



## Research report

# Convergence of interoception, emotion, and social cognition: A twofold fMRI meta-analysis and lesion approach



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## ABSTRACT

Guided by indirect evidence, recent approaches propose a tripartite crosstalk among interoceptive signaling, emotional regulation, and low-level social cognition. Here we examined the neurocognitive convergence of such domains. First, we performed three meta-analyses of functional magnetic resonance imaging studies to identify which areas are consistently coactivated by these three systems. Multi-level Kernel Density Analysis (MKDA) revealed major overlaps in the right anterior insular and frontotemporal regions (viz., the orbitofrontal and inferior frontal gyri, the amygdala, and mid temporal lobe/subcortical structures). Second, we explored such domains in patients with fronto-insulo-temporal damage. Relative to controls, the patients showed behavioral impairments of interoception, emotional processing, and social cognition, with preservation of other cognitive functions. Convergent results from both studies offer direct support for a model of insular-frontotemporal regions integrating interoception, emotion, and social cognition.

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## 1. Introduction

### 1.1. Network models of interoception, emotion, and social cognition

Interoception, the sensing of internal bodily signals (Cameron, 2001; Craig, 2002), has been recently linked to emotion recognition and social cognition (Craig, 2009b; Garfinkel & Critchley, 2013; Ibanez & Manes, 2012; Uddin, Kinnison, Pessoa, & Anderson, 2014). The integration of these three domains likely depends on the insular cortex (IC), whose anterior portion (aIC) plays a crucial role in interoception (Caruana, Jezzini, Sbriscia-Fioretti, Rizzolatti, & Gallese, 2011; Decety, Michalska, & Kinzler, 2012; Ibanez & Manes, 2012; Melloni, Lopez, & Ibanez, 2014; Saarela et al., 2007; Singer et al., 2004). As part of the salience network and the ventral attention system, the right aIC is assumed to reorient attention towards emotionally salient stimuli (Corbetta, Patel, & Shulman, 2008; Eckert et al., 2009; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Menon & Uddin, 2010; Nelson et al., 2010; Seeley et al., 2007). The IC features profuse connections with the medial prefrontal cortex (mPFC, including the anterior cingulate cortex, ACC) and the posterior bank of the superior temporal sulcus (pSTS), forming a network that is consistently engaged during social and emotion recognition tasks. The pSTS is sometimes denoted as temporo-parietal junction (TPJ), roughly characterized as an area at the border between the temporal and parietal lobes (surrounding the superior end of the STS) which is consistently activated during social cognition tasks (Melloni et al., 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). These regions integrate signals from distant hubs, bringing together different functional networks (Ibáñez et al., 2016; Liang, Zou, He, & Yang, 2013; van den Heuvel & Sporns, 2013). This is especially true of the IC, which constitutes a “rich club” integrating global information patterns from all over the brain (Harriger, van den Heuvel, & Sporns, 2012; van den Heuvel & Sporns, 2011; Sepulcre, Sabuncu, Yeo, Liu, & Johnson, 2012; Sporns, 2014).

Further insights into the functional organization of this fronto-insulo-temporal network come from functional activation and lesion studies (Adolphs, Damasio, & Tranel, 2002; Cauda et al., 2012; Chang, Yarkoni, Khaw, & Sanfey, 2013; Kelly et al., 2012; Khalsa, Rudrauf, Feinstein, & Tranel, 2009), which reveal multiple connections between the IC and structures subserving interoceptive, emotional, and social processes, such as the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortices (dlPFCs), the ACC, the medial and lateral temporal lobes, the ventral striatum, and the amygdala (Mufson & Mesulam, 1982; Viskontas, Possin, & Miller, 2007). In sum, as indicated by anatomical (Couto, Sedeno, et al., 2013; Mesulam & Mufson, 1982a, 1982b), lesion (Calder, Keane, Manes, Antoun, & Young, 2000; Couto, Adolphi, Sedeno, et al., 2015; Couto, Sedeno, et al., 2013; Khalsa et al., 2009), and functional (Cauda et al., 2012; Kelly et al., 2012; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010) studies, the IC interacts with frontotemporal networks to coordinate social cognition, emotion, and interoception. To date, however, no study has directly examined the convergence of these domains, arguably because of the methodological challenges implied by the task.

### 1.2. Interoception and emotion

One of the key sources of interoceptive signals related to emotion is the heartbeat. Indeed, heartbeat detection (HBD) tasks are the gold standard to assess cardiac interoception (Khalsa et al., 2008). In such tasks, moment-to-moment encoding of heartbeat signals activates the IC, the ACC, and the secondary somatosensory cortex (S2) (Bechara & Naqvi, 2004; Canales-Johnson et al., 2015; Critchley, Wiens, Rotshstein, Ohman, & Dolan, 2004; Ferri, Ardizzi, Ambroseccchia, & Gallese, 2013; Pollatos, Kirsch, & Schandry, 2005a; Pollatos, Schandry, Auer, & Kaufmann, 2007). Moreover, performance in the HBD task correlates with the volume of the right aIC –and so do negative affective states (Bechara & Naqvi, 2004; Critchley et al., 2004).

Interoception has also been associated with emotional processing (Couto, Adolphi, Velasquez, et al., 2015). Autonomic changes (e.g., increase in heart rate) signal emotional modulations, suggesting emotional self-assessment entails interoceptive processes (Lee & Siegle, 2012). Recent evidence suggests a proportional relationship between emotional experience and interoceptive sensitivity (Critchley et al., 2004; Pollatos, Kirsch, & Schandry, 2005b; Werner, Duschek, Mattern, & Schandry, 2009), indexed by IC activity (Critchley et al., 2004). Moreover, interoceptive and emotional processes yield overlapping activations in the aIC and the ACC (Craig, 2002; Critchley, Mathias, & Dolan, 2001; Damasio et al., 2000; Terasawa, Fukushima, & Umeda, 2013). A meta-analysis of 162 neuroimaging studies revealed that the IC is one of the most consistently activated areas in the emotion literature (Kober et al., 2008). Taken together, this evidence further highlights interoception as an element for emotional processing and self-awareness.

### 1.3. Interoception and social cognition

Central monitoring and the representation of bodily signals have been further associated with social cognition. Although social cognition is a complex domain involving many sub-components, we focus here on the most classically associated processes: cognitive and affective Theory of Mind (ToM, the attribution of cognitive and affective mental states to oneself and others; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). ToM is one of the most essential aspects of social cognition (Kanske, Bockler, Trautwein, & Singer, 2015), and there is evidence for its specific association with interoception (Brewer, Happe, Cook, & Bird, 2015; Couto et al., 2014). For example, good interoceptive skills seem necessary to develop ToM (Keysers & Gazzola, 2007). Such domain is compromised following bilateral IC degeneration (Couto, Manes, et al., 2013). In addition, meta-analytic evidence has revealed IC involvement in non-story-based ToM studies (Mar, 2011). Finally, the interoceptive network is connected with regions that subserve varied social cognition domains, particularly the aIC and the ACC (Denny, Kober, Wager, & Ochsner, 2012; Fan, Duncan, de Greck, & Northoff, 2011; Kennedy & Adolphs, 2012; Mar, 2011; Van Overwalle, 2009; Van Overwalle & Baetens, 2009). Taken together, these results suggest that both social cognition and emotion processing are modulated by interoceptive sensing.

#### 1.4. Emotions and social cognition

Several models propose that social behaviors are triggered by the contextual appraisal of environmental and internally driven emotional signals (Adolphs, 2009; Corbetta et al., 2008; Decety & Jackson, 2004; Ibanez et al., 2016; Ibanez & Manes, 2012; Lamm, Meltzoff, & Decety, 2010; Lamm & Singer, 2010). The IC is considered a relay area for interoceptive/emotional signals and higher-level (social cognition) information (Gu, Hof, Friston, & Fan, 2013). It is involved in the experience, recognition, and imagination of emotions (Jabbi, Bastiaansen, & Keysers, 2008; Jabbi & Keysers, 2008; Sprengelmeyer et al., 2010), including social processes like empathy and moral cognition (Caruana et al., 2011; Decety et al., 2012; Saarela et al., 2007; Singer et al., 2004). Indeed, IC injuries disturb the ability to recognize or name basic emotions (Adolphs, Tranel, & Damasio, 2003; Calder et al., 2000). Together, these studies highlight the central role of the IC in a broad network that integrates basic emotions and social cognition.

