CORTEX 86 (2017) 22–32

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

Altered functional connectivity of interoception in illness anxiety disorder

Dario Grossi [a], Mariachiara Longarzo [a,*], Mario Quarantelli [b], Elena Salvatore [c], Carlo Cavaliere [d], Paolofabrizio De Luca [e], Luigi Trojano [a] and Marco Aiello [d]

[a] Department of Psychology, Second University of Naples, Italy
[b] Institute of Biostructure and Bioimaging, National Research Council, Naples, Italy
[c] Department of Neuroscience Reproductive Sciences and Odontostomatology, University Federico II, Naples, Italy
[d] IRCCS SDN, Naples, Italy
[e] Center for Psychosomatic Psychotherapy, Naples, Italy

ARTICLE INFO

Article history:
Received 28 January 2016
Reviewed 22 May 2011
Revised 22 July 2016
Accepted 28 October 2016
Action editor Marco Catani
Published online 5 November 2016

Keywords:
Interoception
rs-fMRI
Functional connectivity
Illness anxiety disorder
Emotion

ABSTRACT

Interoception collects all information coming from the body and is sustained by several brain areas such as insula and cingulate cortex. Here, we used resting-state functional magnetic resonance imaging to investigate functional connectivity (FC) of networks implied in interoception in patients with Illness anxiety disorders (IADs). We observed significantly reduced FC between the left extrastriate body area (EBA) and the paracentral lobule compared to healthy controls. Moreover, the correlation analysis between behavioural questionnaires and ROI to ROI FC showed that higher levels of illness anxiety were related to hyper-connectivity between EBA and amygdala and hippocampus. Scores on a questionnaire for interoceptive awareness were significantly correlated with higher FC between right hippocampus and nucleus accumbens bilaterally, and with higher connectivity between left anterior cingulate cortex (ACC) and left orbitofrontal cortex (OFC). Last, patients showed increased interoceptive awareness, measured by Self-Awareness Questionnaire (SAQ), and reduced capability in recognizing emotions, indicating inverse correlation between interoception and emotional awareness. Taken together our results suggested that, in absence of structural and micro-structural changes, patients with IADs show functional alteration in the neural network involved in the self-body representation; such functional alteration might be the target of possible treatments.

Abbreviations: IAD, illness anxiety disorder; ACC, anterior cingulate cortex; AIC, anterior insular cortex; EBA, extrastriate body area; rs-fMRI, resting state functional magnetic resonance imaging.

* *Corresponding author*. Department of Psychology, Second University of Naples, Viale Ellittico, 31 Caserta, Italy.
E-mail address: mariachiara.longarzo@unina2.it (M. Longarzo).

http://dx.doi.org/10.1016/j.cortex.2016.10.018
0010-9452/

1. Introduction

Illness anxiety disorder (IAD) is defined as a condition characterized by preoccupation with having or acquiring a serious, undiagnosed, medical illness, with high level of anxiety about health issues; IAD individuals are too much alarmed and act out excessive health-related behaviours, e.g., checking the body for signs of illness or showing avoidance behaviour (DSM-5, 2013). In IAD, formerly termed hypochondriasis (DSM-IV, 2013), illness preoccupation lasts for six months at least, but the dreaded illness may change over time.

According to one interpretative hypothesis (Marcus, Gurley, Marchi, & Bauer, 2007), a person with a premorbid tendency to be attentive toward own bodily signals might misinterpret bodily sensations and believe that they are signs of an illness. As a consequence, that person could become anxious and worried for those specific sensations, show anxiety-related behaviours (such as reassurance seeking or medical checks), overestimate the probability to have a serious illness, and activate catastrophic beliefs. Barsky, Wyshak, and Klerman (1990), in their "Somatosensory Amplification Model", subsumed that hypochondriac subjects tend to focus on their somatic sensations and to experience them as intense and disturbing. In this regard, attention allocation seems to be crucial in developing and maintaining hypochondriasis because patients tend to selectively direct their attention toward internal or external signs of health threat (Gropalis, Bleichhardt, Hiller, & Witthöft, 2012). According to Barsky et al. (1990), dysfunctional beliefs about symptoms and illnesses represent risk factors for IAD, as bodily sensations foment anxiety and preoccupation, and in its turn anxiety increases those sensations. The background of such vicious circle is that individuals are more responsive to, and aware of, their interoceptive signals.

Interoception refers to processing of all information coming from one's own body, reflects the capability to be responsive to, and to be aware of one's own physical sensations, varies from person to person, and contributes to maintain homeostasis (Craig, 2002). Interoceptive stimuli include heartbeat, hunger, thirst, breathing, visceral sensations, i.e., information less distinct than that provided by the "exteroceptive" somatosensory systems (e.g., touch or skin temperature; Craig, 2002).

Terasawa, Shibata, Moriguchi, and Umeda (2012) distinguished three aspects of interoception: interoceptive "sensitivity" assessed by objective tests on interoceptive accuracy, such as heartbeat perception task (Shandry, 1981); interoceptive "awareness" that implies cognitive appreciation of internally generated sensations and refers to the capability of being aware of bodily feelings and of expressing them; interoceptive "sensibility" that expresses one's own tendency to be focused on internal states. In their studies, Salkovskis, Rimes, Warwick, and Clark (2002) and Barsky et al. (1990) demonstrated the association between interoceptive sensitivity and IAD. In line with these findings, a previous study on healthy individuals demonstrated a direct link between hypochondriac trait and interoception awareness, assessed by specific questionnaires (Longarzo et al., 2015). Such findings suggest that high interoception awareness may be related with strong and even excessive concern for one's own bodily sensations.

Interoceptive monitoring is based on a wide neural network including the insula, the anterior cingulate cortex (ACC), and somatosensory and ventromedial prefrontal cortices (Craig, 2009; Critchley, Wiens, Rotshtien, Ohman, & Dolan, 2004; Deveue et al., 2007; Pollatos, Gramann, & Schandry, 2007). ACC is also the origin of reciprocal projections to the insula (Medford & Critchley, 2010; Taylor, Seminowicz, & Davis, 2009). Seeley et al. (2007) suggested that insula and ACC are key regions for the "salience network" responsible for processing emotional and motivational value of stimuli; thus, the anterior insular cortex (AIC) and ACC participate in the self-awareness system that integrates affective, physiological and cognitive awareness. Lane, Sechrest, Riedel, Shapiro, and Kaszniak (2000) maintained that AIC is implicated in the generation of feelings, whereas ACC is engaged in directing attention and in facilitating autonomic responses. So, the combined action of AIC and ACC seems to provide the neural basis of self-awareness (Craig, 2009).

Another possible key node in the system of mental representation of one's self, relatively neglected in previous research, is the extrastriate body area (EBA) in the lateral occipitotemporal cortex. Structurally, EBA is related to middle and frontal regions through the inferior fronto-occipital fasciculus, projects to the insula and finally reaches the medial prefrontal cortex. EBA is activated when viewing total or partial body images (Downing, Jiang, Shuman, & Kanwisher, 2001), and recent studies suggested that it could be involved in bodily self-consciousness (Limanowski, Lutti, & Blankenburg, 2014; Serino et al., 2013). Nonetheless, EBA has not been previously thoroughly investigated in relation to altered self-awareness of body state.

