



## Neural substrates of interoceptive sensibility: An integrated study in normal and pathological functioning

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### ABSTRACT

In early studies interoception strictly referred to the awareness of visceral sensations, but recent theories have expanded this concept to denote the ongoing status of the body, including somatosensory feelings. Here, we integrated data from normal and pathological functioning to disclose neural underpinnings of interoceptive sensibility, taking into account the crucial distinction between visceral and somatosensory feelings. Twenty-seven healthy young individuals underwent structural MRI (including T1w images and DTI). Voxel-wise analyses of the gyrification index (GI) and fractional anisotropy (FA) data were performed to assess the relation between interoceptive sensibility and surface morphometry and anatomical connectivity. Thirty-three unilateral brain-damaged patients took part in this study for Voxel-Based Lesion-Symptom Mapping (VLSM) and track-wise hodological lesion-deficit analysis (TWH). All participants completed the Self-Awareness Questionnaire (SAQ), a self-report tool assessing interoceptive sensibility of visceral (F1) and somatosensory feelings (F2). Tract-Based Spatial Statistics showed that F2 was positively associated with FA in the bilateral anterior thalamic radiation, corticospinal tract, cingulum, forceps, inferior longitudinal, fronto-occipital, superior longitudinal, and uncinate fasciculi; no significant association was detected for F1. However, F1 was positively associated with GI in the left anterior cingulate cortex. VLSM showed that F1 mainly relies on the right posterior insula, whereas F2 is related mostly to subcortical nuclei and surrounding white matter in the right hemisphere. Accordingly, patients with disconnection of the anterior thalamic projection, corticospinal tract, inferior fronto-occipital, inferior longitudinal, uncinate and superior longitudinal fasciculus III showed lower scores on F2. Overall, results support the dissociation between interoceptive sensibility of visceral and somatosensory feelings.

### 1. Introduction

Interoception has been described as “the body-to-brain axis of sensation” (Garfinkel et al., 2015), in which information from the body allows for the subjective evaluation of one’s state, namely ‘how you feel’ (Craig, 2002). It involves the processing of stimuli such as heartbeat, thirst, dyspnea, ‘air hunger’, sensual touch, itch, warmth, or the distension of the bladder, and it is classically counterposed with exteroception, that concerns the perception of stimuli located outside the

body (Craig, 2002, 2009; Koeppe et al., 2020; Nord and Garfinkel, 2022).

Interoception is a multi-dimensional construct that can be operationalized along three main dimensions as follows (Garfinkel and Critchley, 2013). Interoceptive accuracy corresponds to the performance on objective behavioral tasks, such as heartbeat detection tasks; interoceptive sensibility, namely, self-evaluated assessment of subjective interoception, tested using interviews and questionnaires; finally, interoceptive awareness is the metacognitive awareness of interoceptive

*Abbreviations:* F1, interoceptive sensibility of visceral feelings; F2, interoceptive sensibility of somatosensory feelings.

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accuracy, that is the correspondence between objective interoceptive accuracy and subjective report (Garfinkel et al., 2015).

The insular cortex is considered the main hub of the interoceptive network (Craig, 2002). Sensory representation of the feelings arising from one's own body is organized according to an integrative progression from the posterior to the anterior portion of the insular cortex: first, each representation is organized somatotopically in the dorsal-posterior insula; these primary representations provide the initial neural template for the representation of any feeling. Thus, the interoceptive image coming from the dorsal posterior insula is abstracted and integrated with information coming from other interoceptive and sensory systems in the middle insula, which is intimately intertwined with other key nodes of the homeostatic control network in the brain (e.g. hypothalamus, amygdala, anterior cingulate and ventral striatum). Finally, a "coherent representation of all salient conditions across all relevant systems at each immediate moment of time" (Craig, 2010, p. 569), that is crucial for human awareness, develops in the anterior insula. Such a representation underpins the development of the "sentient self" and allows the subjective evaluation of one's own conditions. Accordingly, whereas the dorsal posterior insula has been found to be activated by different kinds of bodily signals, including heat stimuli, itch, thirst, hunger and affective touch (Craig, 2002; Björnsdotter et al., 2009), the prominent role of the anterior insular cortex in bodily awareness is further demonstrated by the relation between the grey matter volume of this portion of the insular cortex and higher-order interoceptive measures (i.e., interoceptive accuracy and sensibility measures; Critchley et al., 2004).

Neural correlates of interoception have been widely investigated in humans using functional magnetic resonance imaging (fMRI). In a seminal fMRI study in which participants performed an interoceptive heartbeat detection task, insular and somatosensory cortices have been found to play a central role in subjective feeling states arising from representations of bodily sensations; the anterior cingulate cortex, ventromedial prefrontal, and lateral prefrontal cortices contributed to the development of "a contextual second-order representation of the self" (Critchley et al., 2004, p. 192). Also, in the same study, the grey matter volume in the right frontal operculum and anterior insular cortex correlated with the subjective ratings of visceral awareness as measured with a body perception questionnaire (i.e. interoceptive sensibility). A recent meta-analysis of fMRI studies found that, overall, interoception (possible differences between different interoceptive dimensions were not considered in this study) relies on a network of areas spanning from the frontal to the parietal and temporal lobe, including the left inferior parietal gyrus, the left medial frontal gyrus, the right thalamus, the right postcentral and precentral gyrus, the cingulate gyrus (middle and anterior cingulate cortex), the right midbrain and the right medial temporal gyrus (Salvato et al., 2020).

