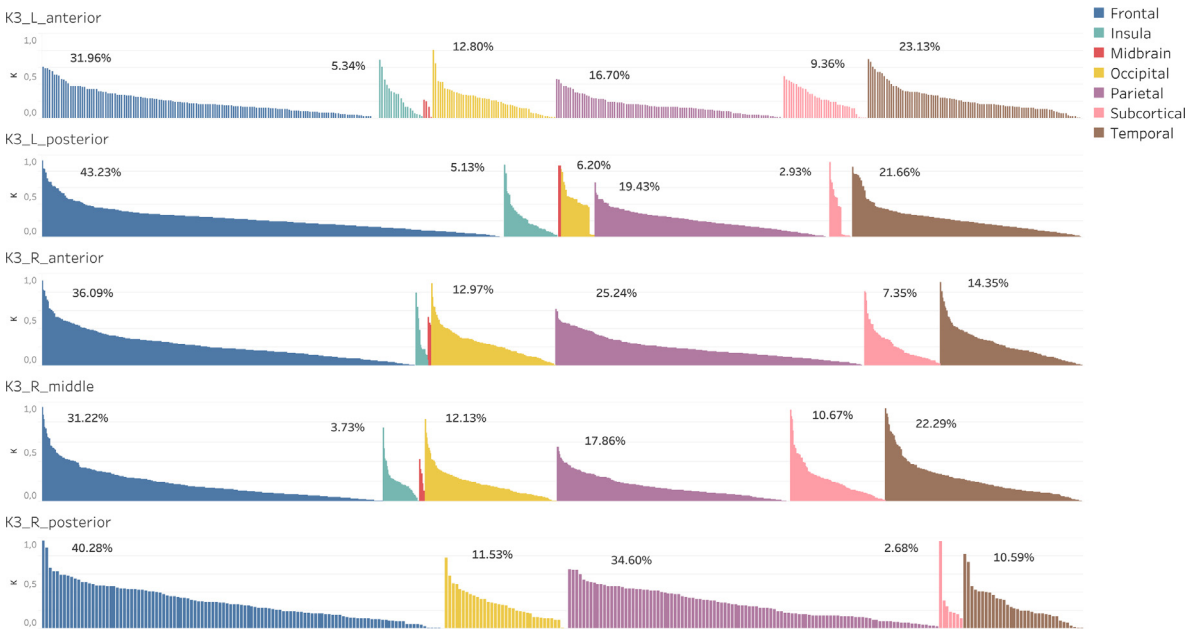

Fig. 7. Distribution of the edges' values for each lobe/group, for the K3 solution. Only lobes/groups accounting at least for the 2% of the total Patel's κ were visualized. Blue = frontal lobe, green = insula (non-root), red = midbrain, yellow = occipital lobe, purple = parietal lobe, pink = subcortical regions, brown = temporal lobe.

Our results point out that, (at least) when the insula is altered, the co-alteration networks reflect the functional connectivity patterns, thus providing support for the nodal stress hypothesis in the development and distribution of alterations (Crossley et al., 2016a, 2014). When impaired, the insular cortex might bring about hyperexcitability to its functionally connected areas, and thereby cause metabolic stress and disruption.

Overall, considering the bipartite parceling the peaks of overlap between co-alteration and co-activation patterns are mainly localized in frontal and subcortical areas. In the patterns based on the tripartite parceling instead, the peaks of overlap are not only mainly localized in frontal and subcortical areas, but also in temporal and parietal sites. This may provide evidence for the more specificity of the solution based on the tripartite parcellation.

However, the uncoupling between co-alteration and co-activation for what concerns subcortical and lower cortical regions suggests that also other mechanisms might take place in the distribution of co-alterations other than the influence of normative connectivity. A shared vulnerability factor (Zhou et al., 2012) is usually expected to play a role in the development of pathological alterations, for instance in the form of a genetic influence (Cauda et al., 2018b). However, our results indicate that such uncoupling might derive also from other biological factors, as the "bottom-up" (from the insula to cortical areas) pathoconnectivity profile is unlikely to be related exclusively to functional aspects of brain organization.

The fact that the insula is more involved in co-alteration patterns with higher-order cortical regions rather than with lower-order areas (such as subcortical and hippocampal structures) deserves an explanation. If pathological alterations are guided by connectivity constraints, which in case of the insula co-alteration network are pre-eminently functional ones, why only the connections between the insula and higher-order areas are involved in patterns of co-alterations, and not those between the insula and lower-order regions? In fact, the insular cortex is strongly connected with both brain sites (cortical and subcortical). Are there biological factors (such as, for instance, cytological or genetic aspects) that make the insula more likely to be co-altered with the former areas rather than with the latter? The question is intriguing and requires further investigations.

4.4. Analysis of behavioral profile

The behavioral profiles of the co-alteration patterns show a prevalence of labels related to the emotional and cognitive spheres, which is consistent with the fact that emotional and cognitive processes are frequently disrupted in many neurological and psychiatric conditions. As we have seen, the insular cortex has important cognitive and interoceptive functions; in particular, it is mainly involved in the processing of salience, attention, emotions, and in the integration of sensory and interoceptive stimuli.