#### 1.5. Study goal

In sum, indirect evidence from multiple sources indicates that fronto-temporo-insular networks subserve the integration of interoceptive signals, emotional processes, and social cognition. However, no study has provided direct empirical evidence of such a connection. Although in the last decade several studies (Craig, 2009b; Danziger, Faillenot, & Peyron, 2009; Garfinkel & Critchley, 2013; Stanley & Adolphs, 2013; Uddin et al., 2014; Wiens, 2005) have highlighted the interrelations among different domains and the possible role of the IC in the corresponding processes, only a few reports (Terasawa et al., 2013; Zaki, Davis, & Ochsner, 2012) have assessed their overlaps – mostly in pairwise comparisons between only two of the domains presently examined. There is a dearth of direct empirical evidence of the convergence among interoception, emotional, and social cognition processes.

Here we explore this hypothesis using a double approach. First, we surveyed the brain signatures of interoception, emotional processing, and social cognition through three meta-analyses of relevant fMRI studies. Second, to assess the role of the aIC in this interaction, we administered tasks tapping the three domains to stroke patients with fronto-insulo-temporal damage and matched controls. In short, via this twofold approach, we seek to examine the organization of a broad network hypothesized to integrate interoception, emotion, and social cognition processes.

## 2. Quantitative meta-analysis

### 2.1. Methods

The meta-analytic approach is highly suitable to detect which effects are robust despite all the variability in the field (Lindquist, Satpute, Wager, Weber, & Barrett, 2015; Schurz et al., 2014). The benefit of meta-analyses lies in the balancing of the individual studies' shortcomings and limited informative value, overcoming the empirical limitations each of them has on their own. To identify reliable experimental

effects, meta-analyses pool data and characterize the degree of agreement across studies, independent from tasks and recordings (Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009). This integrative approach is suitable to provide statistical evidence of convergent findings across studies and average results to identify brain areas that show consistent activity.

Using Multi-level Kernel Density Analysis (MKDA), we analyzed the distribution of peak coordinates reported in several studies using varied methodological designs (Kober et al., 2008; Kober & Wager, 2010; Wager, Lindquist, & Kaplan, 2007; Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). Coordinates originally reported in Talairach stereotactic space were converted to MNI space, which is widely used in the field and minimizes localization errors in meta-analytical results (Carmack et al., 2004). The MKDA method performs multiple nested analyses on individual peaks and interprets their contrast as a random effect. In a nutshell, the MKDA is a 'random effects' approach (Fan et al., 2011; Kober & Wager, 2010; Wager et al., 2009), given that: a) it nests peak activation coordinates within contrasts, and contrasts within studies; b) it models the variability across peaks within a contrast, rather than just counting all the peaks as if they all belonged to the same study or contrast – so that effects are assumed to vary randomly between samples; c) it assesses statistical significance density maps by comparing against the following null hypothesis: activated regions in the resulting pair-wise contrast maps are randomly distributed throughout the brain (Kober & Wager, 2010; Wager et al., 2009). See [Supplementary Data](#) for a comparison between the different available methods for voxel-wise meta-analyses of fMRI studies.

Prior meta-analyses (Fox, Parsons, & Lancaster, 1998; Laird et al., 2005; Wager, Jonides, & Reading, 2004; Wager, Phan, Liberzon, & Taylor, 2003) have treated peaks within each voxel as a fixed effect. This procedure ignores the fact that points are not independent of one another (they are nested within contrasts within studies). An important consequence is that any single study that has a large number of peaks (due to differences in reporting, voxel size, and thresholding) can dramatically influence the analyses. In contrast, the Peak Density Method presently used respects the data's multidimensionality, as it treats peaks as random rather than fixed factors. This means modeling the variability across peaks within a contrast, rather than just counting all the peaks as if they all belonged to the same study or contrast (see [Supplementary Data](#) for a detailed discussion). To this end, we created one Contrast Indicator Map (CIM) for each contrast. CIMs were created for each set of coordinates by convolving a 10-mm spherical kernel around each peak. The resulting maps contained "active" voxels that were within 10 mm of a reported peak for that contrast. Spherical kernels of 10 mm were chosen because they match roughly the three dimensional spatial resolution of the reported data and due to its general acceptance in MKDA use (Kober & Wager, 2010; Salimi-Khorshidi et al., 2009; Wager et al., 2004; Wager et al., 2007). The combined CIMs are weighted by the square root of the sample size of the contrast, reflecting the proportion of contrasts yielding activations near each voxel. Also, studies using fixed effects analyses are down-weighted by a factor of .75 (see [Supplementary Information](#)).

Hence, the crucial measure of interest is the number of contrasts that produced activation near a voxel, rather than the number of individual activation peaks. Thus, MKDA avoids bias towards any single study that reports multiple nearby peaks, as these are treated as spatially independent. This might reflect low spatial smoothness in the data, reporting conventions, low thresholds, or the voxel sizes used (Wager et al., 2008). The MDKA approach allows weighting contrasts by study sample size and quality (Wager et al., 2009), so that reports with fewer participants or fixed effect designs are given less weight, while studies with a larger number of participants or random effect designs are given more weight. The meta-analysis statistic at each voxel, reported in text and tables as the ‘z statistic’ (Kober et al., 2008), is the proportion difference of contrasts that activated within 10 mm (kernel region) of that voxel, weighted by the sample size and quality (fixed vs random effects) of the study (Buhle et al., 2014; Denny et al., 2012; Kober et al., 2008; Mende-Siedlecki, Said, & Todorov, 2013). Thus, z-values (maximum statistic values) are based on weighted CIMs rather than studies, and represent the weighted percentage of CIMs that reported activation in each cluster (Kober et al., 2008).

The general null hypothesis states that peak coordinates of activated regions are randomly distributed across the brain. If the number of nearby activations for a peak coordinate is greater than the number expected by chance, the null hypothesis is rejected. Given that the MKDA method does not differentiate between a peak coming from a study applying correction and a peak not applying it, only those voxels which survive whole-brain correction have been considered significant, which is in itself a reliable procedure (Cacioppo, Bianchi-Demicheli, Frum, Pfaus, & Lewis, 2012; Juan et al., 2013; Kober et al., 2008). MKDA does so by identifying maps of activated clusters according to a ‘height’ or ‘extent’ based threshold. The height-based threshold encloses voxels that have proportions of contrasts inside the 10 mm kernel region that exceed the maximum expected over the entire brain by chance ( $p < .05$ , family wise error rate – FWE corrected) and reducing to this level the Type I error at any single voxel. The extent-based threshold selects contiguous voxels outside the 10 mm of the clusters for the height-based threshold, that show greater activation than would be expected at a given level of chance ( $p < .05$ ) and which are secondary FWE-corrected for spatial extent at  $p < .05$ . Beyond that, a combined map of voxels meeting both criteria (height and extent) is computed. Finally, both visual and statistical overlaps with conjunction analysis were conducted as explained below. For further details about MKDA (Kober & Wager, 2010; Wager et al., 2008; Wager et al., 2007) and its relationship to other meta-analytical approaches, see [Supplementary Material](#).

Relevant studies were selected through an extensive computer-based search of peer-reviewed functional neuroimaging studies. We relied on the following sources: MEDLINE library, life science journals, and online books indexed in PubMed. Also, we used the Sleuth Software (BrainMap Development Team, Version 2.0.3, Research Imaging Center,

University of Texas Health Science Center at San Antonio) to search the BrainMap database for published functional neuroimaging experiments.

Each study was then checked for content relevance. The studies included in the meta-analyses of emotion and social cognition were published from the year 1999 onwards. The reference lists of identified papers were reviewed to ensure the inclusion of all relevant studies that fit our criteria: (1) description of standard Talairach (Talairach & Tournoux, 1988) or Montreal Neurological Institute (MNI) coordinates (to enable comparison of reported peak activation across studies); (2) samples composed of unmedicated and untrained healthy adults; (3) studies in which the threshold of significance has been established at the whole-brain level; (4) measurement of regional cerebral blood flow (e.g., through PET) or blood oxygenation (e.g., through fMRI); (5) employment of image subtraction to determine activation foci; and (6) Tasks which tap core processes of emotion, social cognition or interoception without assessing related high-level processes or pursuing more specific goals (such as correlations and/or interactions with other psychological constructs or demographic features). All three meta-analyses included studies with varied tasks. In particular, the interoception meta-analyses were not limited to cardiac interoception, as a recent meta-analysis [44]. This inclusive criterion was chosen to ensure each domain was fully represented and the number of studies was balanced across domains. Following previous recommendations (Lindquist et al., 2015; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Vytal & Hamann, 2010; Wager et al., 2008), only activations were included, because deactivations have been less consistently reported and prove more difficult to interpret. Furthermore, interpretations of reported deactivations are unclear, since their neural mechanisms remain largely unknown (Gusnard & Raichle, 2001; Hutchinson et al., 1999). The key words used to search the databases as well as number of studies, contrasts, and participants for each meta-analysis are shown in [Table 1](#) (see also [Supplementary Data](#) and [Supplementary Tables I–III](#)).