The boundary between interoceptive and exteroceptive sensations becomes less clear when proximal senses, such as touch or taste, are considered (Herman et al., 2021). Indeed, information coming from senses such as touch, smell, and taste requires close proximity to the body; these sensory channels thus differ from exteroceptive sensory modalities, such as audition and vision, because they respond more directly to bodily needs and are associated with emotional processing (Couto et al., 2015; Herman et al., 2021). Accordingly, most recent definitions of interoception highlight the role of different kinds of bodily signals in maintaining homeostatic control, and have broadened to include signals related to tickle, affective touch and skin temperature, that follow different pathways from signals originated from exteroceptive information, and are centrally carried by fibers ascending the same spinothalamic tract followed by visceral signals (Craig, 2002; Critchley and Garfinkel, 2017; Nord and Garfinkel, 2022).

Two recent functional neuroimaging studies directly compared processing of stimuli coming from visceral organs to that of interoceptive stimuli perceived through more peripheral sensory organs. Stern et al. (2017) found that interoceptive processing of visceral stimuli (i.e. heartbeat) yielded greater activity than interoceptive processing of

proximal exteroceptive stimuli (i.e. skin temperature) in the supplementary motor area, the dorsal anterior cingulate cortex, the middle and the anterior insular cortex, the precentral and inferior frontal gyri; instead, the opposite contrast showed that the processing of proximal exteroceptive stimuli yielded to greater activity than the processing of visceral stimuli in the right posterior insula, the superior regions of the somatosensory cortex, the occipital cortex, the temporal regions, and the limbic areas (including the hippocampus and the amygdala). A more recent study by Herman and colleagues (2020) found that interoceptive processing of visceral (e.g. cardiac events) and proximal exteroceptive stimuli (e.g. tactile events) roughly overlapped in the insular cortex, in the parietal and the occipital lobes; however, connectivity between the right insular cortex and the occipito-parietal regions was greater during conscious detection of cardiac events as compared with somatosensory sensations.

Preliminary results in brain-damaged patients support the idea that interoceptive processing of visceral and proximal exteroceptive stimuli is dissociated. Couto et al. (2015) described two rare patients with focal lesions of the insular cortex or its subcortical tracts, finding that processing of visceral stimuli (i.e. heartbeat) was impaired in the former, whereas processing of proximal exteroceptive stimuli (i.e. taste, smell, and pain recognition) was impaired in the latter. In a recent group-study, Raimo et al. (2020) found that patients with a lesion in the right hemisphere and extrapersonal and/or personal neglect had significantly lower interoceptive sensibility of visceral sensations compared to healthy controls and patients with a lesion in the left hemisphere; instead, they showed similar interoceptive sensibility toward proximal exteroceptive sensations.

Although these findings suggest that differences exist between brain networks supporting interoceptive processing of signals coming from visceral organs and from proximal senses, only a few interoceptive modalities have been investigated in most previous studies (Couto et al., 2015; Stern et al., 2017; Herman et al., 2021). Moreover, whereas these studies assessed interoceptive attention or detection (Stern et al., 2017; Herman et al., 2021-), brain networks supporting interoceptive sensibility for different kinds of bodily signals have not been well characterized so far. Thus, here we integrated data collected in healthy participants with those on brain-damaged patients to disclose possible similarities and differences between neural correlates of interoceptive sensibility of visceral and somatosensory feelings. To this aim, in Study 1 we performed surface-based morphometry and TractBased Spatial Statistics (TBSS) analyses in healthy individuals to investigate structural brain correlates and white matter contribution to interoceptive sensibility towards visceral and somatosensory feelings. Based on previous evidence that individual differences in high-level cognitive processes in healthy individuals - including those in awareness and emotional control (Luders et al., 2012) - may be specifically in relation with measures of cortical folding (Gautam et al., 2015; Gregory et al., 2016), here we assessed the relation between interoceptive sensibility of visceral and somatosensory sensations and cortical gyrification. Also, since the results of Study 1 revealed a significant contribution of several tracts to interoceptive sensibility toward somatosensory feelings, we further explored the contribution of the disconnection of these tracts in brain-damaged patients, by using a track-wise hodological analysis (TWH; Study 2). Since no study has investigated neural correlates of interoceptive sensibility of visceral and somatosensory feelings in brain-damaged patients, a voxel lesion-symptom mapping (VLSM) analysis was also conducted in Study 2. Based on previous studies and results, we hypothesized that patients with a lesion to the insular cortex showed lower scores on interoceptive sensibility (Grossi et al., 2014) and that a possible dissociation may occur between visceral and somatosensory feelings (Raimo et al., 2020). Right-hemispheric dominance for interoceptive neural networks was expected as well (Raimo et al., 2020; Grossi et al., 2014).

## 2. Study 1: interoceptive sensibility in healthy individuals

### 2.1. Method

#### 2.1.1. Participants

Twenty-seven healthy volunteers (mean age: 25.518 years, SD = 3.355; 15 females) took part in the study. The sample size was determined based on previous studies using surface-based morphometry and Tract-Based Spatial Statistics (Wang et al., 2018; Xiao et al., 2015; Yu et al., 2016; Lin et al., 2012). All participants were right-handed and had a normal audition and normal or corrected-to-normal vision. The study was designed following the principles of the Declaration of Helsinki and was approved by the local ethical committee. Informed consent was obtained from all individual participants included in the study.

### 2.2. Procedure

#### 2.2.1. Assessment of interoceptive sensibility

All participants completed the Self-Awareness Questionnaire (SAQ; Longarzo et al., 2015), a self-report instrument that assesses the frequency of common bodily feelings. To the best of our knowledge, this is the only instrument, psychometrically validated for use with Italian individuals, that allows to investigate interoceptive sensibility of both visceral and somatosensory sensations, also allowing to consider different sources of interoceptive information (e.g. heart, stomach, bladder, skin, pain perception).

