Viewing socio-affective stimuli increases connectivity within an extended default mode network

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ABSTRACT

Empathy is an essential ability for prosocial behavior. Previous imaging studies identified a number of brain regions implicated in affective and cognitive aspects of empathy. In this study, we investigated the neural correlates of empathy from a network perspective using graph theory and beta-series correlations. Two independent data sets were acquired using the same paradigm that elicited empathic responses to socio-affective stimuli. One data set was used to define the network nodes and modular structure, the other data set was used to investigate the effects of emotional versus neutral stimuli on network connectivity. Emotional relative to neutral stimuli increased connectivity between 74 nodes belonging to different networks. Most of these nodes belonged to an extended default mode network (eDMN). The other nodes belonged to a cognitive control network or visual networks. Within the eDMN, posterior STG/TPJ regions were identified as provincial hubs. The eDMN also showed stronger connectivity to the cognitive control network encompassing lateral PFC regions. Connector hubs between the two networks were posterior cingulate cortex and ventrolateral PFC. This stresses the advantage of a network approach as regions similarly modulated by task conditions can be dissociated into distinct networks and regions crucial for network integration can be identified.

1. Introduction

Neuroimaging studies on social cognition have consistently found activity in a set of brain regions including the medial prefrontal cortex (mPFC), the precuneus and posterior cingulate cortex (PCC), the temporo-parietal junction (TPJ) and posterior superior temporal gyrus (Lieberman, 2007; Van Overwalle, 2009; Li et al., 2014). These regions are often referred to as a "mentalizing" or "theory of mind" network (Van Overwalle and Baetens, 2009; Schurz et al., 2014). Interestingly, this network largely overlaps with the default mode network possibly reflecting humans' predisposition to think about one's own and other's mental state (Schilbach et al., 2008; Li et al., 2014). Most of these brain regions have also been implicated in the empathic response to others' emotions (Shamay-Tsoory et al., 2009; Krämer et al., 2010; Fan et al., 2011; Lamm et al., 2011; Li et al., 2014; Paulus et al., 2014). Empathy is an essential ability for prosocial behavior in humans, which is typically divided into affective and cognitive empathy (Zaki and Ochsner, 2012). Affective empathy is the emotional response to the affective state of others and relates to vicarious sharing of emotion, whereas cognitive empathy refers to the ability to understand other's feelings and perspective. The terms cognitive empathy, perspective taking, metalizing, and theory of mind (TOM) are often used synonymously. Besides regions listed above, brain areas frequently linked to empathy include the anterior insula (AI), the inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC), and the inferior parietal lobe (IPL) (Zaki and Ochsner, 2012).

Although above-mentioned brain regions have frequently been called "network", merely co-activated brain regions do not constitute a network as a network is not fully characterized by its nodes. A network can only be fully understood through the links between the nodes, so-called edges, which reflect the interdependencies within the network. Numerous studies have examined functional or effective connectivity between individual nodes of the mentalizing or empathy networks (Li et al., 2014). For instance, several studies using seed-

based analyses of functional connectivity consistently showed stronger connectivity between the pSTG/TPJ and the mPFC as well as between the mPFC and the AI with respect to empathy and social cognition (Decety et al., 2008; Mason et al., 2008; Atique et al., 2011; Meyer et al., 2013). Functional connectivity analyses also showed increased connectivity between the PCC and the AI and ACC when observing others in pain (Zaki et al., 2007).