Several neurofunctional studies demonstrated reduced fronto-insular functional connectivity (FC), associated with reduced interoceptive abilities, in patients with major depressive disorder (Mutschler, Ball, Wankerl, & Strigo, 2012; Sliz & Hayley, 2001; Veer et al., 2010). Enhanced insular response has been reported in anxiety disorders, e.g., in specific phobia (Wright, Martis, Mc Mullin, Shin, & Rauch, 2003), often associated with increased interoceptive abilities (Baur, Hänggi, Langer, & Jäncke, 2013; Paulus & Stein, 2010; Olatunji, Deacon, Abramowitz, & Valentiner, 2007). Moreover, Stein, Simmons, Feinstein, and Paulus (2007), in an fMRI study, found that anxiety-prone subjects showed increased bilateral insular activation during an emotion face assessment task.

To our knowledge, no studies explored FC in IAD. If an alteration of body representation and of bodily signals is associated to IAD, as mentioned above, it should be expected that interoceptive processes might be dysregulated, with detectable alterations in the FC of body representation areas.

The main aim of the present study was to investigate the FC of the key brain regions involved in bodily self-awareness and in the salience network in patients with IAD compared with a matched sample of healthy subjects. It is important to underline that most neurofunctional studies on IAD patients investigated brain activity or connectivity during the

execution of a task, whereas here we used a resting-state paradigm to test the hypothesis of altered FC in these patients.

We also characterized the psychological and cognitive features of our sample of IAD patients. With respect to cognitive aspects, only a handful of studies have evaluated neuropsychological aspects of hypochondriasis or somatoform disorders, providing inconsistent results. Some authors reported a bias toward illness-related information in memory tasks (Brown, Kosslyn, Delamater, Fama, & Barsky, 1999; Martin, Buech, Schwenk, & Rief, 2007; Pauli & Alpers, 2002), whereas Durso, Reardon, Shore, and Delys (1991) did not find health-related biases in information processing in their sample of patients with hypochondriasis. To the best of our knowledge, no study assessed cognitive abilities in IAD subjects by means of standardized and validated neuropsychological tests, and no information is available about the relationships between interoceptive awareness, emotion and cognitive abilities. Gathering information about psychological and cognitive features of IAD individuals allowed us to explore their relationships with functional neuroimaging data.

2. Materials and methods

2.1. Participants

We enrolled 22 patients aged 20 to 70 (6 females; mean age 38.9 ± 10.2 years; mean education 13.2 ± 3.5 years), with diagnosis of IAD according to standard diagnostic criteria (DSM-5, 2013). Independent expert psychiatrists and psychotherapists afferent to the clinical service of our Psychology Department made the diagnosis. All enrolled patients achieved scores higher than the diagnostic cut-off on a specific questionnaire for hypochondriasis, the illness attitude scale (IAS; Kellner, 1987).

Individuals were included in the study if they met the following inclusion criteria: no history of brain injury, stroke, or any other major clinical condition; no current or past history of alcohol or drug abuse; normal age- and education-adjusted scores on mini mental state examination (MMSE; Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996) and on frontal assessment battery (FAB; Apollonio et al., 2005), to exclude presence of general cognitive impairment.

We also recruited a sample of 14 healthy subjects (9 females; mean age 38.85 ± 14.01; mean education 16.14 ± 3.20), matched with patients for sex, age and formal education, and free of neurological or psychiatric disorders.

All participants provided their written informed consent and did not receive any reward for their participation. The study was approved by the local Ethics Committee (SUN and IRCCS SDN).

2.2. MRI data acquisition

All participants provided their written consent to undergo magnetic resonance imaging study at the IRCCS SDN, Naples. Structural and functional images were acquired at 3 tesla (Achieva Philips Medical System, Best, The Netherlands), equipped with a standard radio-frequency head coil. To reduce motion artefacts, foam pads were used to immobilize the participant's heads. The acquisition protocol includes: an anatomical 3D T1 weighted volume, along with DTI and rs-fMRI sequences. Anatomical images were acquired via a high resolution, T1-weighted 3D MPRAGE sequence (TR = 7.1 msec; TE = 3.2 msec; flip angle = 9°; voxel size = 1 × 1 × 1 mm). rs-fMRI images were acquired using a GRE-EPI sequence signal (TR = 2000 msec; TE = 40 msec; thickness = 4 mm; matrix size = 128 × 128; FOV = 230 mm; voxel size = 4 × 4 × 4 mm), providing 32 interleaved images per volume, parallel to the AC–PC line and covering the whole brain. Diffusion weighted images were acquired with diffusion gradients oriented along 32 non-collinear directions. Specific DTI parameters were: Repetition Time (TR) = 9300 msec, Echo Time (TE) = 102 msec, flip angle = 90°, slice thickness 2 mm, Field of view (FOV) = 256 mm, acquisition matrix size = 128 × 128, voxel size = 2 × 2 × 2 mm^3, diffusion weighting b = 1000 sec/mm^2, number of slices: 50, voxel size = 2 × 2 × 2 mm^3.

In addition, morphological clinical sequences including FLAIR (fluid attenuated inversion recovery) T2-weighted, T2W-TSE, and T2D-FFE images were was also acquired in order to assess the presence of macroscopic abnormalities which implicate the exclusion of he subjects from the study, for a total acquisition time of 41 min.

2.2.1. fMRI data processing

fMRI data were pre-processed and analysed using the CONN FC toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), a Matlab (Mathworks Inc.) toolbox containing libraries for fMRI analysis that relies on the Statistical Parametric Mapping 8 package (SPM8, the Wellcome Department of Neurology, London U.K.; Friston, Williams, Howard, Frackowiak, & Turner, 1996).

Image pre-processing steps included anatomical segmentation, normalization to Montreal Neurological Institute (MNI) space, spatial smoothing (FWHM = 8 mm), band-pass filtering (.01–01 Hz) and regressing out signal contributions for head motion, white matter and cerebro-spinal fluid (Whitfield-Gabrieli & Nieto-Castanon, 2012). Signal contributions for micro-head movements were accounted for using the image "scrubbing" (Power, Barnes, Snyder, Schlaggar, & Petersen, 2011) ART method. fMRI volumes were finally smoothed with an isotropic Gaussian filter of 8 mm (FWHM). All described steps are part of the standard pre-processing procedure implemented in CONN. The seeds for the EBA networks were defined as spheres with radius of 6 mm and centres at [53.89, −66.78, 8.33] (right EBA) and [−53.67, −68.11, 9.00] (left EBA) MNI X, Y and Z coordinates, as suggested in Lamm and Decety (2008), the seed for salience network was defined in the left/right dorsal ACC [−6.00, 18.00, 28.00] [6.00, 18.00, 28.00] as suggested in Pannekoek et al. (2013). The seed for the default mode network was defined in the left/right posterior cingulate cortex [−2.00, −52.00, 26.00] [2.00, −52.00, 26.00] as suggested in Pannekoek et al. (2013). Further seed regions involved in the salience network were obtained from the CONN default atlas (Tzourio-Mazoyer et al., 2002): right/left frontal orbital cortex, right/left amygdala, right/left thalamus, right/left hippocampus and right/left accumbens. Voxel-wise maps relative to each RSN were generated considering the Pearson correlation coefficients between the

time course of each voxel and the time course averaged over the seed sphere. We also computed the Pearson's correlation coefficients between the fMRI time courses averaged across each ROI for the purposes of ROI to ROI analysis.