The SAQ is composed of 35 items that are rated on a 5-point Likert scale. Total SAQ score ranges between 0 and 140, with lower scores meaning lower interoceptive sensibility. The SAQ has a 2-factor structure: Factor 1 (F1, calculated on items 3, 6, 7, 12, 13, 17, 19, 21, 23, 26, 27, 30, 32, 33, 35) is mainly associated with visceral sensations (e.g., "I feel a burning sensation in my stomach"), whereas Factor 2 (F2, calculated on items 4, 9, 10, 11, 14, 15, 16, 18, 24, 25, 28, 30, 31, 34) mainly reflects sensibility to somatosensory sensations (e.g., "I feel pins and needles") (Longarzo et al., 2015). Average score in the sample included in this study was 9.93 (SD = 5.54) for F1 and 13.52 (SD = 5.95) for F2. SAQ score were not significantly different between male and female participants (F1:  $t = 1.751$ ,  $p = 0.092$ ; F2:  $t = 0.206$ ,  $p = 0.839$ ).

### 2.3. Image acquisition

For each participant, we collected a three-dimensional, high-resolution T1-weighted structural image (TR = 13 s, TE = 5.8 ms, flip angle = 8 deg,  $256 \times 228$  image matrix,  $0.5 \times 0.5$  mm in-plane resolution, 342 contiguous 0.5 mm thick sagittal slices, acquisition time: 483 s) and a diffusion-weighted image, acquired using echo-planar imaging (TE/TR: 77/6700 ms, matrix:  $112 \times 110$ , 60 axial slices, voxel size:  $2 \times 2 \times 2$  mm, phase-encoding direction: AP, acquisition time: 580 s) with 64 isotropically distributed orientations for the diffusion sensitizing gradients at a b value of  $1000 \text{ s/mm}^2$  and 1 b = 0 images. Images were collected using a Philips Achieva scanner, operating at 3T. Head movements were minimized with mild restraint and cushioning.

### 2.4. Image analyses

#### 2.4.1. Surface-based morphometry

A voxel-wise surface-based morphometry analysis was performed on T1-weighted images, using the Computational Anatomy Toolbox (CAT12), an extension to SPM12. T1 images were manually checked for scanner artefacts and gross anatomical abnormalities. The images were then normalized using high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) normalization and segmented into grey matter (GM), white matter and cerebrospinal fluid (CSF). Gyrfication Index (GI) was estimated in native space before any spatial normalization, based on absolute mean curvature (Luders et al., 2006). The extraction of the cortical surface resulted in the

construction of a mesh of the central surface; the local absolute mean curvature of this central surface was then calculated averaging the mean curvature values from each vertex point within 3 mm from a given point. The GI maps were smoothed using a 20-mm FWHM kernel. A multiple linear regression analysis was then performed at the second level using scores on factors F1 and F2 on the SAQ as predictors.

#### 2.4.2. DTI analysis

DTI data were preprocessed using ExploreDTI and analyzed using the FMRIB Software Library (FSL 4.1.7) for Tract-Based Spatial Statistics (TBSS; Smith et al., 2004). DTI images were corrected for subject motion and eddy current induced geometric distortions using ExploreDTI; then, tensor was estimated at each voxel, visually inspecting for possible errors. FA images were finally exported and used in the group analysis. A voxel-wise analysis of the FA data was performed using TBSS (Smith et al., 2006). First, all subjects' FA data were aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton, and the resulting data were used in permutation-based nonparametric analyses. Skeletonized FA values were thresholded at  $FA > 0.20$  before analyses. We then performed two multiple regression analyses on whole-brain skeletonized FA, with scores on factors F1 and F2 of the SAQ as predictors. Nonparametric permutation-based analyses were performed with 10,000 permutations, and results were assessed for significance setting alpha at 0.05 corrected for multiple comparisons using threshold-free cluster enhancement (Smith and Nichols, 2009).

### 2.5. Results

#### 2.5.1. Surface-based morphometry

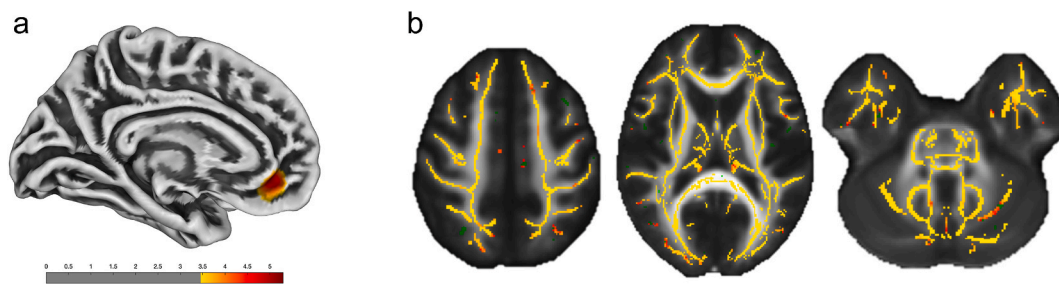
A positive association was found between scores on F1 of the SAQ and GI in one cluster in the left anterior cingulate gyrus (peak at MNI:  $-10, 40, -7$ ) ( $t(1,24) = 3.466$ ,  $p_{FWE} < 0.05$  at the cluster level;  $p_{uncorrected} < 0.001$  at the peak level) (Fig. 1a). No significant association was detected between scores on F2 and GI.

#### 2.5.2. DTI analysis

No significant association was detected between scores on F1 and FA measures. Conversely, results of the TBSS analysis showed a significant positive association between scores on F2 and FA in the bilateral anterior thalamic radiation, corticospinal tract, cingulum, and forceps, as well as in the bilateral inferior fronto-occipital, uncinate, inferior and superior longitudinal fasciculus (Table 1 and Fig. 1b).