The insula is an essential part of the salience network (SN), along with the dorsal anterior cingulate cortex (dACC) and other subcortical and limbic structures (Seeley et al., 2007; Uddin, 2015). This important network has a pivotal role in processing the perception of behaviorally significant stimuli as well as in coordinating the use of brain resources (Uddin et al., 2013, 2011). In fact, being an essential hub of the SN, the insula (especially the right one) is involved in the dynamic coordination of two other important brain networks, the DMN and the central executive network (CEN) (Chen et al., 2013; Goulden et al., 2014; Sridharan et al., 2008; Supekar and Menon, 2012). The insular cortices seem therefore involved in a plurality of functions associated with subjective salience, independent of the nature of the stimuli, being those homeostatic, emotional or cognitive (Bartra et al., 2013; Craig, 2002). Also, it has been found that dysfunction of the SN can occur in many brain conditions, including dementia, schizophrenia, psychosis, bipolar disorder, addiction, anxiety, depression, obsessive-compulsive disorder, chronic pain, and autism spectrum disorder (Di Martino et al., 2009; Etkin et al., 2009; Goodkind et al., 2015; Hamilton et al., 2012; Kapur, 2003; Klin et al., 2003; Li et al., 2010; Palaniyappan and Liddle, 2012; Schroeter et al., 2008; Seeley et al., 2012; Simons et al., 2014). Furthermore, the insular cortex plays a fundamental role in the emotional evaluation of bodily states. Specifically, the coordinated activity of insula, amygdala and prefrontal cortex is pivotal for regulating emotions, both in normal and pathological conditions (Foland et al., 2008; Lee et al., 2012).

In sum, with regard to the solution based on two parcels, the anterior sub-network seems to be more oriented towards the processing of interoception and perception, whereas the posterior sub-network ap-

pears to be more associated with the processing of emotion. These two sub-networks show comparable scores for the functions of action and cognition. Instead, with regard to the solution based on three parcels, the anterior sub-network appears to be more oriented towards the processing of action and cognition, while the middle sub-network appears to be more oriented towards the processing of perception and interoception and the posterior sub-network towards the emotional processing.

4.5. Limitations and future directions

The principle limitation of our study is that we cannot say how differently brain disorders are supposed to impact on the insular cortex. We know that a great number of conditions affect this cortical area but we do not know which parts of the insula are the most affected and by which disorders. However, we decided to consider all brain disorders in the BrainMap database because the aim of this study was to achieve the most comprehensive investigation about the pathological processes affecting the insula. Indeed, the leave-one-pathology-out analysis suggested that none of the included disorder is guiding the results (Tab. S5). There was also the methodological constraint of analyzing the most numerous sample of studies to achieve a better statistical outcome. As in any meta-analysis, the data selection procedure could be affected by biases. However, the implemented fail-safe analysis (Fig. S3) suggested a good robustness of the results at least to the drawer-effect. This approach was intended to provide useful insight for further examinations with more specific aims. Related to this, we could not use a more fine-grained parcellation, since this was not supported by a sufficient amount of data to achieve reliable results. The selection of any predetermined parcellation is *per se* a questionable step. However, in doing this we opted for a solution with high multimodal consensus, as explained above.

Future investigations need to explore the directionality, both spatial and temporal, followed by alterations across the different brain areas when a pivotal hub, like the insula, is initially affected. Although regions presenting high node degrees are thought to be pathoconnectivity hubs, we cannot infer from our data whether alterations first originate in the insula and then propagate to other areas or vice versa.

Conclusion

This study performed a pathoconnectivity network analysis of the insula, one of the most connected and important hubs of the both health and pathological brain. Our findings indicate that the insula is altered by a variety of brain disorders. This result is in line with recent research that found the insula to be among the most affected brain areas by a wide range of brain diseases (Cauda et al., 2019) as well as in six different important psychiatric conditions – i.e., schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety (Goodkind et al., 2015). Our analysis not only confirms that finding, but provides further evidence that the insula is significantly affected by both neurological and psychiatric disorders. Its central and intense activity may account for the fact that this area appears to be so vulnerable to neuronal alterations.

The insula pathoconnectivity network analysis reveals 1) that the pattern of distribution of GM alterations associated with the insular cortex is composed of areas that are mainly located in cortical rather than in subcortical sites; 2) that the insula co-alteration patterns correlate, and overlap, well with the corresponding co-alteration patterns; and that 3) these co-alteration patterns may implicate the disruption of cognitive (i.e., salience) and emotional processes. The fact that higher-order areas appear to contribute more to the co-alteration network of the insula than lower-order regions suggests that, along with functional connectivity constraints, other factors (perhaps biological ones, such as cytological and genetic mechanisms) may play a role in the development of patterns of co-alterations.

These findings provide evidence that the brain areas that are altered along with the insula are not randomly disrupted but tend to be altered on the basis of their functional connectivity. Finally, the significant coherence between the co-alteration and co-activation of the insula suggests that alterations caused by brain disorders can exhibit a distribution according to the logic of functional network architecture. This might be typical whenever brain hubs are involved in the alteration process. According to this view, brain hubs may lie at the center of networks composed of co-altered areas. If confirmed by future studies, this finding will help to better address the issue of how brain connectivity can predict regional alteration profiles and severity of symptoms in both neurological and psychiatric disorders.

CRediT author statement

Andrea Nani: Conceptualization, Methodology, Writing – Original draft, Writing – Review, Visualization. **Jordi Manuello**: Conceptualization, Methodology, Formal Analysis, Writing – Original draft, Writing – Review, Visualization. **Lorenzo Mancuso**: Methodology, Formal Analysis, Writing – Review, Visualization. **Donato Liloia**: Data curation, Writing – Original draft, Writing – Review. **Tommaso Costa**: Conceptualization, Methodology, Formal Analysis. **Alessandro Vercelli:** Conceptualization, Writing – Original draft. **Sergio Duca**: Writing – Original draft. **Franco Cauda**: Conceptualization, Supervision, Funding acquisition.

Data and code availability

Both VBM and functional meta-analytic data are freely available as part of the BrainMap database.

Kelly's insula ROIs can be freely downloaded from http://fcon_1000.projects.nitrc.org.

No specific tools where developed to perform the analyses described.

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Declaration of Competing Interest

The authors report no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117481.

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