2.2.2. Anatomical data processing

GM tissue density map employed in voxel based morphometry (VBM) was carried out from the segmentation produced within the spatial normalisation procedure. The covariate variable of total intracranial volume (TIV) was obtained by calculating the volumes of each tissue class (GM, WM and CSF) and then adding these results. Before statistical analysis, GM density maps were smoothed with an isotropic Gaussian filter of 8 mm (FWHM).

2.2.3. DTI data processing

Diffusion imaging data pre processing and analysis were carried out using standard pipelines. The diffusion data were pre processed using the FDT tool, part of the FSL data analysis package (Smith et al., 2004). Data were first corrected for distortions caused by eddy currents and motion. After skull-stripping, diffusion tensors were fitted to the corrected data using DTIFIT.

Fractional anisotropy (FA) and mean diffusivity (MD) values were derived from the tensors. Voxel-wise statistical analysis of these data was then carried out using tract-based spatial statistics (Smith et al., 2006), also part of the FSL data analysis package.

2.2.4. Statistical analyses for neuroimaging

For VBM and the sixteen seed-based FC maps the differences between the imaging variables of IAD patients and controls were assessed by two-sample *t*-test in SPM. Subject's age was used as covariate for all the measures; in addition for VBM comparison the TIV was included as covariate.

Results were considered statistically significant under $p < .05$ FWE corrected at cluster level with minimum cluster extent of 50 voxels.

For TBSS, FA and MD maps were compared between the two groups by non parametric permutation analysis applied to the General Linear Model (Bullmore et al., 1999) (5000 permutations), including age as nuisance covariate, using a $p < .05$ threshold free cluster enhancement approach (Smith et al., 2006).

For all neuroimaging analysis both IAD > controls and IAD < controls contrasts were assessed.

Furthermore, in order to explore the relationships between clinical scores and neuroimaging data, we estimated the correlation between ROI to ROI FC, GM density and FA/MD with scores on questionnaires for hypochondriasis and interoceptive awareness (see below) across all subjects by means of SPM's multiple regression implemented in CONN. The scores on questionnaires for hypochondriasis and interoceptive awareness were corrected for severity of depressive symptomatology and trait anxiety, as assessed by means of specific questionnaires (see below), in keeping with previous studies according to which hypochondriac symptoms are positively correlated with measures of anxiety and depression (Scarella, Laferton, Ahern, Fallon, & Barsky, 2016). Multiple regression results were considered significant at $p < .05$, false discovery rate (FDR) corrected.

2.3. Clinical and neuropsychological assessment

All recruited subjects completed a battery including questionnaires assessing interoceptive awareness, attitudes associated to hypochondriasis, anxiety and depression symptoms.

Interoceptive awareness was assessed by the Self-Awareness Questionnaire (SAQ, Longarzo et al., 2015), an extended version of a questionnaire used in brain-damaged patients (Grossi et al., 2014). The questionnaire includes 35 items to be rated on a 5-point Likert scale (0 = never; 1 = sometimes; 2 = often; 3 = very often; 4 = always; max total score = 140). We identified two-factor structure of SAQ, the first (F1) mainly related to visceral sensations and the second (F2) mainly related to somatosensory sensations. Mean score achieved by normal subjects is 27.4 (score range: 2–78; Longarzo et al., 2015).

In order to investigate attitude, fear and beliefs associated with hypochondriac behaviour we used the illness attitude scale (IAS; Kellner, 1987) that includes 27 items rated on a 5-point Likert scale (from 0 = no to 4 = most of the time). Higher scores indicate more severe hypochondriac symptoms. The IAS has been shown to reliably identify hypochondriac patients (score > 50; Kellner, 1987; Italian version by Fava, Grandi, Rafanelli, Fabbri, & Cazzaro, 2000).

For assessing severity of illness anxiety, we used the Hypochondriasis-Yale-Brown Obsessive Compulsive Scale-Modified (H-YBOCS-M; Skritskaya et al., 2012) that investigates three aspects: illness worries, illness-related behaviours and avoidance. This is a valid and reliable instrument, easy to administrate, but it did not provide a cut-off value for clinical use.

Since anxiety is a condition associated with IAD, the degree of its severity has been measured using the State Trait Anxiety Inventory (STAI Y1 and Y2; Spielberger, Gorsuch, & Lushene, 1970), a self-report questionnaire including 40 items rated on a 4-point Likert scale. Responses for S-anxiety scale, assessing intensity of current feelings "at this moment", are 1 = not at all; 2 = somewhat; 3 = moderately so; 4 = very much so. Responses for the T-anxiety scale, assessing frequency of feelings "in general", are: 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always. The threshold value predictive of anxiety symptoms is set at a score of 40.

To assess depressive symptoms we used the Beck depression inventory (BDI-II; Beck, Steer, & Brown, 1996), a 21-item self-report questionnaire. Each item has four alternative responses that correspond to the symptom severity: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Scores 0–13 indicate absence of depressive symptoms; scores between 14 and 19 denote mild depressive symptoms; scores between 27 and 29 moderate depressive symptoms; scores between 30 and 63 severe depressive symptoms.

Furthermore, all subjects underwent a neuropsychological battery including: Rey 15 Words (Rey, 1958) and Digit Span (Wechsler, 1955) to assess verbal memory; the Corsi test (Spinnler & Tognoni, 1987) to assess spatial memory; executive functions were assessed by the Wisconsin card sorting test (WCST; Berg, 1948), Stroop Test (Stroop, 1935), trail making test A & B (Mondini, Mapelli, Vestri, & Bisiacchi, 2003; Reitan, 1958), Tower of London test (Shallice, 1982) and

phonological fluency test (Novelli et al., 1986). Raven's coloured progressive matrices (Basso, Capitani, & Laiacona, 1987) assessed visuo-spatial functions. All tests were given in their Italian standardized version; participants' scores were evaluated with respect to age- and education-adjusted Italian normative values.

In addition, we administered the Baron-Cohen eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) in order to investigate the affective component of Theory of Mind that corresponds to the capability to recognize complex emotions and attribute them to other persons.

2.3.1. *Statistical analysis of behavioural data*

On behavioural and cognitive measures we run a multivariate analysis of variance (MANOVA), with the Group (IAD patients *vs* controls) as the independent factor and total scores on each clinical scale and cognitive task as dependent variables, to detect possible differences between groups. Additionally, we computed Spearman's coefficients to ascertain whether performances on the SAQ and its subscales were related with hypochondriac, anxiety and depression symptoms, and with results obtained on the Eyes test. Statistical analyses were run using SPSS software (IBM).

3. Results

3.1. *Neuroimaging data*

No participant was excluded for the presence of relevant brain structural changes or excessive head motion.

No significant differences were found between the two groups at VBM and TDSS analyses.

Regarding seed to voxel FC, visually compared to control subjects, patients showed, at a purely qualitative level, an asymmetrical pattern of connectivity between EBA seed and EBA region of contra-lateral side, compared to control subjects (Fig. 1). Moreover, a reduced co-activation among EBA seed and bilateral precuneus/precentral gyrus cortices was evident, mainly for left EBA seed.