The results were visualized using the Caret Software (version 5.65, Van Essen Laboratory, Saint Louis; <http://brainvis.wustl.edu>). Activation maps containing the combined results from extent- and height-based thresholds were projected onto the left and right hemispheres of the PALS atlas (Population-Average, Landmark and Surface based atlas, Van Essen Laboratory, Saint Louis; <http://sumsdb.wustl.edu/sums/humanpalsmore.do>) using MNI-Talairach coordinate space. Overlapping brain foci were displayed by mapping both activation maps to the surface and adjusting the  $p$  values to .05 corrected for multiple comparisons by FWE. The left and right cortical surfaces were inflated to reveal the major sulci of the brain and to facilitate data visualization. To extract the significant areas activated in the overlap, we performed a conjunction analysis on the three MKDA-corrected maps (at .05 FWE, via Bonferroni tests, [Fig. S1](#)) using SPM-8 (Statistical Parametric Maps, Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>).

**Table 1 – Keywords and number of studies, contrasts and participants for meta-analyses on 3 domains.**

	Key words	n of studies	n of contrasts	n of participants
Interoception	“fMRI” <OR> “functional neuroimaging” <AND> “interoception” <OR> “cardiac interoception” <OR> “visceral perception” <OR> “body emotions” <OR> “bodily emotions” <OR> “heartbeat” <OR> “heartbeat detection”	34	66	730
Emotion recognition and experience	“fMRI” <OR> “functional neuroimaging” <AND> “emotion” <OR> “emotion recognition” <OR> “emotion perception”	178	405	2602
Social cognition	“fMRI” <OR> “functional neuroimaging” <AND> “social cognition” <OR> “theory of mind” <OR> “mentalizing” <OR> “empathy”	63	123	1438

## 2.2. Results

### 2.2.1. Interoception

The meta-analysis of interoception showed the greatest likelihood of activation within the right aIC ( $z = .31$ ). The subsequent clusters in likelihood included the left insula ( $z = .21$ ), the right claustrum ( $z = .19$ ), the right pulvinar thalamic nucleus ( $z = .18$ ), the right inferior parietal lobe ( $z = .16$ ), the left cingulate gyrus ( $z = .14$ ), and the left parahippocampal gyrus ( $z = .07$ ; see [Table 2](#)).

### 2.2.2. Emotion

Greatest activation increases in the MKDA maps of emotions were concentrated in a large cluster ranging from the left inferior frontal gyrus ( $z = .08$ ) to the left ( $z = .21$ ) and right ( $z = .17$ ) amygdalae, the left aIC ( $z = .07$ ), the left claustrum ( $z = .11$ ), the basal ganglia (right globus pallidus,  $z = .1$ ; head of the right caudate,  $z = .06$ ), and the thalamus (medial dorsal nuclei,  $z = .08$ ). Significant activation was also found in the right aIC ( $z = .09$ ), the ACC ( $z = .07$ ), the bilateral inferior frontal gyri ( $z = .07$ ), the right superior temporal gyrus ( $z = .05$ ), the right parahippocampal

**Table 2 – Greatest likelihood of activation revealed by the meta-analysis on interoception.**

Name	Brodmann area	x	y	z	Voxels	Volume (mm <sup>3</sup> )	Max stat
Right anterior insula	13	40	12	6	452	3616	.31
Right anterior insula	13	34	18	10	73		.25
Left anterior insula	13	-40	12	8	94		.2
Right insula	13	40	10	4	379		.31
Left insula	13	-40	6	8	222	1776	.21
Left insula	13	-40	2	8	128		.21
Left insula	13	-46	-24	24	612	4896	.15
Right claustrum		40	-8	8	11	88	.19
Left claustrum		-36	12	-2	772	6176	.13
Left cingulate gyrus	24	-2	6	32	1785	14280	.14
Right superior temporal gyrus	39	54	-52	24	370	2960	.11
Left parahippocampus	27	-10	-38	0	246	1968	.07
Right thalamus		14	-30	-6	603	4824	.12
Right thalamus		16	-16	16	16	128	.16
Right thalamus (Pulvinar)		20	-34	2	40	320	.07
Right thalamus (Pulvinar)		16	-28	18	23	184	.09
Left thalamus (Medial Dorsal Ncl.)		-2	-10	2	6184	49472	.12
Right posterior thalamus (Pulvinar Ncl.)		18	-24	8	53	424	.18
Left nucleus caudatus (Caudate Head)		-2	12	-6	208	1664	.13
Right nucleus caudatus		12	-4	18	148	1184	.07
Right inferior parietal lobe	40	64	-42	28	35	280	.16
Left inferior parietal lobe	40	-50	-30	38	1005	8040	.13
Left inferior parietal lobe	40	-38	-42	44	171	1368	.07
Left inferior parietal lobe	40	-42	-30	46	14	112	.06
Right postcentral gyrus	2	56	-24	36	282	2256	.10
Right postcentral gyrus	3	44	-22	52	25	200	.07
Left postcentral gyrus	3	-58	-14	24	10	80	.08
Left cerebellum (Culmen)		-4	-64	-6	198	1584	.08
Left cerebellum (Culmen)		-12	-38	-10	941	7528	.14
Left cerebellum (Culmen)		-30	-50	-14	276	2208	.13

Significance level: <.05.

Minimum number of voxels is 10.

gyrus ( $z = .17$ ), the bilateral fusiform gyri ( $z = .09$ ), and the right inferior occipital gyrus ( $z = .06$ ). In the cerebellum, significant activated areas were identified in the culmen ( $z = .03$ ) and the declive (right,  $z = .07$ ; left,  $z = .09$ ; Table 3).

### 2.2.3. Social cognition

The meta-analysis of social cognition showed the most significant clusters were located in the cingulate gyrus ( $z = .19$ ) and right superior temporal gyrus (STG,  $z = .18$ ). A similar

cluster with lower likelihood appeared in the left STG ( $z = .17$ ). The subsequent clusters comprised the left middle frontal gyrus ( $z = .16$ ), the posterior cingulate gyrus ( $z = .16$ ), the left inferior frontal gyrus ( $z = .15$ ), the left insula ( $z = .15$ ), and the bilateral middle temporal gyrus ( $z = .15$ ). Other areas that showed significant activation were the ACC ( $z = .14$ ), the right supramarginal gyrus ( $z = .14$ ), the left amygdala ( $z = .13$ ), the right lingual gyrus ( $z = .12$ ), and the left superior frontal gyrus (SFG;  $z = .12$ ; Table 4).