However, these previous studies only examined bilateral connections between different nodes of the mentalizing network and did not consider the network as a whole. Others used meta-analytic connectivity analyses to study what the authors called the "extended social-affective default mode network" (Amft et al., 2014). They identified several clusters within this network such as PCC/precuneus and mPFC related to mentalizing or TPJ and anterior middle temporal gyrus related to language and social cognition. The amygdala and the hippocampus formed an additional cluster related to emotion processing and memory (Amft et al., 2014). Although this approach can be helpful to characterize relations between brain regions across a wide range of tasks and possibly test hypotheses of distinct sub-networks or modules for social cognition (Lieberman, 2007), it is still based on co-activation patterns which do not allow for inferring the strength of connectivity between brain regions or the role of nodes within a network. It is thus not possible to derive an informative connectivity matrix which contains the information on the connectivity between individual nodes from co-activation patterns alone. It is also conceivable that distinct brain regions do not show changes in activity contrasting different experimental conditions, but exhibit altered connectivity. Information on networks derived from co-activations may thus be incomplete. Approaches which allow deriving network matrices from the data in combination with graph-theory-based techniques overcome these limitations. Graph-theory-based approaches are very powerful to characterize the topological organization of neural systems in humans and animals and can be applied to both functional and structural imaging data (Rubinov and Sporns, 2010). This method has been successfully used to study neural networks in different cognitive tasks and in neurological or psychiatric disease states. Graph theory provides measures to quantify topological properties of brain networks at different levels. At the lowest (local) level of network organization, the connectivity between nodes and the individual nodes' centrality in the network can be assessed (Bullmore and Sporns, 2009). The community structure (or network modules) can be considered an intermediate level of network organization (Sporns, 2013). A network module structure is a subdivision of a network into groups of nodes in a way that maximizes the number of within-group edges, and minimizes the number of between-group edges. Looking at the brain data from the perspective of network modules helps to reduce the complexity of the data and allows identifying changes in the large-scale network induced by experimental manipulations (Sporns, 2013). At the highest level of network organization, the network topology is investigated and metrics are derived which describe the network as a whole. Frequently the network's similarity to random, regular or small-world networks is evaluated and it is studied how psychiatric or neurological diseases might affect the topology.

The present study aimed to investigate the neural processing underlying the empathic response to socio-affective stimuli from a network perspective. From a neurobiological point of view it is evident that empathy is mediated by several brain structures working in concert. Network analyses can thus be considered as a consequent step towards understanding the neural correlates of empathy and to study the role and importance of the brain regions within this network.

We used an empathy paradigm which has previously been shown to reliably activate the regions of the mentalizing or extended social—emotional default mode network (Krämer et al., 2010; Beyer et al., 2014). In this paradigm, black/white drawings of social scenes encompassing a single or two persons in an emotionally neutral or negative context were presented and participants were asked to simply

watch the pictures attentively. Drawings of objects were used as control condition. For the present work, we utilized two independent data sets with the exact same experimental paradigm. The first data set (cohort one; N=17) was used to identify network nodes which are relevant for processing social stimuli. This data set corresponds to a previously published study (Krämer et al., 2010). The actual network analysis, i.e. the determination of network edges and the investigation of network properties, was then performed on a second, independent data set (cohort two; N=27). The links between nodes were defined by their functional connectivity, namely beta-series correlation (Rissman et al., 2004). With this approach, we first examined on the intermediate network level, what modules can be identified within those brain regions which are activated by socio-affective visual stimuli and how these modules interact in a socio-affective compared to a neutral context. We expected to identify the extended social-affective default mode network and to find enhanced connectivity within this module in the emotional relative to neutral condition. Second, we asked what the most relevant nodes ("hubs") within and between modules are and how edges within and across modules are altered by the experimental conditions. Based on above-mentioned seed-based connectivity analyses, we were particularly interested in what role mPFC, precuneus and TPJ play within and across modules.

2. Materials and methods

2.1. Participants

The analysis presented in this work utilized two independent data sets. Data-set one comprised seventeen healthy subjects (11 women; age=27.8 ± 4.8 years). The univariate analysis of this data set has been reported previously (Krämer et al., 2010). In the present study, this data set was used to identify relevant brain regions for the network analysis and the modular structure of these brain regions. The network analysis itself was performed in an independent data-set. For data-set two, twenty-seven different healthy subjects were recruited (21 women; age=23.0 ± 3.3 years). All participants were right-handed (except for one woman in group one) and free of any psychiatric and neurological disorder (self-report). In each group, one female subject was excluded due to excessive head motion during the functional imaging, leaving sixteen and twenty-six subjects for the final analysis. In accordance with the Declaration of Helsinki, all subjects gave their written informed consent before participation. The study was approved by the ethics committees of the University of Magdeburg (cohort 1) and the University of Barcelona (cohort 2).