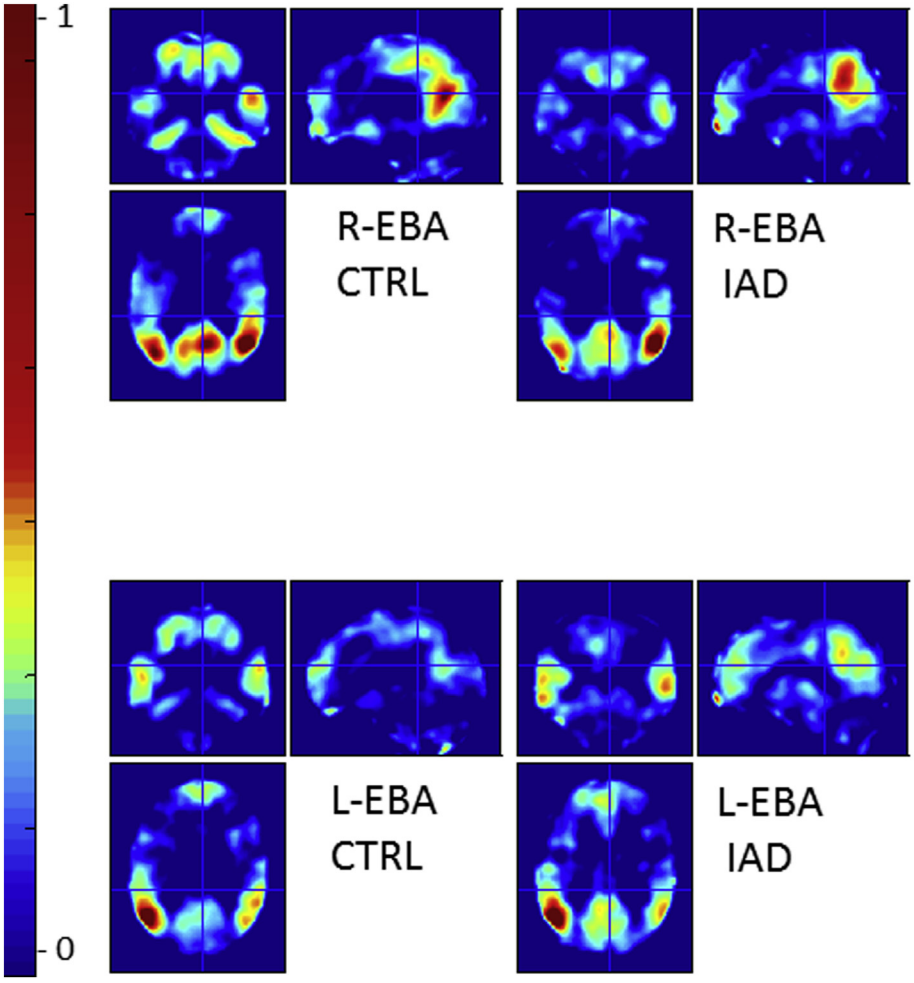

Fig. 1 – EBA networks averaged across subjects of each group. The colour of each voxel represents the magnitude of Pearson's correlation coefficient between the fMRI signal averaged on sphere ROI placed at right-EBA (top) and left-EBA (bottom). Colour map ranges from 0 (blue, no correlation with EBA seed) to 1 (red, maximum correlation with EBA seed). Slices are displayed according to the neurological convention. *Note*. R-EBA CTRL = right extrastriate body area of control subjects; L-EBA CTRL = left extrastriate body area of control subjects; R-EBA IAD = right extrastriate body area of illness anxiety disorder patients; L-EBA IAD = left extrastriate body area of illness anxiety disorder patients.

Statistical analysis demonstrated significantly lower ($p < .001$, FWE corrected at cluster level) connectivity between left EBA and right paracentral lobule in IAD patients (Fig. 2). No significant differences of FC emerged from the other seeds.

ROI to ROI analysis showed that FC of right EBA, right amygdala and right hippocampus was significantly and positively correlated with the IAS score. Moreover, the SAQ score significantly and positively correlated with FC between right hippocampus and left/right accumbens, and between left ACC and left orbitofrontal cortex (OFC) (see Table 1).

3.2. *Behavioural data*

MANOVA on clinical scores revealed significant differences between IAD patients and controls on all clinical scales (Table 2), whereas we did not observe significant differences between the two groups on the neuropsychological battery. Patients were characterized by mild depressive symptoms on BDI-II, moderate state anxiety (STAI Y1) and high trait anxiety (STAI Y2). Correlation analysis in the group of IAD patients showed positive correlation between total scores of the two measures of hypochondriac symptoms, IAS and H-YBOCS ($p = .002$). The IAS total score was moderately correlated with two factors of H-YBOCS-M: illness worries ($p = .005$) and illness-related behaviours ($p = .004$). Moreover, the factor "treatment experience" of IAS was moderately correlated with total score of H-YBOCS-M ($p = .009$) and with the factors "illness worries" ($p = .004$) and "illness-related behaviours" ($p = .004$). The H-YBOCS-M was moderately correlated also with STAI Y2 ($p = .008$); STAI Y2 moderately correlated also with BDI-II ($p = .006$). In addition, the factor "hypochondriac beliefs" of the IAS was positively correlated with SAQ total score ($p = .004$) and with the F1 of the SAQ ($p = .001$), mainly related to visceral sensations. Moreover, we found negative correlation between F2 of the SAQ, mainly related to somatosensory sensations, with the Baron-Cohen Eyes Test ($p = .002$). All correlations in the patient group are summarized in the bivariate correlation matrix (Supplementary Table 1).

On all clinical questionnaires, the healthy subjects showed scores below the cut-off values. Correlation analysis indicated a positive correlation between total score of the SAQ with BDI-II, and between both SAQ F1 ($p = .001$) and SAQ F2 (.004) with the BDI-II. In addition, we found moderate correlation between SAQ and STAI Y2 (.006). All correlations in the control group are summarized in the bivariate correlation matrix (Supplementary Table 2).

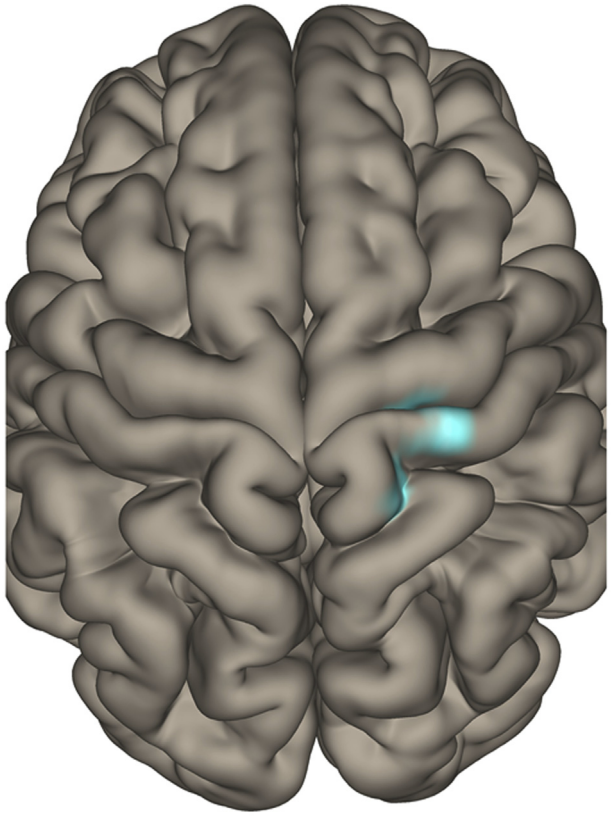

Fig. 2 – Areas on statistically significant ($p < .05$ FWE corrected at cluster level) lower connectivity with left EBA seed between IAD and control groups. Significant cluster (Blue) is shown on a 3D rendering of cortical surface displayed according to the neurological convention.