### 2.6. Interim discussion

Results of Study 1 showed relevant differences in the association of interoceptive sensibility towards visceral and somatosensory feelings with individual variations in cortical morphometry and anatomical connectivity. Specifically, we found that only individual variations in interoceptive sensibility towards visceral sensations were associated with differences in gyrfication in the left anterior cingulate cortex. Moreover, whereas no association was found between interoceptive sensibility towards visceral feelings and differences in white matter structure, interoceptive sensibility towards somatosensory sensations significantly predicted fractional anisotropy in a wide network including the thalamus, the anterior cingulate, the prefrontal and orbitofrontal cortex, premotor and somatosensory areas, as well as superior and medial temporal, superior and posterior parietal and occipital regions. To our knowledge, this is the first study specifically investigating the relation between white matter structure and interoceptive sensibility in healthy participants. Present findings thus suggest that whereas



**Fig. 1.** Results of Study 1. a) Results of the voxel-wise analysis on cortical gyrification. Left-hemisphere cluster showing a significant association between gyrification index and scores on F2 of the SAQ. The color bar represents t-statistics. b) Results of the TBSS analysis. Mean fractional anisotropy skeleton (showed in green) overlaid on the mean fractional anisotropy map in the axial plane. Voxels which values of fractional anisotropy were significantly predicted by scores on F2 (interoceptive sensibility of somatosensory feelings) are overlaid in red-yellow.

**Table 1**

Results of the TBSS analysis. For voxels which values of fractional anisotropy was significantly predicted by scores on F2, we report the mean probability (expressed as a proportion) of being a member of a specifically labelled region according to the JHU White-Matter Tractography Atlas (Hau et al., 2016; Schwartz et al., 2012). R = Right hemisphere; L = Left hemisphere.

Tract	<i>p</i>
Anterior thalamic radiation L	1.265260
Anterior thalamic radiation R	1.087710
Corticospinal tract L	0.715724
Corticospinal tract R	0.712630
Cingulum (cingulate gyrus) L	0.302692
Cingulum (cingulate gyrus) R	0.136356
Cingulum (hippocampus) L	0.098290
Cingulum (hippocampus) R	0.123533
Forceps major	0.816236
Forceps minor	1.942040
Inferior fronto-occipital fasciculus L	1.200270
Inferior fronto-occipital fasciculus R	1.323510
Inferior longitudinal fasciculus L	1.095710
Inferior longitudinal fasciculus R	0.821374
Superior longitudinal fasciculus L	1.349680
Superior longitudinal fasciculus R	1.147160
Uncinate fasciculus L	0.433639
Uncinate fasciculus R	0.231937
Superior longitudinal fasciculus (temporal part) L	0.603401
Superior longitudinal fasciculus (temporal part) R	0.411381

individual variations in the sensibility towards visceral feelings are related to differences in cortical morphometry in one key region within the interoceptive network, namely the anterior cingulate cortex, somatosensory feelings are associated with differences in anatomical connectivity between nodes of the same network.

Notably, the anterior thalamic radiations link the anterior thalamic nuclei to the anterior cingulate cortex (Jang and Yeo, 2013), which, together with the insula (to which it is functionally and structurally connected), is acknowledged as a key region in the interoceptive network (Critchley et al., 2004; Craig, 2009). More specifically, this region has been proposed to be pivotal for motivational aspects of interoceptive processing (Craig, 2002), and, more generally, to act as an integrative hub for bodily perception (Kleckner et al., 2017).

These findings are also in line with the results of a relation between increased FA in the cingulum, likely in its anterior cingulate/rostral portion (Heilbronner and Haber, 2014; Bubb et al., 2018). Interestingly, also FA in the parahippocampal/temporal portions (Heilbronner and Haber, 2014; Bubb et al., 2018) of the cingulum was related to F2, in line with recent evidence that the hippocampus may be implicated in interoceptive processing, possibly supporting contextual memory for the internal state of the organism (Lathe et al., 2020; Yoo et al., 2017).

Concerning the corticospinal tract (CST), it originates from different parietal and frontal areas, including the premotor cortex, the supplementary and pre-supplementary motor area, the primary motor and

primary somatosensory cortex (Archer et al., 2018), passing through the posterior limb of the internal capsule. This bundle represents the most direct pathway for motor control since spinal motoneurons are directly targeted by neurons in the CST; however, it has been recently highlighted that the CST also participates in the modulation of sensory feedback, targeting interneurons in the dorsal horn that are involved in light-touch perception, and that integrate such sensory signals with motor information coming from the cerebellum and primary motor regions (Bourane et al., 2015; Moreno-López et al., 2016).

The branches of the superior longitudinal fasciculus (SLF), instead, connect different portions of the frontal and parietal cortex; specifically, the superior branch (SLF I) connects the superior frontal gyrus to the superior parietal lobule and the precuneus, the middle branch (SLF II) links the middle frontal gyrus to the angular gyrus, whereas the lower branch of the SLF (SLF III) connects the inferior frontal gyrus to the supramarginal gyrus (Kamali et al., 2014; Rojkova et al., 2016). Interestingly, the bilateral supramarginal gyrus, as well as the left superior parietal lobule, the left precuneus, and the right angular gyrus, are consistently activated by tasks entailing the use of different types of body representation, namely both those oriented to action (bilateral supramarginal gyrus, left superior parietal lobule and precuneus, right angular gyrus) and those not-oriented to action (left superior parietal lobule, right supramarginal gyrus) (Di Vita et al., 2016). Present findings are thus in line with the possibility that variations in fractional anisotropy in the SLF may be in relation to differences in the anatomical connectivity between parietal regions supporting body processing, and prefrontal regions, that may correspond to variations in body awareness and integration of somatosensory information (Fox et al., 2014).