2.2. Empathy paradigm

Exactly the same paradigm was used in both cohorts. For the measurement of neural responses to socio-emotional stimuli, participants were presented with black-and-white drawings of five categories: emotionally neutral situations involving one person only (one person performing a neutral action, such as ironing), emotionally neutral situations involving two persons (two people interacting in a neutral manner, such as playing chess), emotionally negative situations involving one person (one person in distress, such as falling off a boat), emotionally negative situations involving two persons (two people interacting in an aversive manner, such as a man hitting a woman) and scenes with objects only (e.g. a desk). Negative emotions included anger, sadness, pain or anxiety. There were three experimental runs employing a slow event-related design (Fig. S1). Pictures were presented in random order but with no more than two successive pictures of the same condition. Each picture was presented for 6 s, followed by a 10 s fixation cross. Each run comprised 40 drawings, 8 per condition. A picture was only shown once in the whole experiment.

In order to ensure participants were paying attention to the stimuli, a short test-phase followed each experimental run during which 10 of

the previously presented pictures were shown again (two per condition). Half of the pictures were shown not in the original orientation but mirrored. Participants had to indicate by button press with the middle or index finger, respectively, whether a given picture was mirrored or not. No fMRI recording was performed during these short memory tests and the participants were informed about the test prior to the experiment.

The paradigm has been used previously (Krämer et al., 2010; Beyer et al., 2014; Buades-Rotger et al., 2016) and stimuli had been previously validated in a behavioral study reported in Krämer et al. (2010). In this study, 29 participants (14 women; mean age=24.3) rated how strong their negative emotional reactions to the scenes were and how negative the feelings of the depicted persons on a 1–7 Likert scale were. For both two- and one-person scenes, emotional pictures were consistently judged to elicit stronger negative emotions (mean=5.05) than neutral pictures (mean=1.45). Moreover, the depicted emotions were rated as more negative in the emotional (mean=6.1) than in the neutral stimuli (mean=1.5). All differences between emotional and neutral stimuli were significant (all $p < .001$; Krämer et al., 2010).

2.3. Image acquisition

2.3.1. Data-set one

A 3-T Siemens Magnetom Allegra Scanner was used to collect structural (T1-weighted MPRAGE sequence; $1 \times 1 \times 1$ mm^3 resolution; 256×256 matrix; 192 sagittal slices) and functional images (single-shot gradient echo echo-planar imaging; TR=2000 ms; TE=30 ms; matrix 64×64; 32 3-mm transversal slices; 0.75 mm gap; 3×3 mm^2 in-plane resolution; flip angle 80°).

2.3.2. Data-set two

Structural and functional MRI was performed using a 3-T Siemens Magnetom Trio Scanner. Functional images were acquired using a single-shot gradient echo echo-planar imaging (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast (TR=2000 ms; TE=29 ms; flip angle=80°; in-plane resolution 1.9×1.9 mm^2; 32 transversal slices; 4 mm slice thickness; 240×240 mm^2 field of view; GRAPPA factor 4). Additionally, structural images of the whole brain using a 3D T1-weighted MPRAGE sequence (TR=2300 ms, TE=3 ms, TI=900 ms, flipangle 9°, $1 \times 1 \times 1$ mm^3 resolution, 240 sagittal slices, 244×244 mm^2 field of view) were acquired.

2.4. Preprocessing

Preprocessing was performed using the SPM8 software package (Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm/). Functional images were preprocessed using standard procedures which included the following steps: (i) The first four images of each dataset were discarded to allow for magnetization equilibrium. (ii) The data was corrected for differences in the image acquisition time between slices. (iii) A six parameter rigid body spatial transformation was performed to correct for head motion during data acquisition. (iv) The structural image was co-registered to the mean functional image. (v) The structural images were spatially normalized to a standard template (Montreal Neurological Institute). (vi) Spatial normalization of the functional images was performed using the normalization parameters estimated in the previous preprocessing step. (vii) The functional images were resampled to 3 mm×3 mm×3 mm. (viii) Spatial smoothing of the functional data was performed with an 8 mm full width half maximum Gaussian kernel.