4. Discussion

We investigated the FC networks implied in interoception in patients with IAD. Our neuroimaging findings showed significantly reduced connectivity between left EBA and the paracentral lobule in IAD patients. Recently, a model of bodily self-consciousness (Serino et al., 2013) considered EBA as a first station for processing unisensory, body related information, that might contribute to build an integrated representation of the self; consistent with this idea, Limanowski et al. (2014) provided evidence for involvement of the EBA in body ownership reporting its activation during the rubber hand illusion condition.

The paracentral lobule is included in the somatosensory network (Lavagnino et al., 2014). In healthy subjects the EBA, and particularly the left EBA, exhibits strong FC with somatosensory and motor cortices (David et al., 2007), whereas we found a reduced FC between EBA and somatosensory areas. Reduced connectivity observed in our sample might reflect a deficit in multisensory integration between visual and somatosensory information. Similarly, Lavagnino et al. (2014) found reduced rs-FC between EBA and paracentral lobule in patients with Bulimia Nervosa and suggested that the reduced connectivity would denote decreased self-related processing of one's own body. FC alteration in this network would point to a reduced functional synchrony, a sort of incomplete correspondence between these areas (Grossi, 2013). The present study, instead, did not show significant differences in the rs-FC of the salience network (AIC and ACC) and no significant results emerged from the remaining measures of FC. These negative findings would add to the specificity of the alteration of FC in the neural networks contributing to interoception in IAD subjects.

Complementary findings were obtained from the analysis of correlation between clinical scores and ROI to ROI FC. Indeed, we observed a positive correlation between score on IAS questionnaire and connectivity between right EBA with

Table 1 – Results of multiple regression analysis. Significant positive correlations of ROI to ROI functional connectivity and IAD clinical scores assessed across all subjects are listed.

Score	ROI seed	ROI target	T	p-unc	p-FDR
IAS	Right EBA	Right amygdala	3.21	.001800	.037798
		Right hippocampus	2.92	.003625	.038057
SAQ	Right Hippocampus	Left accumbens	3.05	.002723	.035554
		Right accumbens	2.96	.003386	.035554
SAQ	Left ACC	Left orbitofrontal cortex	3.57	.000772	.016222

Table 2 – Score range, means (and standard deviations; s.d.) for clinical and neuropsychological data for patients (N = 22) and controls (N = 14), and summary of Multivariate analysis of variance (F).

	Patients Score range	Patients *Mean* and S.D.	Controls Score range	Controls *Mean* and S.D.	F
SAQ	18–84	40.45 (17.19)	6–49	20.85 (12.54)	13.53*
IAS	28–98	57.32 (18.16)	11–33	24.00 (6.33)	43.34**
H-YBOCS-M	6–49	27.40 (12.34)	0–26	6.85 (8.17)	30.18**
BDI-II	2–33	16.04 (9.50)	0–14	4.92 (4.92)	16.23**
STAI Y1	27–62	42.63 (9.33)	25–47	32.78 (6.38)	11.95*
STAI Y2	37–64	51.45 (7.16)	28–52	36.14 (7.86)	36.25**
Rey 15 words (i.r.)	21–64	48.63 (10.97)	36–64	55 (7.58)	3.59
Rey 15 words (d.r.)	6–15	11.18 (2.28)	8–15	11.78 (2.15)	.62
Recognition	9–15	14.5 (1.30)	13–15	14.78 (.57)	.59
Verbal span	4–8	6.13 (1.08)	4–8	4.71 (1.20)	.95
Corsi test	4–8	5.59 (1.22)	4–7	5.71 (1.13)	.09
Wcst categories	3–6	5.86 (.63)	3–6	5.57 (1.08)	1.03
Wcst (t.e.)	0–23	3.54 (5.02)	0–22	3.71 (7.04)	.007
Stroop I (t.t.)	30–72	43 (10.20)	31–76	44.42 (13.66)	.12
Stroop II (t.t.)	44–94	70.36 (12.89)	54–97	65.07 (10.84)	1.62
Stroop III (t.t.)	86–186	119.68 (27.22)	80–170	108.5 (28.51)	1.39
Stroop III (t.e.)	0–4	1.04 (1.04)	0–1	.21 (.42)	2.03
Tmt a	16–69	31.18 (12.05)	14–57	32.07 (12.63)	.04
Tmt b	42–198	87.27 (42.63)	29–200	74.71 (42.65)	.74
Phonological fluency	24–56	39.77 (7.91)	21–68	45.28 (10.83)	3.11
Tower of London	18.2–18.8	18.64 (.16)	18.4–18.8	18.63 (.30)	.01
Raven matrices	27–36	31.90 (4.10)	27–36	33.5 (2.82)	1.61
Eyes test	15–30	24.90 (3.50)	20–31	25.42 (3.25)	.19

Note. (i.r. = immediate recall; d.r. = delayed recall; t.e. = total errors; t.t. = total time).
**Significant correlation at level .001; *Significant correlation at level .01.

right amygdala and right hippocampus, indicating that the stronger the illness anxiety levels, the more intense FC between these areas. The amygdala is strongly involved in fear and emotion processing and is altered in general anxiety disorder (Makovac et al., 2016), whereas the hippocampus has been shown to receive sensory (de Curtis & Paré, 2004) and interoceptive information (Kassab & Alexandre, 2015) among others. Considering that persistent anxiety state could modify autonomic regulation (Chalmers, Quintana, & Abbott, 2014), we could suggest that the enhanced FC of these areas with EBA in individuals with higher illness anxiety levels could be related to a deficit in emotion regulation, with more intense fear/anxiety signals related to self-body signals. Cumulating the above data, we could suggest that EBA on one hand showed a reduced connectivity with somatosensory areas, a finding possibly related to defective multisensory integration, whereas on the other hand it showed increased connectivity (related to severity of illness anxiety levels) with limbic areas, a finding likely related to body-selective emotion dysregulation.

We also found that higher scores on the questionnaire for interoceptive awareness (SAQ) were significantly correlated with higher FC between right hippocampus and nucleus accumbens bilaterally, and with higher FC between left ACC and OFC. As mentioned above, the hippocampus is related to the interoceptive perceptual system (Craig, 2009; Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000), and also responds to interoceptive stimuli specifically (Araujo, Kaplan, Damasio, & Damasio, 2015), suggesting that it is involved in maintaining interoceptive features of episodic memory (Kassab & Alexandre, 2015). The nucleus accumbens has strong anatomical and functional connections with the hippocampus (Ding, 2013): hippocampus and nucleus accumbens share intrinsic functional connectivity (IFC) and are both involved in motivational behaviour and emotional memory (Blessing, Beissner, Schumann, Brünner, & Bär, 2016). Motivationally important events, signalled in the accumbens could impact memory formation in the hippocampus (Kahn & Shohamy, 2013). Since it has been recently observed that this network is dysfunctional in anxiety disorders (Blessing et al., 2016), we could hypothesize that a similar dysfunction, with hyperconnectivity between these regions, could be related to a sharpened awareness of self-body signals.

We also observed that higher scores on the SAQ were significantly and positively correlated with FC between left ACC and left OFC. ACC is a region where all physiological, affective and emotional information coming from the insula integrate, contributing to self-awareness (Medford & Critchley, 2010). Functional imaging studies reported ACC hyperactivation in several anxiety disorders (social anxiety, post traumatic stress disorder) and found that its activation is correlated with subjective anxiety levels in specific phobia (for a review see Duval, Javanbakht, and Liberzon, 2015). OFC connectivity has shown to be altered in social anxiety (Geiger et al., 2016) and in response to negative affective stimuli (Mareckova et al., 2016). Therefore, the increased connectivity between ACC and OFC related to higher scores on the SAQ might reflect the same hyperactivation between these regions found in patients with anxiety disorders, characterized by recurrent and intrusive anxiety-related thoughts (for a review see Del Casale et al., 2011).