In a similar vein, the inferior fronto-occipital fasciculus connects the occipital pole, the lingual gyrus, the inferior and middle occipital gyri to the inferior, middle, and superior frontal gyrus, as well as to the orbital gyrus (Rojkova et al., 2016; Wu et al., 2016; Sarubbo et al., 2013), stemming between the posterior part of the putamen and the claustrum (Hau et al., 2016). The inferior longitudinal fasciculus, instead, connects extrastriate visual association areas to lateral and medial anterior temporal regions, including the parahippocampal gyrus and amygdala (Catani et al., 2003), and it has been previously implicated in object recognition and emotional processing (Herbet et al., 2018), as well as in visuo-haptic processing (Lee Masson et al., 2017). Finally, the uncinate fasciculus links the parahippocampal gyrus, the amygdala, and the temporal pole, by passing through the anterior floor of the external capsule between the insula and the putamen, to the frontal lobes, and specifically to the orbital cortex, the cingulate gyrus (BA32) and frontal pole (Rojkova et al., 2016; Catani and Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2012), in line with its proposed role in emotion regulation (Schmahmann et al., 2008; Mohamed Ali et al., 2019). It is thus possible that the relation between higher interoceptive sensibility towards somatosensory sensations and increased FA in these tracts may reflect increased integration of visual with somatosensory and emotional information. This would be in line with evidence that an

increased focus on somatic (skin temperature) compared to visceral (heartbeat) sensations entails the activation of the lateral occipital cortex (Stern et al., 2017), and with a broad literature suggesting that visual information affects the representation of one's body at multiple stages (see Azañón et al., 2016, for a review).

Interestingly, alterations of white matter pathways corresponding to those reported above, namely the internal capsule, the corticospinal tract, and the inferior fronto-occipital fasciculi, have been reported in chronic fatigue syndrome (Finkelmeyer et al., 2017), that has been associated with an altered representation or processing of interoceptive signals (Stephan et al., 2016; Bonaz et al., 2021). Also, increases in fractional anisotropy in the corticospinal tract, the superior longitudinal fasciculus, the uncinate fasciculus, and the forceps minor have been reported after different types of mindfulness training (Hölzel et al., 2016; Luders et al., 2012; Tang et al., 2010; Fox et al., 2014), that have been shown to generally improve body awareness and the maintenance of attention to internal and external stimuli (Hölzel et al., 2011).

Overall, results of the TBSS analysis suggest that individual differences in interoceptive sensibility towards somatosensory stimuli may be in relation to white matter variations in pathways mediating the integration of somatomotor and visual information with that related to body awareness and motivational/emotional salience.

### 3. Study 2: interoceptive sensibility in patients with brain damage

#### 3.1. Method

##### 3.1.1. Participants

Thirty-three patients (age: mean 57.667; SD 13.423; 13 females) with post-acute (days since stroke: mean 50.545; SD 33.995) unilateral lesion (6 with a lesion in the left hemisphere and 27 with a lesion in the right hemisphere) took part in this study. Twenty-three suffered from an ischemic stroke, whereas 10 suffered from hemorrhagic stroke.

Patients were recruited from a population of in-patients at the IRCCS Fondazione Santa Lucia (Rome), from May 2017 and May 2019. The present sample partially overlaps with that of previous studies from our group (Raimo et al., 2020; Boccia et al., 2020; Teghil et al., 2020).

The sample size was determined based on previous similar studies using voxel lesion-symptom mapping (Di Vita et al., 2019; Grossi et al., 2014) and inclusion/exclusion criteria were determined a priori, as follows. None of the participants had a previous history of psychiatric and/or neurological disorders; also, none of them showed cognitive decline and/or deficit in abstract reasoning. Among the patients, only those suffering from vascular stroke (hemorrhagic and/or ischemic) were included. To exclude the presence of cognitive decline, patients underwent the Mini Mental State Examination (MMSE) (Magni et al., 1996; Measso et al., 1993).

The study was carried out following the Declaration of Helsinki and Ethical approval was obtained from the Ethics Committee of the Fondazione Santa Lucia IRCCS (Rome). Informed written consent was obtained from all participants.

#### 3.2. Procedure

All patients completed the SAQ, as for Study 1; F1 and F2 scores were computed as well. Average score was 6.88 (SD = 5.76) for F1 and 10.48 (SD = 4.51) for F2. SAQ scores were not significantly different between male and female participants (F1:  $t = 0.893$ ;  $p = 0.379$ ; F2:  $t = 0.357$ ;  $p = 0.724$ ).

#### 3.3. Neuroimaging acquisition and lesion analyses

All patients had clinical MRI (N = 18) or CT (N = 15) scan examination. Lesion mapping was performed using MRICron, rotating the MNI template from the MNI space to the subject space. The lesion was then

manually drawn on the reoriented template and subsequently taken back to the MNI space by using the inverse rotation (Doricchi and Tomaiuolo, 2003). Then, lesions were included in a topological lesion deficit analysis, namely Voxel Lesion Symptom Mapping (VLSM) analysis, to analyze the relation between tissue damage and behavior, on a voxel-by-voxel basis (Bates et al., 2003). Since the sensibility of the VLSM analysis for injury along long white matter tracts, which can per se lead to behavioral impairment, is poor (Gleichgerricht et al., 2017), and due to our experimental hypotheses arising from the results of Study 1, we performed a track-wise hodological lesion-deficit analysis (TWH; Thiebaut de Schotten et al., 2014). Combining VLSM and TWH allows for a comprehensive investigation of the grey and white matter lesion correlates of interoceptive sensibility.