We tested if subjects had to be excluded from the analysis due to strong head motion. The six realignment parameters, i.e. three displacements and three elementary rotations with respect to the first image in the series, were used as an estimator for the head motion. The displacements were required to be smaller than 3.0 mm (minimum to maximum) and the individual rotations smaller than 3.0°.

2.5. Univariate analysis

To identify relevant brain regions in cohort one and to assess whether we replicated the results of our first study (Krämer et al., 2010) in the current cohort two, we performed univariate analyses. Functional images were analyzed using a general linear model (GLM). On the single subject level, a design matrix was defined which included one regressor for each of the five conditions (8 trials per run for each condition; duration 6 s). Brain activity during each trial was modelled using the canonical hemodynamic response function (HRF). The design matrix also included the six motion regressors (x, y, z, pitch, roll, yaw) estimated in the motion correction step during the preprocessing to minimize signal-correlated motion effects. A high-pass filter of 128 s was applied to the data. Classical parameter estimation was performed with a one-lag autoregressive model AR(1) to account for serial correlations in fMRI time series due to aliased biorhythms and un-modelled neuronal activity.

Four contrasts were defined on single subject level: neutral single (weighting neutral trials containing non-social pictures of neutral valence positively), neutral social, emotional single and emotional social, each against baseline. We set up a 2×2 factorial GLM on the second level (group level) with the factors emotion (two level: negative or neutral) and social (two level: one person only or two persons interacting). The design matrix included the main effects and interaction.

2.6. Network analysis

We chose a graph theory based approach for our network analyses. A graph consists of a set of nodes which are connected by edges. Nodes represent brain regions, i.e. a collection of voxels which are spatially connected. Edges are defined by the functional connectivity between nodes. The data from cohort one was used to select the network nodes on the basis of a univariate analysis and to derive the modular structure of the brain network. The actual network analysis was then carried out using the data from cohort two and the connectivity within and between network modules and network nodes was investigated. The analysis approach is depicted in Fig. 1. Cohort one was used to select the network nodes and to derive the community structure. The actual connectivity analysis was carried out on the new data set of cohort two. By this approach we avoided any bias due to double dipping (Kriegeskorte et al., 2009). Often network nodes are derived from literature which might be problematic when the comparability of the experimental paradigms is not obvious or when the study cohorts show differences in demographics. In the present analysis we used exactly the same paradigm. Furthermore, both cohorts are highly similar in terms of the relevant demographic properties, i.e. age, gender, handedness and education level (college students). In the following we describe our approach in more detail.

2.6.1. Network nodes

We used a whole brain atlas provided by Craddock et al. (2012). The atlases by Craddock et al. have been made publicly available at: http://www.nitrc.org/projects/cluster_roi/. They were generated via spatially constrained spectral clustering and differ in their level of clustering, i.e. the number and size of the individual clusters. In the present work, we used an atlas showing the highest number of nodes which subdivides the brain into N=773 regions. In comparison to anatomical atlases like the AAL or the Harvard-Oxford atlas this atlas provides a much finer parcellation of the whole brain leading to network nodes which are functionally more homogeneous as they contain a smaller number of voxels (Göttlich et al. 2013).