**Table 3 – Greatest likelihood of activation revealed by the meta-analysis on emotion.**

Name	Brodmann area	x	y	z	Voxels	Volume (mm <sup>3</sup> )	Max stat
Left inferior frontal gyrus (OFC)	47	-38	28	-10	193		.07
Left inferior frontal gyrus	9	-46	16	22	244	195	.07
Left inferior frontal gyrus (OFC)	13	-32	12	-16	259		.08
Left inferior frontal gyrus (OFC)	47	-44	22	-4	402		.08
Right inferior frontal gyrus	45	46	24	0	121		.07
Right inferior frontal gyrus	9	46	16	22	178		.07
Left medial frontal gyrus	9	-2	52	26	231	184	.08
Medial frontal gyrus	6	-2	20	44	18		.06
Superior frontal gyrus	6	0	14	52	28		.06
Right superior frontal gyrus	6	2	16	46	82	656	.06
Anterior cingulate gyrus	24	0	40	4	124	992	.07
Mid cingulate gyrus	32	2	18	40	13		.06
Mid cingulate gyrus	32	2	14	44	23		.06
Right anterior insula	13	40	20	2	1236	9888	.09
Right anterior insula	13	38	18	-2	432		.09
Right anterior insula	13	32	26	-10	209		.07
Right anterior insula	13	44	22	12	139		.08
Left anterior insula	13	-34	16	-2	137		.07
Left insula	13	-42	14	-2	124		.07
Right insula	13	40	8	6	118		.07
Right claustrum		30	22	8	35	280	.03
Right claustrum		34	12	2	39		.06
Left claustrum		-34	-6	-10	173		.11
Right parahippocampus/amygdala		22	-4	-14	1220	9760	.17
Right parahippocampus/amygdala		22	-4	-16	1069		.17
Right parahippocampus (Uncus)	34	14	-8	-28	13	104	.03
Left parahippocampus (Uncus)	36	-24	-4	-32	11	88	.03
Left parahippocampus/amygdala		-22	-4	-16	1107		.21
Left parahippocampus	35	-18	-18	-18	25	200	.03
Left thalamus (Medial dorsal Ncl.)		-4	-20	2	224		.08
Left thalamus (Medial dorsal Ncl.)		-6	-16	10	44		.06
Left thalamus		-12	-8	-4	346		.1
Right thalamus (Medial Dorsal Ncl.)		2	-14	4	190		.08
Right caudate head		6	14	-6	27	216	.06
Left putamen (Lentiform Ncl.)		-24	0	-10	3199	25592	.21
Right globus pallidus (Lentiform Ncl.)		22	0	-6	151		.1
Right medial temporal gyrus	21	54	-42	8	106	848	.06
Right temporal lobe (Fusiform gyrus)	37	38	-52	-16	424	3392	.09
Right Temporal Lobe (Fusiform gyrus)	37	40	-48	-18	245		.09
Right temporal lobe (Fusiform gyrus)	37	48	-50	-10	22	176	.03
Right temporal lobe (Fusiform gyrus)	37	40	-56	-6	1185	9480	.03
Left temporal lobe (Fusiform gyrus)	37	-40	-64	-14	548	4384	.09
Left temporal lobe (Fusiform Gyrus)	37	-42	-54	-16	184		.07
Right inferior occipital gyrus	17	16	-94	-2	41	328	.03
Right inferior occipital gyrus	19	44	-76	-4	17	136	.06
Right cerebellum (Declive)		36	-58	-14	179		.07
Right cerebellum (Culmen)		50	-52	-24	14	112	.03
Left cerebellum (Culmen of vermis)		-2	-66	2	4244	33952	.03
Left cerebellum (Declive)		-38	-68	-12	364		.09

Significance level:  $<.05$ .

Minimum number of voxels is 10.

**Table 4 – Greatest likelihood of activation revealed by the meta-analysis on social cognition.**

Name	Brodmann area	x	y	z	Voxels	Volume (mm3)	Max stat
Left inferior frontal gyrus	45	-48	24	0	402	3216	.15
Left inferior frontal gyrus	47	-48	28	-6	142		.15
Left inferior frontal gyrus	45	-54	22	16	68		.12
Left inferior frontal gyrus	45	-52	24	6	61		.13
Left inferior frontal gyrus	47	-44	26	-14	50		.12
Right inferior frontal gyrus	45	54	28	6	114	912	.14
Right medial frontal gyrus	9	48	20	24	63	504	.13
Left medial frontal gyrus	9	-2	36	28	2642	21136	.1
Left medial frontal gyrus	6	-4	54	32	289		.16
Left medial frontal gyrus	47	-44	36	-16	43	344	.05
Left medial frontal gyrus	32	-4	16	46	21		.12
Left superior frontal gyrus	6	-6	16	48	31	248	.12
Left superior frontal gyrus	6	-4	14	54	10		.12
Left superior frontal gyrus	8	-18	54	32	16	128	.05
Right precentral gyrus/frontal lobe	44	54	18	4	24	192	.06
Left insula		-42	22	-4	81		.15
Anterior cingulate cortex	32	0	48	-12	94	752	.14
Cingulate gyrus	31	0	-54	30	318	2544	.19
Cingulate gyrus	31	2	-54	30	249		.19
Posterior cingulate gyrus	23	-4	-50	26	69		.16
Right claustrum		36	14	0	166	1328	.09
Left putamen/lentiform Ncl.		-22	2	-2	2913	23304	.07
Left parahippocampus/amygdala		-22	-8	-18	94	752	.13
Right superior temporal gyrus	22	52	-44	10	545	4360	.18
Right superior temporal gyrus	38	50	10	-26	181	1544	.15
Right superior temporal gyrus	22	50	-38	2	177		.18
Right superior temporal gyrus	22	56	-50	16	147		.17
Right superior temporal gyrus	41	52	-40	12	140		.15
Right superior temporal gyrus	38	48	12	-28	120		.15
Right superior temporal gyrus	39	62	-60	24	38	304	.05
Right superior temporal gyrus	38	42	20	-36	34	272	.05
Left superior temporal gyrus	9	0	56	26	543	4344	.17
Left superior temporal gyrus	22	-52	-58	20	203	1624	.16
Left superior temporal gyrus	22	-52	-58	20	183		.16
Right medial temporal gyrus	38	52	8	-22	73		.15
Left medial temporal gyrus	21	-58	-8	-14	204	1632	.15
Left medial temporal gyrus	21	-58	-6	-16	122		.15
Left medial temporal gyrus	21	-56	-12	-14	82		.15
Left medial temporal gyrus	22	-56	-42	2	20	160	.11
Left medial temporal gyrus	37	-48	-68	12	20		.12
Right supramarginal gyrus	40	54	-48	22	81		.14
Right lingual gyrus	17	14	-92	4	12	96	.12
Right precuneus	23	4	-62	22	57	456	.07
Left precuneus	31	-10	-56	30	12	96	.07

Significance level: &lt;.05.

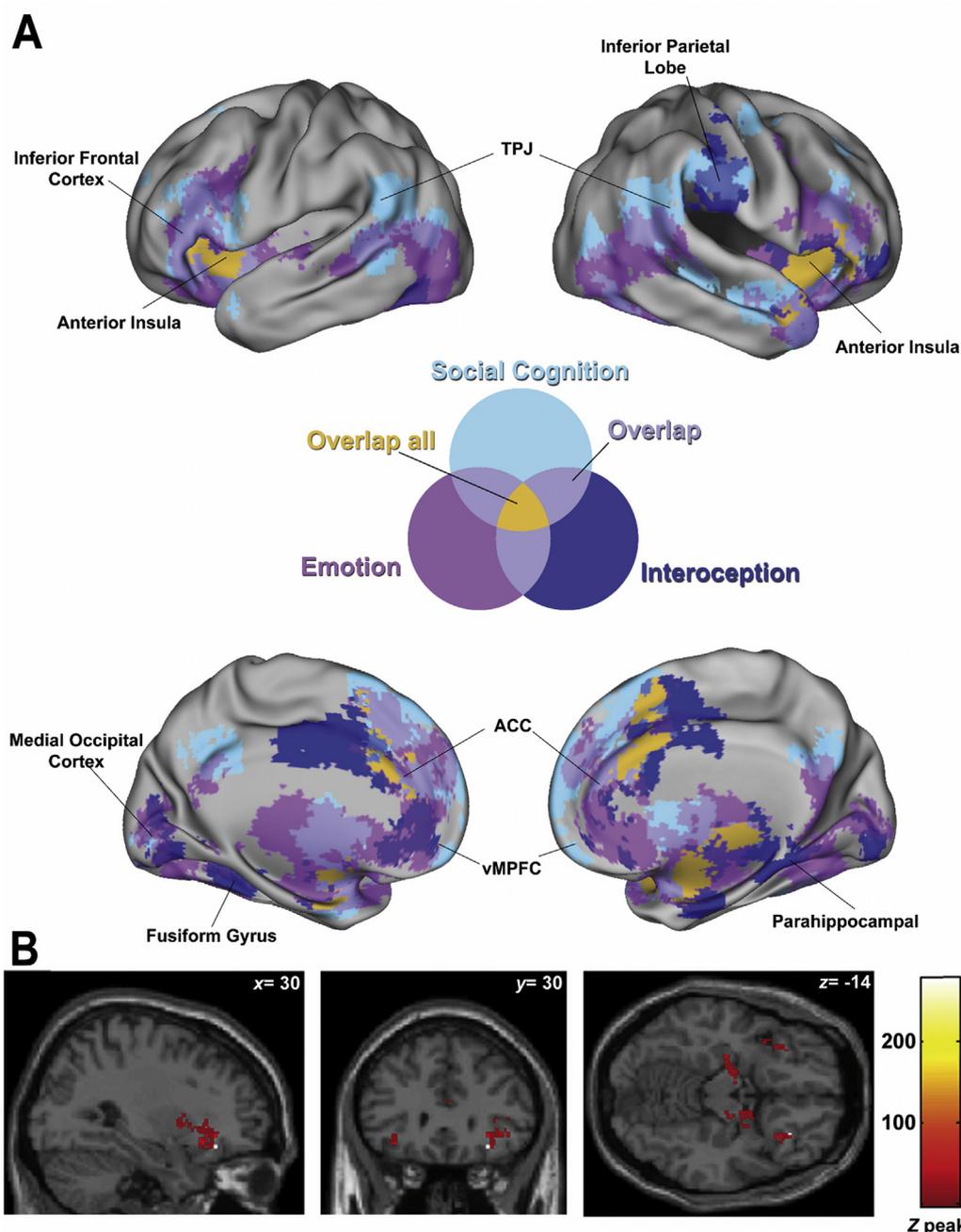
Minimum number of voxels is 10.