The behavioural results we collected showed that patients significantly differed from healthy controls on all clinical scales, in absence of any cognitive impairment. Consistent with the correlational data between FC and clinical scales, the significantly higher scores on the interoceptive awareness questionnaire (SAQ) would suggest that the patients showed an increased attention in evaluating their health status with respect to control subjects, in line with the idea that the preoccupation for bodily sensations might originate from a more accurate interoception, and this process could contribute to maintain the hypochondriac condition (Krautwurst, Gerlach, Gomille, Hiller, & Witthöft, 2014). It is worth underlining that this is the first study in which interoceptive awareness has been investigated in IAD patients, whereas most previous studies investigated the relationships between interoceptive sensitivity and health anxiety, providing inconclusive results and not clarifying if health anxiety is associated with higher or reduced interoceptive sensitivity (Krautwurst et al., 2014). The high scores obtained on trait anxiety scale might suggest that anxiety is not related to a specific situation but is a more stable and pervasive characteristic in these patients (Julian, 2011). As expected, we found a positive correlation between IAS and H-YBOCS-M (total scores and relative subscales) confirming that patients experienced strong concerns for their own health status (Salkovskis & Warwick, 2001). The positive correlation observed between H-YBOCS-M and STAI Y2 is related to the anxious trait typical of the patients with IAD (Rachman, 2012), but in our sample the positive correlation between STAI Y2 and BDI-II could suggest that anxiety and depression traits were interrelated and might influence each other.

Interestingly we found a significant correlation between the "hypochondriac beliefs" factor of the IAS with the total score and the F1 score of the SAQ. This finding might suggest that preoccupation for one's own health might be influenced by interoceptive awareness, in line with the hypothesis that high interoception awareness may lead to strong concern for one's own bodily sensations (Longarzo et al., 2015). Moreover, we found negative correlation between F2 of the SAQ and Baron-Cohen Eyes test; this result supports the link between interoception and emotion, and would suggest that high interoceptive awareness could interfere with the capability to recognize others' emotions. The relationships between interoceptive awareness and emotion perception has been investigated by several studies proposing that updated information about one's own internal state might create a neural subjective frame from which first-person experience can be reported (e.g., Park, Correia, Ducorps, & Tallon-Baudry, 2014). Adolphs, Damasio, Tranel, Cooper, and Damasio (2000) and recently Tamietto et al. (2015) reported that insular and somatosensory damage prejudice emotion perception. Other studies, instead, explored the relationships between interoceptive awareness and empathy, providing contrasting results. In healthy subjects Fukushima, Terasawa, and Umeda (2011) and Ernst et al. (2014) reported positive correlations between interoception and empathy, whereas Handford, Lemon, Grimm, and Vollmer-Conna (2013) and Ainely, Maister, and Tzakiris (2015) reported no correlations between high interoceptive awareness and the capability in recognizing other's emotions. The negative correlations between scores on interoceptive awareness and Eyes test we found in IAD patients might suggest an inverse association between patients' focalization on one's own body and the ability to attend to (and process) others' emotions. However, such hypothesis should be addressed on a larger sample of patients by using a wider battery of emotion recognition tests, since the Eyes test is considered a valid ToM and emotion recognition test, but assesses individuals' ability to infer others' emotions by partial cues.

In line with previous studies showing reciprocal influences between cognitive and emotional regions and cognitive processes in hypochondriac patients (van den Heuvel et al., 2011, 2005), the present behavioural findings are consistent with the idea that IAD patients' attention is strong focalized on the body, and this might lead patients to misinterpret bodily signs as symptoms, with consequent high anxiety levels (Salkovskis, 1988; Salkovskis & Warwick, 2001).

Significant positive correlations between interoception and depressive and anxiety symptoms were found in healthy subjects, thus confirming that the constructs of interoception, anxiety and depression are interrelated even in individuals without clinical conditions (Pollatos, Traut-Mattausch, & Schandry, 2009). Therefore, we believe that the present study advances knowledge about interoception, suggesting that altered interoceptive awareness is a key component of IAD.

One limitation of the present work lies in the fact that, given the exploratory nature of the work, we did not use a functional localizer to define the EBA regions on individual basis, which would have been preferable, given the individual variability of this structure (Peelen & Downing, 2007; Weiner & Grill-Spector, 2011). Nonetheless we could observe a pattern of reduced FC with the paracentral lobule, and increased FC with right mesial temporal lobe, as a function of increased anxiety scores. These findings are consistent with the idea that this region is involved in building a body representation, although they clearly need to be confirmed by further studies including functional localization of the EBA.

In conclusion, we showed that abnormal FC, i.e., abnormal temporal synchrony in spontaneous activity patterns, is present between brain areas underlying self-body awareness in patients with IAD. These patients showed altered interoceptive awareness, which might represent a key clinical characteristic. The lack of significant volumetric and microstructural alterations of both grey and white matter suggests that such

disorder specifically interferes with FC. The selective alteration of FC we reported here might open the way for possible application of non-invasive brain stimulation interventions in IAD patients (Shafi, Westover, Fox, & Pascual-Leone, 2012).

Funding

This work was not supported by any funding.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2016.10.018.

REFERENCES

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *The Journal of Neuroscience, 20*(7), 2683–2690.

Ainley, V., Maister, L., & Tsakiris, M. (2015). Heartfelt empathy? No association between interoceptive awareness, questionnaire measures of empathy, reading the mind in the eyes task or the director task. *Frontiers in Psychology, 6*, 554.

Apollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., et al. (2005). The frontal assessment battery (FAB): Normative values in an Italian population sample. *Neurological Sciences, 26*(2), 108–116.

Araujo, H. F., Kaplan, J., Damasio, H., & Damasio, A. (2015). Neural correlates of different self domains. *Brain and Behavior, 5*(12).

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry, 42*(2), 241–251.

Barsky, A. J., Wyshak, G., & Klerman, G. L. (1990). The somatosensory amplification scale and its relationship to hypochondriasis. *Journal of Psychiatric Research, 24*(4), 323–334.

Basso, A., Capitani, E., & Laiacona, M. (1987). Raven's coloured progressive matrices: Normative values on 302 adult normal controls. *Functional Neurology, 2*(2), 189–194.

Baur, V., Hänggi, J., Langer, N., & Jäncke, L. (2013). Resting-state functional and structural connectivity with in an insula-amygdala route specifically index state and trait anxiety. *Biological Psychiatry, 73*, 85–92.

Beck, A., Steer, R., & Brown, G. (1996). *The Beck depression inventory – second edition manual*. San Antonio, TX: The Psychological Corporation.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology, 39*(1), 15–22.

Blessing, E. M., Beissner, F., Schumann, A., Brünner, F., & Bär, K. J. (2016). A data-driven approach to mapping cortical and subcortical intrinsic functional connectivity along the longitudinal hippocampal axis. *Human Brain Mapping, 37*(2), 462–476.

Brown, H. D., Kosslyn, S. M., Delamater, B., Fama, J., & Barsky, A. J. (1999). Perceptual and memory biases for health-related information in hypochondriacal individuals. *Journal of Psychosomatic Research, 47*, 67–78.