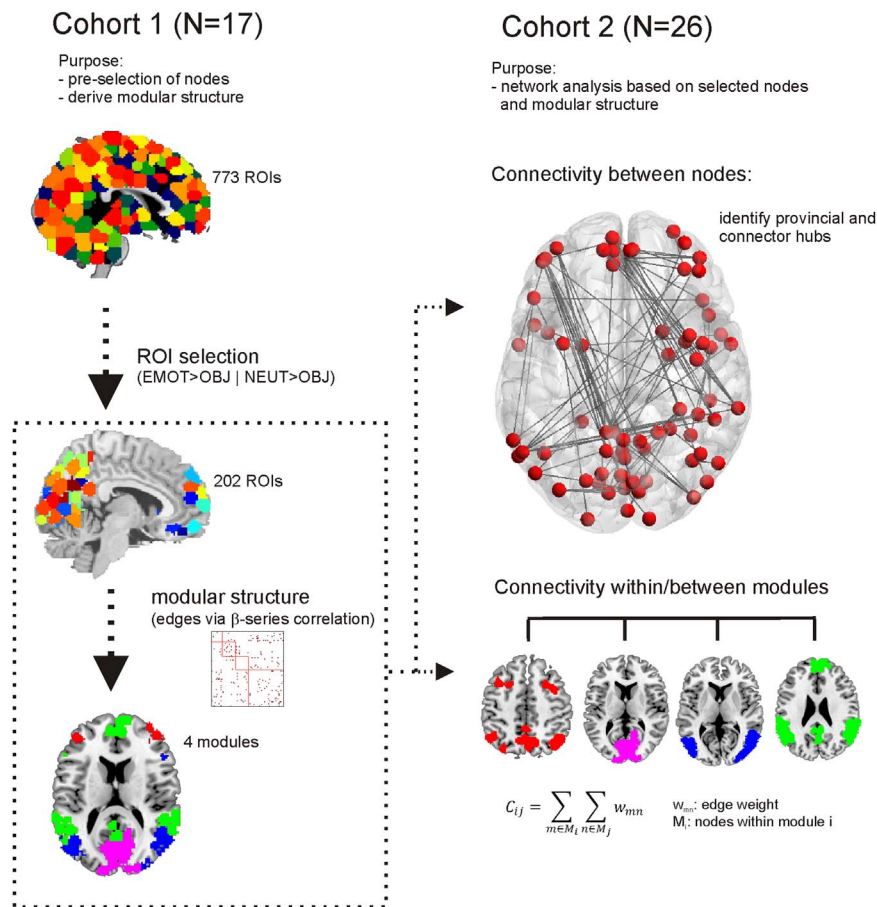To select brain regions which are relevant for processing emotional

Cohort 1 (N=17)

Purpose:
- pre-selection of nodes
- derive modular structure

773 ROIs

ROI selection
(EMOT>OBJ | NEUT>OBJ)

202 ROIs

modular structure
(edges via β-series correlation)

4 modules

Cohort 2 (N=26)

Purpose:
- network analysis based on selected nodes and modular structure

Connectivity between nodes:

identify provincial and connector hubs

Connectivity within/between modules

$$C_{ij} = \sum_{m \in M_i} \sum_{n \in M_j} w_{mn}$$

w_{mn}: edge weight
M_i: nodes within module i

Fig. 1. Analysis flow chart. Cohort one was used to select network nodes relevant for processing socio-affective stimuli employing a univariate activation analysis. The functional connectivity between the nodes (i.e. edges) was then established correlating regional β–series. This resulted in an undirected network matrix which consisted of five modules. The actual network analysis was then carried out on an independent data set (cohort 2). We investigated the connectivity within and between network modules and the connectivity between network nodes to identify provincial and connector hubs.

and social stimuli, we performed a univariate analysis on each brain region in data from cohort one. The same approach as described in Section 2.5 was used but the GLM was evaluated on mean regional time courses within each of the 773 regions instead of the classical voxel-level analyses. Any brain region which showed a significant activation (p < 0.01; uncorrected; 773 statistical tests) contrasting emotional and neutral stimuli with object stimuli was selected for the subsequent network analysis. The rationale behind this approach and the choice of the rather lenient p-threshold was to decrease the number of nodes used in the network analysis but at the same time to keep regions relevant for processing emotional and social stimuli. The number of brain regions pre-selected by this approach was n=202. The relevant brain regions, which were identified based on cohort one, served as nodes for the network analysis conducted with data from the independent cohort two (Fig. 1).