#### 2.2.4. Overlap among the three domains

The images resulting from each meta-analysis overlapped in several regions (Fig. 1). These included the aIC (right > left), the right ACC, and the right temporal pole. Interoception and emotion yielded overlapping activity over a broad network which included the bilateral insula, the left basal ganglia, the medial anterior temporal lobe (mATL), the subgenual ACC, the ventral mPFC, the inferotemporal (fusiform gyrus), and the occipital cortices. Interoception and social cognition shared the bilateral IC, the bilateral mPFC and ACC, the right S2, the right inferior parietal lobule, and the medial occipital cortex. Finally, emotion and social cognition showed related

activation in the bilateral pSTS, the inferior frontal gyrus, the bilateral basal ganglia, the bilateral mPFC, the medial occipital cortex, the bilateral precuneus, the medial ATL, and the lateral right temporal pole.

A conjunction analysis performed over the three MKDA maps revealed common activations throughout an insular-frontotemporal network: the right aIC, the ACC, the bilateral parahippocampal gyrus, the hippocampus, the right amygdala, the inferior frontal gyrus, and the right globus pallidus ( $p < .001$ , FWE corrected; Fig. 1B and Table 5). In sum, the three meta-analyses revealed overlaps in cortico-subcortical fronto-temporo-insular networks, in agreement with abundant



**Fig. 1** – A. Meta-analyses of cortical overlap (yellow). Significantly activated (meeting height- or extent-based threshold at  $p < .05$ , FWE corrected) clusters from studies of interoception (blue), emotion (violet), and social cognition (cyan). B. Conjunction analysis of interoception, emotion, and social cognition activation maps (MKDA). The regions highlighted include the right anterior insula and the amygdala, as well as the right frontal opercula, the right hippocampus, and the parahippocampal gyrus.

research on interoception and social cognition, in general, and the mentalizing network, in particular. Crucially, significant overlaps emerged in the right aIC, frontal and ATL structures, and the amygdala, all of which play well established roles in affective and cognitive integration (Adolphs, 2002; Craig, 2009a; Lamm & Singer, 2010; Singer, Critchley, & Preusschoff, 2009).

### 3. Lesion study

#### 3.1. Methods

##### 3.1.1. Participants

Thirty-seven subjects participated in this study. Sociodemographic, neuropsychological, affective, and experimental data

**Table 5 – Overlap of three meta-analyses activations (MKDA) for interoception, emotion and social cognition domains, sorted by cluster size.**

Region	Brodmann area	x	y	z	Voxels	Cluster size (in voxels)	Z peak
R insula	13	36	18	0	410	1014	249.2
R frontal inferior operculum	46	40	18	8	27	1014	249.2
R frontal inferior gyrus <i>Pars Triangularis</i>	46	44	22	14	115	1014	249.2
R orbitofrontal	47/11	2	42	-8	99	1014	249.2
L insula	13	-42	16	0	529	1001	126.5
L putamen	–	-18	8	-4	9	1001	126.5
L supplementary motor area	6/8	2	12	50	91	882	100.7
R mid cingulate	32	4	12	42	180	882	100.7
L anterior cingulate	25	0	26	22	229	882	100.7
L amygdale	–	-20	-6	-16	17	552	94.8
R pallidum	–	18	4	-2	25	552	94.8
L pallidum	–	-12	-2	-2	27	552	94.8
R superior temporal gyrus	38	46	-6	-12	34	34	7.22
R thalamus	–	6	-16	4	10	10	28.81

Significance level:  $p < .001$  FWE corrected.

were collected and are reported in Table 6. All participants read and signed an informed consent form prior to the beginning of the study and all protocols were performed in accordance with relevant guidelines and regulations of the Declaration of Helsinki. All protocols of this study were approved by the ethics committee of the Institute of Cognitive Neurology (INECO).

**3.1.1.1. PATIENT SAMPLE.** Seventeen individuals were selected from the outpatient population of the INECO. All patients were recruited from a previous ongoing protocol (Garcia-Cordero et al., 2015; Sandra Baez et al., 2014), and presented predominantly fronto-insulo-temporal brain lesions (Fig. 2) due to ischemic stroke (chronic cerebrovascular lesions acquired at least 6 months before testing), and reported no history of

psychiatric conditions. All patients included in the lesion study were cognitively stable, according to a neurological assessment. Their diagnoses were made by stroke specialists. No patients with tumors, hemorrhagic stroke, or brain trauma were included in the study.

**3.1.1.2. CONTROL SAMPLE.** The control group comprised 20 individuals with no history of neurological or psychiatric conditions. They were matched to the patient group in terms of demographic variables (age, gender, laterality, education). Sociodemographic and neuropsychological data are presented in Table 6.

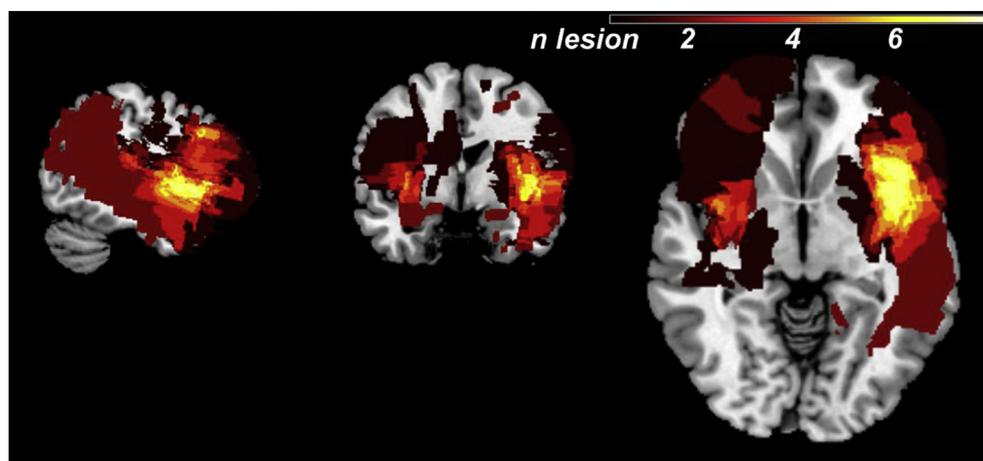
### 3.1.2. Instruments and procedures

**3.1.2.1. NEUROPSYCHOLOGICAL EVALUATION AND AFFECTIVE SCREENING.** General cognitive state was assessed with the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Executive functions were evaluated with the INECO Frontal Screening (IFS) (Torralva, Roca, Gleichgerricht, Lopez, & Manes, 2009) which assesses six executive domains via eight subtests (tapping motor programming, conflicting instructions, motor inhibitory control, numerical working memory, verbal working memory, spatial working memory, abstraction capacity, and verbal inhibitory control). The overall score, reflecting general executive functioning, is calculated as the sum of each of the eight subtests. Intelligence was measured through the Word Accentuation Test (WAT) for pre-morbid IQ (Burin, Jorge, Arizaga, & Paulsen, 2000). Depression and anxiety were assessed via the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996) and the State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), respectively.