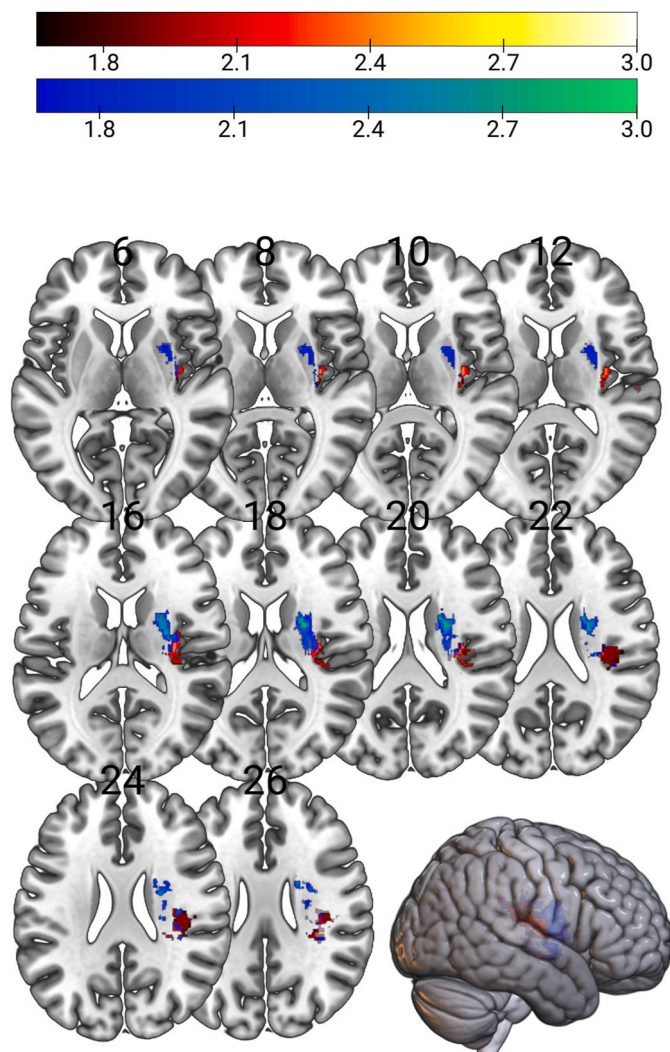
We performed a VLSM (Bates et al., 2003) through the Non-Parametric Mapping software (NPM; Rorden et al., 2007). F1 and F2 scores entered the VLSM analysis, with a non-parametric Brunner Munzel (BM) test for continuous variables and 2000 permutations. Only voxels damaged in at least 15% of the sample were considered. Multiple comparison issues were accounted for by using False Discovery Rate (FDR) correction ( $p < 0.05$ ).

Considering the results of Study 1 and the involvement of white matter suggested by VLSM results for F2 (see the Result section below), we further explored the white matter contribution to interoceptive sensibility of somatosensory feelings through a TWH. We used Tractotron, as part of the BCB toolkit (<http://www.brainconnectivitybehaviour.eu/>), to identify the tracts that could be affected by the lesion of each patient. Tractotron automatically computes the overlap of each segmented lesion with the map of the tracts. We mapped the lesion from each patient onto tractography reconstructions of white matter pathways obtained from a group of healthy controls (Rojkova et al., 2016). A tract was considered disconnected when a lesion overlapped with a voxel that belonged to this tract with a probability that was above chance level (probability  $> 0.5$ ). TWH was performed on tracts disconnected in at least 40% of patients, among those disclosed by Study 1. Patients were grouped as disconnected if the probability of the tract to be disconnected exceeded 50%; otherwise, they were classified as spared. F2 scores of spared and disconnected groups of patients were compared with those of 36 healthy individuals from our previous studies (Raimo et al., 2020), matched for age ( $t_{76} = 0.346$ ;  $p = 0.635$ ), gender ( $\chi^2 = 3.249$ ;  $p = 0.071$ ) and education ( $t_{76} = 1.424$ ;  $p = 0.079$ ), using a Kruskal-Wallis H. Post hoc pairwise comparisons for significant effects were performed by using the Mann-Whitney test (significance level was set at  $p = 0.025$  since we performed two sets of comparisons, namely spared vs. controls and disconnected vs. controls).

#### 3.4. Results

Results of the VLSM showed that voxels of lesions mainly located in the right posterior insula were significantly associated with F1 (Fig. 2). Specifically, patients with lesions in the posterior insular cortex, only marginally extending to the putamen and the surrounding white matter, showed lower scores on F1. Instead, F2 was mainly related to voxels in the putamen (Fig. 2), also extending to the surrounding white matter (further details about white matter contribution are widely reported below, in the results of the TWH analysis); patients with lesioned voxels in this region showed lower scores on F2.

In Study 1, we found that several white matter tracts, in both hemispheres, were associated with F2. Considering only tracts damaged in at least 40% of patients, among those associated with F2 according to the results of Study 1 – namely, Anterior Thalamic Projections, Cortico Spinal Tract, Inferior Fronto Occipital fasciculus, Inferior Longitudinal, and Superior Longitudinal Fasciculus III, and Uncinate Tract in the right hemisphere – we tested whether patients (with spared or disconnected tract) differed from controls. We found a significant main effect of the group (Fig. 3) in all the investigated tracts (Anterior Thalamic Projections: Kruskal-Wallis  $H = 9.155$ ,  $p = 0.010$ ; Cortico Spinal Tract:



**Fig. 2.** Results of the VLSM analysis. Voxels of lesions associated with interoceptive sensibility of visceral feelings are showed in red-to-yellow patches. Voxels of lesions associated with interoceptive sensibility of somatosensory feelings are showed in blue-to-green patches.

Kruskal-Wallis  $H = 8.760$ ,  $p = 0.013$ ; Inferior Fronto Occipital fasciculus: Kruskal-Wallis  $H = 7.063$ ,  $p = 0.029$ ; Inferior Longitudinal fasciculus: Kruskal-Wallis  $H = 7.063$ ,  $p = 0.029$ ; Superior Longitudinal Fasciculus III: Kruskal-Wallis  $H = 6.718$ ,  $p = 0.035$ ; Uncinate Tract: Kruskal-Wallis  $H = 8.129$ ,  $p = 0.017$ ). Post hoc pairwise comparisons between patients with spared tracts and controls failed in finding significant effects (all  $ps > 0.080$ ). Instead, patients with disconnected tracts showed lower scores on F2 (all  $ps < 0.019$ ).