Bullmore, E. T., Suckling, J., Overmeyer, S., Rabe-Hesketh, S., Taylor, E., & Brammer, M. J. (1999). Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Transactions on Medical Imaging, 18*, 32–42.

Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Frontiers in Psychiatry, 5*, 80.

Craig, A. D. (2002). How do you feel now? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience, 3*, 655–666.

Craig, A. D. (2009). How do you feel now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*, 59–70.

Critchley, H. D., Wiens, S., Rotshtien, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience, 7*, 189–195.

de Curtis, M., & Paré, D. (2004). The rhinal cortices: A wall of inhibition between the neocortex and the hippocampus. *Progress in Neurobiology, 74*(2), 101–110.

David, N., Cohen, M. X., Newen, A., Bewernick, B. H., Shah, N. J., Fink, G. R., et al. (2007). The extrastriate cortex distinguishes between the consequences of one's own and other's behavior. *NeuroImage, 36*(3), 1004–1014.

Del Casale, A., Kotzalidis, G. D., Rapinesi, C., Serata, D., Ambrosi, E., Simonetti, A., et al. (2011). Functional neuroimaging in obsessive-compulsive disorder. *Neuropsychobiology, 64*(2), 61–85.

Deveue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., et al. (2007). Here I am: The cortical correlates of visual self-recognition. *Brain Research, 1143*, 169–182.

Ding, S. L. (2013). Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum in human, monkey, and rodent. *Journal of Comparative Neurology, 521*(18), 4145–4162.

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science, 293*(5539), 2470–2473.

Durso, F. T., Reardon, R., Shore, W. J., & Delys, S. M. (1991). Memory processes and hypochondriacal tendencies. *Journal of Nervous and Mental Disease, 179*, 279–283.

Duval, E. R., Javanbakht, A., & Liberzon, I. (2014). Neural circuits in anxiety and stress disorders: A focused review. *Therapeutics and Clinical Risk Management, 11*, 115–126.

Ernst, J., Böker, H., Hättenschwiler, J., Schüpbach, D., Northoff, G., Seifritz, E., et al. (2014). The association of interoceptive awareness and alexithymia with neurotransmitter concentrations in insula and anterior cingulate. *Social Cognitive and Affective Neuroscience, 9*(6), 857–863.

Fava, G. A., Grandi, S., Rafanelli, C., Fabbri, S., & Cazzaro, M. (2000). Explanatory therapy in hypochondriasis. *Journal of Clinical Psychiatry, 61*, 317–322.

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S. J., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine, 35*, 346–355.

Fukushima, H., Terasawa, Y., & Umeda, S. (2011). Association between interoception and empathy: Evidence from heartbeat-evoked brain potential. *International Journal of Psychophysiology, 79*(2), 259–265.

Geiger, M. J., Domschke, K., Ipser, J., Hattingh, C., Baldwin, D. S., Lochner, C., et al. (2016). Altered executive control network resting-state connectivity in social anxiety disorder. *The World Journal of Biological Psychiatry, 17*(1), 47–57.

Gropalis, M., Bleichhardt, G., Hiller, W., & Witthöft, M. (2012). Specificity and modifiability of cognitive biases in hypochondriasis. *Journal of Consulting and Clinical Psychology, 81*(3), 558–565.

Grossi, D. (2013). Come il cervello rappresenta se stesso: Alcune considerazioni. *Rivista internazionale di filosofia e psicologia, 4*(2), 204–209.

Grossi, D., Di Vita, A., Palermo, L., Sabatini, U., Trojano, L., & Guariglia, C. (2014). The brain network for self-feeling: A symptom-lesion mapping study. *Neuropsychologia, 63*, 92–98.