**3.1.2.2. INTEROCEPTIVE MEASURES.** We assessed interoception through a behavioral HBD task (Couto et al., 2014; Melloni et al., 2013; Sedeno et al., 2014; Yoris et al., 2015). Participants were required to track heartbeats by tapping a computer keyboard, while electrocardiograms were recorded (see Supplementary Material). First, in a motor control condition, each participant was instructed to follow an audio recording

**Table 6 – Socio-demographic, neuropsychological and affective screening data.**

	Patients (N = 17)	Controls (N = 20)	p
<b>Demographic</b>	M (SD)	M (SD)	
Age	56.82 (14.39)	57.75 (12.29)	.869
Gender (males:females)	9:8	9:11	.630
Laterality (R:L)	14:3	19:1	.104
Education	15.19 (4.27)	14.95 (3.35)	.626
<b>Neuropsychological</b>			
IQ (WAT)	67.80 (7.43)	69.73 (4.22)	.522
Cognitive state (MMSE)	28.73 (1.48)	29.00 (1.35)	.780
Executive functions (IFS)	21.91 (4.00)	24.25 (1.93)	.091
Motor programming	2.88 (.33)	2.95 (.22)	.729
Conflicting instructions	2.88 (.33)	3.00 (.00)	.557
Motor inhibitory control	2.12 (1.27)	2.65 (.81)	.244
Numerical working memory	3.41 (1.06)	3.10 (.97)	.407
Verbal working memory	1.70 (.59)	1.85 (.49)	.517
Spatial working memory	2.00 (.93)	2.60 (.94)	.091
Abstraction capacity	2.20 (.50)	2.45 (.60)	.104
Verbal inhibitory control	4.70 (1.53)	5.40 (.94)	.167
<b>Affective screening</b>			
Depression (BDI)	12.31 (9.22)	7.83 (4.91)	.295
State anxiety (STAI-S)	31.79 (5.43)	29.54 (3.62)	.350
Trait anxiety (STAI-T)	41.08 (12.73)	39.54 (9.05)	.979



**Fig. 2 – Overlap of the fronto-insular lesions created by adding the MNI warped images over a single-subject T1 scan. The lesions were analyzed in terms of lesion overlaps with MRICron. Lesion overlap across patients was mapped on a standard brain. The colorbar indicates number of subjects sum overlap. Areas with greater lesion overlap across patients are shown brighter.**

of a sampled heartbeat. Next, they followed their own heartbeat with no external cues or feedback (intero condition). These two conditions provided a measure of audio-motoric performance and a cardiac interoceptive measure. The output variables considered were reaction times, number of correct responses (matched to a heartbeat within a heart rate-based time window; see [Supplementary Materials](#) for additional details), and interoceptive accuracy (a composite of the previous measures).

**3.1.2.3. EMOTION RECOGNITION MEASURES.** The patients and controls completed two computerized emotion recognition tasks: one involving visual facial stimuli, the *emotional morphing task* (Couto, Sedeno, et al., 2013; Hurtado, Haye, Gonzalez, Manes, & Ibanez, 2009) and another one employing verbal auditory stimuli, the *prosody test* (Couto, Sedeno, et al., 2013; Scott et al., 1997). In both cases we measured accuracy and reaction times.

The facial expression recognition task featured six basic emotions (happiness, surprise, sadness, fear, anger, and disgust) taken from the Pictures of Affect Series (Ekman & Friesen, 1976). Each stimulus was morphed for each prototype emotion and for a neutral state (Young et al., 1997) and was presented in twenty 500-msec frames. During the Emotional Morphing Task, the 48 morphed facial stimuli were randomly presented on a computer screen until the patient indicated a response on the keyboard. Participants were asked to respond as soon as they recognized the facial expression, and then to identify it from a forced choice list of six options. This task measures the accuracy of emotion recognition and reaction times.

The second task (Scott et al., 1997) comprised six disyllabic concrete nouns with neutral meaning selected from a larger sample of words used in previous studies (Couto, Sedeno, et al., 2013). These were produced with six different intonations conveying happiness, anger, fear, disgust, sadness, and a neutral emotion. The stimuli were presented binaurally. After each presentation, the patients viewed a forced-choice list of six emotions and chose the one they felt best described the word perceived.

**3.1.2.4. SOCIAL COGNITION MEASURES.** Low-level social cognition was assessed via the *Reading-the-Mind-in-the-Eyes* test, an instrument tapping theory-of-mind skills. This validated task was administered following previously reported procedures (Baez et al., 2012, 2013; Couto et al., 2014; Couto, Sedeno, et al., 2013; Manes et al., 2011). Participants were presented with 36 images, showing facial regions from the midway along the nose to just above the eyebrows, and they were asked to choose which of four words best described what the person in the picture was thinking or feeling. Task performance was measured by considering accuracy. For additional details on each of these tasks, see [Supplementary Data](#).

**3.1.2.5. NEUROLOGICAL AND NEUROPSYCHOLOGICAL ASSESSMENT.** The patients underwent a neurological examination. MRI lesions were visually inspected by two experts in clinical neuroimaging (BC and FM). Subsequently, the patients and control subjects were assessed with the neuropsychological and affective screening questionnaires, the HBD task, the emotion recognition tests, and the social cognition test.

## 3.2. Data analysis

### 3.2.1. Behavioral data analysis

Demographic data for each group were compared using independent samples student's *t*-tests for numerical variables and chi-square tests for categorical variables. Neuropsychological and experimental data were compared via Mann–Whitney tests for non-normally distributed data. All statistical analyses were performed using the IBM SPSS 22.0 software package.

### 3.2.2. Physiological data analysis

Electrocardiogram recordings during the HBD task were analyzed with *ad hoc* scripts, as follows: first, we extracted heartbeat peaks from the electrocardiogram signal with MATLAB's peakfinder function (Yoder, 2009); second, we tracked and assigned each electrocardiogram peak to the corresponding keyboard taps using a heart-rate-dependent

time window (HR < 69, window = 650 msec; HR > 69 and HR < 99, window = 700 msec; HR < 99, window = 750 msec); third, we considered the previous pairings and calculated reaction times and accuracy as previously described (Couto et al., 2014; Melloni et al., 2013; Sedeno et al., 2014).

### 3.3. Results

#### 3.3.1. Sociodemographic, clinical, and neuropsychological results

The groups exhibited no significant differences in age, gender, laterality or years of education. Analysis of neuropsychological data revealed no significant differences (see Table 6) in general cognitive state (MMSE), executive functions (IFS) or intelligence (WAT). Finally, no significant differences were found for depression (BDI), anxiety state (STAI-S) or trait anxiety (STAI-T).

#### 3.3.2. HBD

No significant accuracy differences emerged between patients ( $M = .54$ ,  $SD = .18$ ) and controls ( $M = .53$ ,  $SD = .26$ ) in the motor control condition of the HBD task ( $U = 81.0$ ,  $p = .938$ ,  $z = -.078$ ). However, in the interoceptive condition, accuracy was greater for controls ( $M = .38$ ,  $SD = .21$ ) than for patients ( $M = .23$ ,  $SD = .17$ ,  $U = 51.0$ ,  $p = .013$ ,  $z = -2.49$ ; see Fig. 3A).

#### 3.3.3. Emotion

Emotion recognition performance revealed impairments in the patient group. Total accuracy in the prosody task was significantly higher for controls ( $M = .71$ ,  $SD = .18$ ) than for patients ( $M = .56$ ,  $SD = .19$ ,  $U = 55.0$ ,  $p = .017$ ,  $z = -2.37$ ; see Fig. 3B). Regarding individual emotions, differences were found for happiness and disgust (see Supplementary Data). Similarly, in the emotional morphing task, patients ( $M = .73$ ,  $SD = .09$ ) were outperformed by controls ( $M = .83$ ,  $SD = .08$ ,  $U = 49.5$ ,  $p = .025$ ,  $z = -2.23$ ; see Fig. 3C). In particular, patients were impaired in the recognition of sadness (see Supplementary Data).

#### 3.3.4. Social cognition

Analysis of accuracy in the *Reading-the-Mind-in-the-Eyes* task showed that patients ( $M = .58$ ,  $SD = .11$ ) performed significantly worse than healthy controls ( $M = .75$ ,  $SD = .10$ ,  $U = 51.00$ ,  $p < .001$ ,  $z = -3.756$ ; see Fig. 3D).