### 3.5. Interim discussion

Overall the results of the VLSM analysis strongly support the idea of a neural segregation between interoceptive sensibility of visceral and somatosensory feelings. Indeed, we found that interoceptive sensibility towards visceral and somatosensory feelings was associated with lesions in different regions: the former was associated with a lesion in the right posterior insular cortex, the latter with a lesion in the right subcortical structures (i.e. putamen) and surrounding white matter. Accordingly, TWH analysis revealed a significant contribution of white matter disconnection in the right hemisphere to interoceptive sensibility of somatosensory feelings. This pattern of results is consistent with the previous report by Couto et al. (2015), in which lesions in the insular

cortex and subcortical structures differently affected internal signal processing (i.e. heartbeat detection task) and processing of external sensations arising from peripersonal space (i.e. taste, smell, pain recognition task), respectively.

Finding a significant association between lesions in the insular cortex and interoceptive sensibility of visceral feelings is consistent with previous data on insular contribution to interoception. Indeed, the insular cortex has been widely demonstrated as the primary site of viscerosensory cortical representation (Critchley and Harrison, 2013). A previous study found that lesions in the insular cortex, the amygdala, and the putamen were associated with lower scores on an interoceptive feelings questionnaire (Grossi et al., 2014). We further expand over this result, providing evidence that the insular cortex is strictly associated with interoceptive sensibility towards visceral feelings, whereas the putamen is strictly associated with interoceptive sensibility towards somatosensory feelings. Interestingly, white matter disconnection in the Uncinate Fasciculus, Superior Longitudinal Fasciculus III, Inferior Longitudinal Fasciculus, Inferior Frontal Occipital Fasciculus, Corticospinal Tract, and Anterior Thalamic Projection yielded to a significant difference in interoceptive sensibility of somatosensory feelings as well: patients with disconnection in abovementioned tracts showed lower scores than controls and patients with spared tracts. This result may be understood in light of the results coming from the first study on healthy participants. Thus, these findings will be discussed in detail in the General discussion.

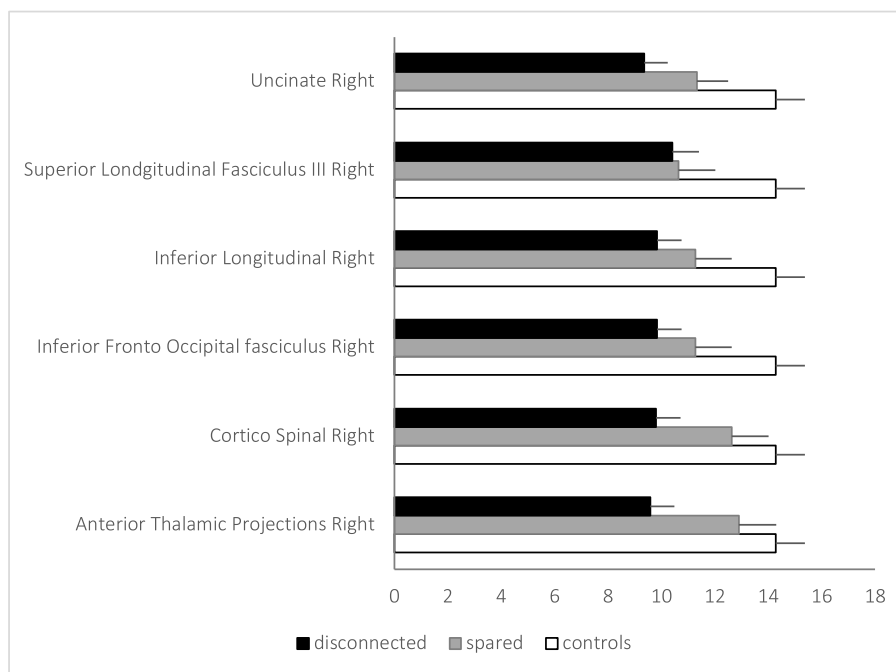
## 4. General discussion

Overall, the results of the VLSM analysis showed that interoceptive sensibility towards visceral and somatosensory sensations rely on different brain regions. On the one hand, interoceptive sensibility towards visceral feelings is lower in patients with a lesion in the insular cortex, expanding and confirming previous results coming from brain-damaged patients (Grossi et al., 2014); on the other hand, a lesion in the subcortical structures, namely the putamen and surrounding white matter, affects interoceptive sensibility towards somatosensory feelings. Interestingly, the results from the surface-based analysis on gyrification index and the TBSS study in healthy participants suggest that interoceptive sensibility towards visceral feelings is associated with morphometric variations in the anterior cingulate cortex, while that towards somatosensory sensations is associated with a wide network spanning from the occipital to the frontal lobe.

Data from the track-wise hodological lesion-deficit analysis support the causal role of this network in interoceptive sensibility of somatosensory feelings, especially those involving the Uncinate Fasciculus, the Superior Longitudinal Fasciculus III, Inferior Longitudinal Fasciculus, Inferior Frontal Occipital Fasciculus, Corticospinal Tract, and the Anterior Thalamic Projection.

As reported above, the uncinate fasciculus links brain nodes of emotion regulation. Instead, the lower branch of the superior longitudinal fasciculus (SLF III) connects brain areas devoted to action and non-action body representation. The corticospinal tract, besides its well-known role in motor control, has been recently highlighted as participating in the modulation of sensory feedbacks and integrating these signals with motor information coming from the cerebellum and primary motor regions. The anterior thalamic radiations are part of a brain network including key nodes of interoception, that is the insula, the anterior cingulate cortex, and the anterior thalamic nuclei.