Handford, C., Lemon, J., Grimm, M. C., & Vollmer-Conna, U. (2013). Empathy as a function of clinical exposure-reading emotion in the eyes. *PLoS One, 8*(6), e65159.
van den Heuvel, O. A., Mataix-Cols, D., Zwitser, G., Cath, D. C., van der Werf, Y. D., Groenewegen, H. J., et al. (2011). Common limbic and frontal-striatal disturbances in patients with obsessive compulsive disorder, panic disorder and hypochondriasis. *Psychological Medicine, 41*(11), 2399–2410.
van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Witter, M. P., Merkelbach, J., Cath, D. C., et al. (2005). Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Archives of General Psychiatry, 62*(8), 922–933.
Julian, L. J. (2011). Measures of anxiety: State-trait anxiety inventory (STAI), beck anxiety inventory (BAI) and hospital anxiety and depression scale-anxiety (HADS-A). *Arthritis Care & Research, 63*(11), 467–472.
Kahn, I., & Shohamy, D. (2013). Intrinsic connectivity between the hippocampus, nucleus accumbens, and ventral tegmental area in humans. *Hippocampus, 23*(3), 187–192.
Kassab, R., & Alexandre, F. (2015). Integration of exteroceptive and interoceptive information within the hippocampus: A computational study. *Frontiers in Systems Neuroscience,* 5, 9–87.
Kellner, R. (1987). *Abridged manual of the illness attitude scale (mimeographed)*. Albuquerque: Department of Psychiatry, University of New Mexico.
Krautwurst, S., Gerlach, A. L., Gomille, L., Hiller, W., & Witthöft, M. (2014). Health anxiety—An indicator of higher interoceptive sensitivity? *Journal of Behavior Therapy and Experimental Psychiatry,* 45(2), 303–309.
Lamm, C., & Decety, J. (2008). Is the extrastriate body area (EBA) sensitive to the perception of pain in others? *Cerebral Cortex, 18*(10), 2369–2373.
Lane, R. D., Sechrest, L., Riedel, R., Shapiro, D. E., & Kaszniak, A. W. (2000). Pervasive emotion recognition deficit common to alexithymia and the repressive coping style. *Psychosomatic Medicine, 62*(4), 492–501.
Lavagnino, L., Amianto, F., D'agata, F., Huang, Z., Mortara, P., Abbate-Daga, G., et al. (2014). Reduced resting-state functional connectivity of the somatosensory cortex predicts psychopathological symptoms in women with bulimia nervosa. *Frontiers in Behavioral Neuroscience, 8*, 270.
Limanowski, J., Lutti, A., & Blankenburg, F. (2014). The extrastriate body area is involved in illusory limb ownership. *NeuroImage, 86*, 514–524.
Longarzo, M., D'Olimpio, F., Chiavazzo, A., Santangelo, G., Trojano, L., & Grossi, D. (2015). The relationships between interoception and alexithymic trait. The Seòf-Awareness Questionnaire in healthy subjects. *Frontiers in Psychology, 7*(6), 1149.
Magni, E., Binetti, G., Bianchetti, A., Rozzini, R., & Trabucchi, M. (1996). Mini-mental state Examination: A normative study in Italian elderly population. *European Journal of Neurology, 3*(3), 198–202.
Makovac, E., Watson, D. R., Meeten, F., Garfinkel, S. N., Cercignani, M., Critchley, H., et al. (2016). Amygdala functional connectivity as a longitudinal biomarker of symptom changes in generalized anxiety. *Social Cognitive and Affective Neuroscience, 11*(11), 1719–1728.
Marcus, D. K., Gurley, J. R., Marchi, M. M., & Bauer, C. (2007). Cognitive and perceptual variables in hypochondriasis and health anxiety: A systematic review. *Clinical Psychology Review, 27*(2), 127–139.
Mareckova, K., Holsen, L. M., Admon, R., Makris, N., Seidman, L., Buka, S., et al. (2016). Brain activity and connectivity in response to negative affective stimuli: Impact of dysphoric mood and sex across diagnoses. *Human Brain Mapping, 37*(11), 3733–3744.
Martin, A., Buech, A., Schwenk, C., & Rief, W. (2007). Memory bias for health-related information in somatoform disorders. *Journal of Psychosomatic Research, 63*, 663–671.
Medford, N., & Critchley, H. D. (2010). Conjoint activity of anterior insular and anterior cingulate cortex: Awareness and response. *Brain Structure & Function, 214*, 535–549.
Mondini, S., Mapelli, D., Vestri, A., & Bisiacchi, P. S. (2003). *Esame neuropsicologico breve* (p. 160). Milano: Raffaello Cortina Editore.
Mutschler, I., Ball, T., Wankerl, J., & Strigo, I. A. (2012). Pain and emotion in the insular cortex: Evidence for functional reorganization in major depression. *Neuroscience Letters,* 520, 204–209.
Novelli, G., Papagno, C., Capitani, E., Laiacona, M., Vallar, G., & Cappa, S. F. (1986). Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. *Archivio di psicologia, neurologia e psichiatria, 47*(4), 477–506.
Olatunij, B. O., Deacon, B. J., Abramowitz, J. S., & Valentiner, D. P. (2007). Body vigilance in nonclinical and anxiety disorders samples: Structure, correlates and prediction of health concerns. *Behavior Therapy, 38*(4), 392–401.
Pannekoek, J. N., Veer, I. M., van Tol, M. J., van der Werff, S. J. A., Demenescu, L. R., Aleman, A., et al. (2013). Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. *European Neuropsychopharmacology, 23*(3), 186–195.
Park, H. D., Correia, S., Ducorps, A., & Tallon-Baudry, C. (2014). Spontaneous fluctuations in neural responses to heartbeats predict visual detection. *Nature Neuroscience, 17*(4), 612–618.
Pauli, P., & Alpers, G. W. (2002). Memory bias in patients with hypochondriasis and somatoform pain disorder. *Journal of Psychosomatic Research,* 52, 45–53.
Paulus, M. P., & Stein, M. B. (2010). Interoception in anxiety and depression. *Brain Structure & Function, 214*(5–6), 451–463.
Peelen, M. V., & Downing, P. E. (2007). The neural basis of visual body perception. *Nature Reviews in Neuroscience, 8*, 636–648.
Pitkänen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat: A review. *Annals of the New York Academy of Sciences, 911*(1), 369–391.
Pollatos, O., Gramann, K., & Schandry, R. (2007). Neural systems connecting interoceptive awareness and feelings. *Human Brain Mapping, 28*, 9–18.
Pollatos, O., Traut-Mattausch, E., & Schandry, R. (2009). Differential effects of anxiety and depression on interoceptive accuracy. *Depression and Anxiety, 26*(2), 167–173.
Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage,* 59(3), 2142–2154.
Rachman, S. (2012). Health anxiety disorders: A cognitive construal. *Behaviour Research and Therapy,* 50(7), 502–512.
Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*(3), 271–276.
Rey, A. (1958). Mèmorization d'une sèrie de 15 mots en 5 rèpètitions. In A. Rey (Ed.), *l'examen clinique en psychologie*. Paris: Presses Universitaires de France.
Salkovskis, P. M. (1988). Phenomenology, assessment and the cognitive model of panic. In S. Rachman, & J. D. Maser (Eds.), *Panic: Psychological perspectives* (pp. 111–136). Hillsdale, NJ, England: Lawrence Erlbaum Associates, Inc.
Salkovskis, P. M., Rimes, K. A., Warwick, H. M., & Clark, D. M. (2002). The health anxiety inventory: Development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychological Medicine, 32*, 843–853.

Salkovskis, P. M., & Warwick, H. (2001). Meaning, misinterpretations, and medicine: A cognitive-behavioral approach to understanding health anxiety and hypochondriasis. In V. Starcevic, & D. R. Lipsitt (Eds.), *Hypochondriasis: Modern perspectives on an Ancient Malady* (pp. 202–222). New York, NY: Oxford University Press.

Scarella, T. M., Laferton, J. A., Ahern, D. K., Fallon, B. A., & Barsky, A. (2016). The relationship of hypochondriasis to anxiety, depressive, and somatoform disorders. *Psychosomatics, 57*(2), 200–207.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349–2356.

Serino, A., Alsmith, A., Costantini, M., Mandrigin, A., Tajadura-Jimenes, A., & Lopez, C. (2013). Bodily ownership and self-location: Components of bodily self-consciousness. *Consciousness and Cognition, 22*, 1239–1252.

Shafi, M. M., Westover, M. B., Fox, M. D., & Pascual-Leone, A. (2012). Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. *European Journal of Neuroscience, 35*(6), 805–825.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society B: Biological Sciences, 298*(1089), 199–209.

Shandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology, 18*, 483–488.

Skritskaya, N. A., Carson-Wong, A. R., Moeller, J. R., Shen, S., Barsky, A. J., & Fallon, B. A. (2012). A clinician-administered severity rating scale for illness anxiety: Development, reliability, and validity of the H-YBOCS-M. *Depression and Anxiety, 29*(7), 652–664.

Sliz, D., & Hayley, S. (2001). Major depressive disorder and alterations in insular cortical activity: A review of current functional magnetic imaging research. *Frontiers in Human Neuroscience, 3*(6), 323.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31*, 1487e1505.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*(Suppl. 1), S208–S219.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *The state-trait anxiety inventory (test manual)* (p. 22). Palo Alto, CA: Consulting Psychologists.

Spinnler, H., & Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *The Italian Journal of Neurological Sciences, 8*, 14–20.

Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *The American Journal of Psychiatry, 164*(2), 318–327.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*, 643–662.

Tamietto, M., Cauda, F., Celeghin, A., Diano, M., Costa, T., Cossa, F. M., et al. (2015). Once you feel it, you see it: Insula and sensory-motor contribution to visual awareness for fearful bodies in parietal neglect. *Cortex, 62*, 56–72.

Taylor, K. S., Seminowicz, D. A., & Davis, K. D. (2009). Two systems of resting state connectivity between the insula and cingulate cortex. *Human Brain Mapping, 30*, 2731–2745.

Terasawa, Y., Shibata, M., Moriguchi, Y., & Umeda, S. (2012). Anterior insular cortex mediates bodily sensibility and social anxiety. *Social Cognitive and Affective Neuroscience, 8*(3), 259–266.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273–289.

Veer, I. M., Beckmann, C. F., van Tol, M. J., Ferrarini, L., Milles, J., Veltman, D. J., et al. (2010). Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Frontiers in Systems Neuroscience, 4*, 41.

Wechsler, D. (1955). *WAIS. Scala d'Intelligenza Wechsler per Adulti*. Firenze 1974: Tr. it. O.S. Organizzazioni Speciali.

Weiner, K. S., & Grill-Spector, K. (2011). Not one extrastriate body area: Using anatomical landmarks, hMT+, and visual field maps to parcellate limb-selective activations in human lateral occipitotemporal cortex. *NeuroImage, 56*, 2183–2199.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity, 2*(3), 125–141.

Wright, C. I., Martis, B., Mc Mullin, K., Shin, L. M., & Rauch, S. L. (2003). Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. *Biological Psychiatry, 54*, 1067–1076.