In sum, we did not find robust evidence of impairment in general cognitive function, executive functions, or intelligence, in the patient sample. Also, their levels of anxiety and depression were similar to those of controls. Conversely, patients exhibited altered cardiac interoception and significant impairments in emotion processing and low-level social cognition. These results remain largely the same with a parametric analysis with corrections for multiple comparisons (see Supplementary Data).

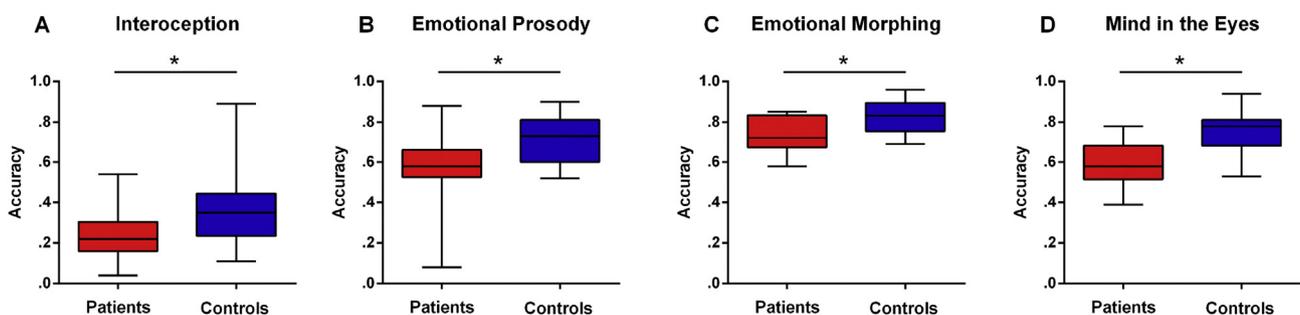
## 4. Discussion

At least since the Williams-Lange theory (Lange & James, 1967), body feelings and visceral signals have been considered to be integrated with emotions. Visceral neural sites related to both these processes – specifically, the anterior IC – have been repeatedly and independently implicated in interoception, emotions, and, more widely, in social cognition. In this work, we provided convergent meta-analytical and experimental evidence on the integration of such three domains in the aIC and its related functional networks.

### 4.1. Meta-analysis of fMRI literature

#### 4.1.1. Interoception

The meta-analysis of interoception studies revealed areas that are typically highlighted in relevant reviews. The areas with highest activation increases were the right aIC and ACC, two core structures in the interoceptive network (Craig, 2002, 2009b; Critchley et al., 2004; Pollatos, Schandry, et al., 2007). The detection of right-sided aIC activity has been reported in studies examining the subjective evaluation of one's physical condition (Craig, 2002; Critchley et al., 2004). Furthermore, the right-sided asymmetry appears to be associated with the nature of afferents. Stimuli such as cardiac perception, visceral perception, air hunger, and pain (as implemented in our meta-analysis) primarily activated the sympathetic afferents that project to the right aIC. Instead, stimuli that induce mainly parasympathetic arousal [i.e., the subjective sense of fullness (Stephan et al., 2003)] provide input to the left aIC (Craig, 2002; Kelly et al., 2012). This is in part consistent with a recent cardiac interoception meta-analysis showing a right hemispheric dominance for cardioception (Schulz, 2016). In contrast with our findings,



**Fig. 3 – Results for behavioral data comparisons. A. Interoception. B and C. Emotion recognition. D. Social cognition. Box-plot diagram shows first and third quartile (bottom and top of the box), the median (second quartile represented by the band inside the box), and the minimum and maximum of all of the data (ends of the whiskers). Statistical analysis revealed significantly worse performance in patients (red) than controls (blue) in all three domains.**

and also with a recent report using a lesion approach (Indira García-Cordero et al., 2016), ACC did not arise as a key structure. Schulz's study sought to reveal neural activity emerging only from tasks involving cardioceptive attentiveness. Thus, differences with the results of our interoception meta-analysis (which included other tasks besides cardioception) could be due to differential processing along interoceptive streams. Supporting this, it has been shown that cardiac interoception impairments can emerge due to focal insular damage, while white matter damage of ACC-insular connections may affect other interoceptive domains (Couto, Adolphi, Sedeño, et al., 2015). Moreover, different interoceptive dimensions present different neuroanatomical correlates (Indira García-Cordero et al., 2016). Thus, although the IC seems to be a critical region for interoception in general, ACC involvement would be dependent on the type or dimensions of interoceptive processing.

Also related to this network, we observed activity in the thalamus, a relay of the lamina-1-spino-thalamo-cortical pathway projecting physiological signals to the interoceptive network (Craig, 2002). Clusters were also identified in areas not typically linked to the interoceptive network (e.g., the inferior parietal lobe and the parahippocampal gyrus). Although these areas were more activated than expected by chance, this may be related to the differential task loads of the reviewed studies, suggesting that not all areas are necessary for interoception.

#### 4.1.2. Emotion

The meta-analysis of emotion studies showed widespread patterns of limbic, subcortical, and brainstem activation, which is consistent with other meta-analytic investigations of this domain (Lindquist et al., 2012; Phan, Wager, Taylor, & Liberzon, 2002, 2004; Wager, et al., 2008). Within our framework, the cluster observed in the IC and the ACC merit particular attention. A network comprising the IC, the ACC, the mPFC, and subcortical regions appears to be the prime candidate for the integration of interoception and emotions. This common ground is supported by several studies that suggest that we refer to our own bodily state when evaluating our emotional state (Dunn et al., 2010; Gu, Liu, Van Dam, Hof, & Fan, 2013; Pollatos et al., 2005a). Different models propose that integrating interoceptive stimuli and exteroceptive environmental stimuli in the aIC leads to the subjective experience of emotion (Craig, 2009b; Critchley, 2009; Gu, Hof, et al., 2013; Kurth et al., 2010; Terasawa et al., 2013). The crucial role of the ACC in emotion processing is broadly accepted (Etkin, Egner, & Kalisch, 2011; Lavin et al., 2013). In light of this background, our findings robustly support the view that the IC and the ACC are critical for interoceptive processes in emotional awareness Wager et al. (2008).

The present work did not discriminate among emotions in terms of valence. However, it is possible that negative and positive emotions could interact differently with the other two domains (interoception and social cognition). This area should be further explored in future studies.

#### 4.1.3. Social cognition

The social cognition meta-analysis results involved the bilateral STG (progressing to pSTS), the bilateral mPFC, the bilateral pSTS, the precuneus, and the right supramarginal gyrus. These findings are highly consistent with other studies that

investigated social cognition and identified what is widely known as the mentalizing network (Adolphs, 2009; Beer & Ochsner, 2006; Denny et al., 2012; Frith & Frith, 2007; Mar, 2011; Van Overwalle & Baetens, 2009). Moreover, the cluster located in the mPFC is consistent with previous findings (Denny et al., 2012; Frith & Frith, 2007), suggesting a role in meta-cognitive processes and activated when thinking about the mental states of oneself and others (Amodio & Frith, 2006; Frith & Frith, 2007). Additional clusters appeared in the ACC, which is recruited in the cognitive-evaluative form of empathy (Fan et al., 2011) and social cognition (Lavin et al., 2013). Additional clusters were identified in the thalamus, the left mid temporal gyrus, and the SFG. Mid temporal gyrus activation in our task may reflect the engagement of listening- and reading-related mechanisms. The left lateralization of these patterns supports this assumption, since language processing distinctively relies on the left hemisphere.

Relative to exhaustive meta-analyses on social cognition [e.g., (Schurz et al., 2014; Van Overwalle, Baetens, Marien, & Vandekerckhove, 2014)], our work includes fewer studies. However, these are focused on specific social domains, as we have deliberately excluded reports assessing high-level social cognition and other related processes (see [Supplementary Data](#) for a discussion on inclusion criterion #6). This study represents a challenging first attempt to explore the associations between social cognition and interoception. To render this aim attainable, we operationalized social cognition by means of its most fundamental and nuclear processes (namely, understanding that others have their own private beliefs and mental states). Future studies should sample dimensions of the social cognition domain more broadly.