In sum, data from healthy individuals coupled with those from patients with brain damage suggest that interoceptive sensibility towards somatosensory feelings requires a complex neural network that allows the multisensory integration of somatomotor and visual information with that related to emotional salience and body awareness, and in which the putamen could be a critical hub. Indeed, the putamen role extends far beyond its well-known involvement in motor processes. For example, it contributes to sensory aspects of pain (Starr et al., 2011) and



**Fig. 3.** Results of the TWH analysis. For each tract, average scores on F2 (interoceptive sensibility of somatosensory feelings) of patients with spared and disconnected tract, as well as those of healthy controls, are shown. Standard errors were plotted as well.

multisensory integration (von Saldern and Noppeney, 2013), which is consistent with the presence of putamen neurons that specifically respond to somatosensory stimuli (e.g. light touch, and deep muscle pressure), visual stimuli, and both visual and somatosensory stimuli (i.e. bimodal neurons) (Graziano and Gross, 1993) in macaques. Results from Study 1 and 2 may appear inconsistent. However, different patterns of results may be framed in the context of the different levels of causal inference of the methods (Poldrack and Farah, 2015). Indeed, Study 1 exploits naturally occurring variations in interoceptive sensibility of healthy individuals, and measures the strength of association between individual differences in this trait and brain structure. Instead, Study 2 exploits brain lesion to provide insight into the causal contribution of specific brain regions or tracts.

Results also suggest that the sensibility towards *visceral feelings* could be less linked to the activity of wide neural networks necessary to integrate different information sources and be more strictly dependent on information processed in the insula and anterior cingulate cortex. Indeed, although negative results should be discussed with caution, no association was found between interoceptive sensibility towards visceral feelings and differences in white matter structure in healthy individuals. Instead, findings from the VLSM and gyrification analyses highlighted the insula and anterior cingulate cortex's role in the interoceptive processing of visceral sensations. These regions are jointly activated in a number of imaging studies involving subjective feelings and bodily information processing (Craig, 2009; Critchley and Harrison, 2013), and von Economo neurons (VENs) have been proposed to be the substrate for interconnections between them (Craig, 2009). We further expand on these findings, suggesting that the insula and anterior cingulate cortex are particularly relevant for the interoceptive sensibility of visceral sensations. In particular, following Craig's awareness model (2009), in patients with brain damage, right posterior insula lesions would interfere with primary interoceptive representations of visceral feelings from the body. Instead, in healthy adults, individual differences in interoceptive sensibility of visceral sensations would become more evident in higher-order grey matter regions, such as the anterior cingulate cortex that, together with the anterior insula, would mediate the re-representation of visceral feelings to build a second-order representation of the self (Craig, 2009; Critchley et al., 2004).

This study focused on one central question: to disclose the neural correlates of interoceptive sensibility of visceral and somatosensory feelings, integrating data from healthy individuals with those from patients with brain damage. Accordingly, we limited our investigation to one specific dimension of interoception, that is interoceptive sensibility. Thus, outstanding questions for future empirical research include disclosing the neural correlates of other interoceptive dimensions (e.g. interoceptive accuracy), taking into account visceral and somatosensory feelings. Indeed, considering that the discrepancy between interoceptive accuracy and interoceptive sensibility is an index that predicts the severity of several clinical disorders (Garfinkel et al., 2016; Paulus and Stein, 2010; Rae et al., 2018), a more complete and integrated understanding of these different dimensions can provide valuable knowledge to improve current treatments.

Another open issue concerns the possible role of gender differences in interoception in the predisposition to develop different clinical disorders. Women have been previously reported to score higher than men on the SAQ, and SAQ scores in women were found to correlate with grey matter volume in different brain regions, including the left insula (Longarzo et al., 2021). Since the present studies were not designed to address the issue of possible gender differences in interoception, future investigations will be needed to better characterize possible variations due to gender in the sensibility towards different categories of bodily signals, also in light of recent suggestions that gender-related differences in interoception may at least partially explain differences in the presentation and prevalence of different psychiatric conditions (Murphy et al., 2019).

To conclude, we should acknowledge that the involvement of the left hemisphere might have been underestimated since only patients without overt language disorders could be included in Study 2. However, several sets of data support the results of the present study, beyond this possible bias. Indeed, data from patients with brain damage (e.g. Grossi et al., 2014) and healthy individuals (e.g. Critchley et al., 2004) demonstrate that interoceptive sensibility is particularly related to the right rather than to the left insula. Also, it is interesting to note that an enhanced risk of cardio-autonomic dysfunction (Meyer et al., 2004) and reduced heart rate variability (Naver et al., 1996) are associated with right insular damage, and, in keeping with this evidence, a

right-hemispheric dominance in processing heart-related interoceptive information has been reported in a meta-analysis by Schulz (2016). Finally, a recent ALE meta-analysis suggests a set of right-lateralized areas, including the precentral and postcentral, and superior temporal gyri, supporting the convergence between interoceptive and exteroceptive information (Salvato et al., 2020). This result ties well with the wide network we detected in the right hemisphere for sensibility towards sensations from the proximal senses.

### Authors' note

In memory of Prof. Dario Grossi, a genius lent to Neuropsychology that, with his strategic foresight and deep knowledge of brain mechanisms, represented a shining lighthouse guiding us to sail together, with his generous optimism as a tailwind, in the sea of neuroscience research.

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### Ethics approval

All the studies reported here were approved by the ethical committee of Fondazione Santa Lucia, Rome.

### Consent to participate

All participants gave their written informed consent to participate in the study.

### Availability of data and material

Data are available upon request to the corresponding author in compliance with the institutional ethics approval.

### Credit author statement

Maddalena Boccia: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing. Alice Teghil: Conceptualization; Data curation; Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing. Simona Raimo: Conceptualization; Data curation; Investigation; Writing – review & editing. Antonella Di Vita: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing. Dario Grossi: Conceptualization; Writing – review & editing. Cecilia Guariglia: Conceptualization; Writing – review & editing. Liana Palermo: Conceptualization; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

### Data availability

Data will be made available on request.

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