#### 4.1.4. A convergent model of interoceptive, emotional, and social processing

As previously suggested (Garfinkel & Critchley, 2013; Uddin et al., 2014), the aIC is critical for the integration of internal sensations with emotional and social information. In our study, the results from the conjunction analysis for these three domains converged in the aIC and the right amygdala. This finding corroborates that, in healthy brains, both structures are related to the integration of bodily signals, emotions, and social processing. The amygdala has been proposed as a hub for social behavior (Adolphs, 2002; Hesse et al., 2016; Kennedy, Glascher, Tyszka, & Adolphs, 2009; Pessoa & Adolphs, 2010). In this sense, it could account for the aversive salience that is typically caused by the detection/awareness of bodily symptoms (Critchley & Harrison, 2013). Common activations were also observed in the right inferior frontal gyrus, the basal ganglia, and the medial ATL. In previous independent studies, these regions have been related to emotions or social behavior, but not to interoception. Nevertheless, recent network models of social cognition (Baez, Garcia, & Ibanez, 2016; Ibanez & Manes, 2012; Kennedy & Adolphs, 2012; Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005) ascribe critical importance to fronto-temporo-insular nodes, which highlight the role of the IC in the evaluative association of the internal milieu and external cues to provide a framework for social behaviors (Ibanez, Gleichgerrcht, & Manes, 2010; Ibanez & Manes, 2012; Kennedy & Adolphs, 2012). The aIC is thus a suitable hub for

orchestrating this association: it conveys a sense of the homeostatic status of the body (Craig, 2003) and it is ubiquitously engaged in affective-cognitive networks (Kelly et al., 2012; Kurth et al., 2010; Uddin et al., 2014).

This work represents a first step towards identifying the convergence of activation between the three domains in an effort to pinpoint the most directly related neural structures. In line with a frequent strategy in the neuroimaging meta-analysis literature (Lindquist et al., 2012, 2015; Vytal & Hamann, 2010), our database did not include contrasts reporting neural deactivations (see [Supplementary Information](#) for a detailed rationale for this exclusion). Problems concerning replicability and bias from small, high-variance studies merit careful attention when interpreting results. Jackknife leave-one-out procedures are often used to detect bias and pinpoint the studies that most contributed to data heterogeneity (Radua & Mataix-Cols, 2009). These procedures were not necessary in this case, since MKDA circumvents the risks above by treating CIMS rather than individual peaks as the unit of analysis, which prevents individual studies from driving the results (Buhle et al., 2014; Cacioppo et al., 2013; Denny et al., 2012; Lindquist et al., 2012, 2015; Mende-Siedlecki et al., 2013; Qin et al., 2012; Taylor et al., 2012; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012) (see [Supplementary Information](#) for an in-depth discussion). Finally, although our results reveal a number of regions known to play a role within a distributed network, future studies should address this directly by performing connectivity analyses.

## 4.2. Lesion study empirical evidence

### 4.2.1. Overall findings

Patients exhibited impaired cardiac interoception in our behavioral HBD task. Abundant research has previously related HBD task performance to the IC, ACC, and somatosensory cortices through different neuroimaging methods such as electroencephalography, functional and structural resonance imaging and intracranial recordings (Canales-Johnson et al., 2015; Critchley et al., 2004; Pollatos et al., 2005a). Since motor tracking abilities were spared, the patients' deficits seem to be purely interoceptive. These results confirm that the IC is relevant for cardiac interoception, as indicated in previous focal IC lesion studies (Couto, Adolphi, Sedeño, et al., 2015; García-Cordero et al., 2016; Khalsa et al., 2009). Patients also showed impaired emotion processing. These findings likely reflect damage to the bilateral amygdalae, the putamen, and the IC (right > left), regions which are largely recognized as participating in emotional processing networks (Adolphs, 2002; Couto, Sedeno, et al., 2013) and contextual social cognition (Baez, Kanske, et al., 2016; Baez, Morales, et al., 2016; Baez, Santamaría-García et al., 2016; Ibanez & Manes, 2012; Melloni et al., 2014; Sedeño et al., 2016). Social cognition impairments were expected and our meta-analytic results highlight the right pSTS and the bilateral aIC as key neuroanatomical candidates for these deficits. Future research could include a battery of both basic (RMET) and complex (e.g., faux pas, false beliefs) tasks in order to assess a broader spectrum of social cognition.

Executive functions have at least partial impact on any task, in proportion to features such as working memory load. Since these domains depend on the frontal lobe, they are difficult to control when patients feature vast and deep damage in such region (Miller & Cummings, 2007). Importantly, patients and controls in our study did not differ in general cognitive state or executive performance. Importantly, patients and controls in our study did not differ in general cognitive state or executive performance. This may be due to the location of stroke-induced lesions in our patient sample (largely fronto-insulo-temporal networks, with a major overlap in the IC, see [Fig. 2](#)). On the other hand, the possibility exists that between-group differences in cognitive function did not emerge due to low sample size. Countering this assumption, in our study the lack of robust differences in general cognitive and executive performance was accompanied by impairments in the domains of interoception, emotion and social cognition. In fact, other reports have shown impairments with similar or lower sample sizes (Baez et al., 2014; Camille et al., 2004; Couto, Adolphi, Sedeño, et al., 2015; Ell, Marchant, & Ivry, 2006; Fleming, Ryu, Golfinos, & Blackmon, 2014; Indira García-Cordero et al., 2016; Melloni et al., 2016; Muller, Machado, & Knight, 2002; Roca, Gleichgerrcht, Ibanez, Torralva, & Manes, 2013; Winkel et al., 2016). Moreover, other confounding factors, such as depression and anxiety, which have been controversial but nevertheless possibly related in some way to our domains of interest, did not differ between groups, highlighting the primary nature of the patients' deficits in interoception, emotion, and social cognition.

As a further assessment of the interrelation among these three domains, future studies could conduct correlation analyses to explore possible associations between behavioral performance patterns in emotion, social cognition, and interoception tasks. Also, future studies with greater sample sizes could conduct voxel-based lesion-symptom mapping (VLSM) analyses to assess the relationship between tissue damage and behavior, as well as correlation analyses between task performances.

### 4.3. Convergent meta-analytic and lesion evidence

The present study offered direct evidence for shared cortico-subcortical networks involving the insula for the processing of interoceptive, emotional, and social information. The association between interoception and emotions by virtue of the IC has been previously proposed based on indirect evidence (Critchley, 2009; Kurth et al., 2010; Pollatos, Gramann, & Schandry, 2007; Pollatos et al., 2005b; Terasawa et al., 2013). We confirmed this convergence by reviewing the joint activation of these three domains in published fMRI data. Specifically, the qualitative anatomical overlap comprised the right aIC, the basal ganglia, and fronto-temporal (medial ATL) nodes. In patients with insular damage, we found impaired cardiac interoception, emotional processing, and low-level social processing. This finding implies that the IC and its networks, including fronto-temporal nodes, play an important role in the common processing and most likely the integration of body signals, leading to the emergence of affective and social behaviors. This tripartite crosstalk has actually been previously proposed (Craig, 2009b; Fukushima, Terasawa, & Umeda, 2011; Garfinkel & Critchley, 2013; Uddin

et al., 2014). Hence, we suggest that the overlapping fronto-insulo-temporal networks may offer neural grounding for the theoretical connection between affective and social functions, as both would emerge under the influence of the bodily sensation. This hypothesis deviates from the classical conception of emotion processing outlined by Cannon and Bard (LeDoux, 2003), according to which the hypothalamus would index emotional relevance, the expression of emotion would be mediated by signals from the hypothalamus to the brainstem, and projections from the hypothalamus to the cortex would subservise conscious experience of emotion. It also highlights the relevance of bottom-up modulation of higher processes accounting for complex social behavior and, even more, their potential interaction with other cognitive-perceptual mechanisms, such as withdrawal or the urge to consume in addictions (Bechara & Naqvi, 2004). Furthermore, it may illuminate the brain mechanisms underlying the psychopathology of clinical affective disorders, such as anxiety, panic or social phobia, in which body signals and cognitive processes might be tightly intermingled.

## 5. Conclusion

We have provided meta-analytic and experimental evidence of the behavioral and neuroanatomical convergence of interoceptive, emotional, and social cognitive processes. Such circuits are mainly located in the IC and distributed throughout associated fronto-temporal nodes. These networks play a relevant role in accomplishing behaviors related to these three domains.

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## Author's contributions

FA, BC, AI designed the study; BC, FM assessed clinical, neuropsychological and MRI evaluations; BC, FR, JL collected data; FA, BC, FR, JD, MS, FM analyzed the data; FA, BC, FR, AI wrote the manuscript; All authors contributed to revising the final version of the manuscript.

## Disclosure

The authors declare that they have no conflict of interest.

## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cortex.2016.12.019>.

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