2.6.2. Network edges

The functional connectivity between brain regions was established by a so-called beta-series correlation analysis using in-house software (BASCO toolbox for MATLAB®; publicly available at http://www.nitrc.org/projects/basco). A detailed discussion of the methods used in this toolbox and its functionality can be found in Göttlich et al. (2015). This approach was first introduced by Rissman et al. (2004) and allows investigating inter-regional functional connectivity in event-related fMRI data. The method is implemented on the basis of a general linear model (GLM) where the evoked activity in each trial is modeled by a separate covariate. This renders a series of beta-values related to a given experimental condition. Estimated movement parameters are

included in the GLM and the classical parameter estimation was performed using SPM8. The method is well-established and has been applied in a multitude of connectivity studies (Rissman et al., 2004; Ye et al., 2011; Brunnlieb et al., 2013).

Given a parcellation of the brain, the mean beta-series were extracted for each ROI and a network matrix was calculated correlating all ROI beta-series applying Pearson's linear correlation. Correlation coefficients were Fisher-z transformed to allow for averaging and statistical testing. We obtained connectivity matrices for each experimental condition: emotional single, emotional social, neutral single and neutral social. One single run contained eight trials for each experimental condition. Combining the data from all three runs, results in twenty-four beta-values, i.e. the length of each beta-series is twenty-four. Correlating N=202 (number of nodes) beta-series results in a symmetric connectivity matrix $(w_{ij})=(w_{ji})$ with 20,301 unique entries counting only off-diagonal elements of the upper triangle. The modulation of functional connectivity by an experimental condition was investigated on group-level using a paired t-test. An FDR procedure was applied to correct for multiple testing.

2.6.3. Network community structure

A graph community structure is a subdivision of a network into groups of nodes which are highly interconnected. The community structures of a network can be considered an intermediate level of network organization. The modular structure of the brain network was derived from cohort one. A mean brain network matrix was calculated by averaging the individual network matrices. The mean network matrix was then thresholded keeping 25% of the strongest connections

and a community structure was identified applying Newman's spectral algorithm (Newman, 2006) as implemented in the Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net/). This algorithm maximizes the number of edges falling within modules minus the expected number in an equivalent network with edges placed at random. The rationale behind the choice of this threshold was that the community structure did not change running the algorithm multiple times despite the heuristics in the algorithm. This resulted in a stable and reproducible subdivision of the network. We applied the same threshold also in previous network analyses (Göttlich et al., 2013, 2014). The community structure was then applied to the network matrices of cohort two to assess condition differences (Fig. 1).

2.6.4. Module connectivity

We investigated the connectivity between network modules. The connectivity C_{ij} between the modules M_i and M_j was defined as follows:

$$C_{ij} = \sum_{m \in M_i} \sum_{n \in M_j} w_{mn}$$

Here, w_{mn} is the weight of the edge connecting node m in module i to node n in module j. Note, that for i=j we obtain the connectivity of nodes within a given module. We previously used a similar approach to investigate differences in resting-state functional connectivity in patients with obsessive compulsive disorder compared to healthy controls (Göttlich et al., 2014).

2.6.5. Degree centrality

In graph theory, centrality measures serve as indicators for the importance of individual nodes within a network. A high centrality indicates hub nodes, i.e. nodes which play a central role in a network either in network integration or by processing information from many nodes in the network, i.e. highly specialized nodes given a certain task. Here, we focused on the measure of degree centrality of a node, which is defined as the number of connections (edges) to other nodes in the network.

2.7. Statistical analysis

When testing for effects in connectivity between nodes (edges) and modules, a paired t-test was performed and 0.05 FDR-corrected results are presented (Storey, 2002).

In the context of the univariate analysis (Section 2.5), statistical maps were assessed for cluster wise significance and a topological FDR correction was applied to correct for multiple testing. The cluster defining threshold was p=0.001. The 0.05 FDR corrected critical cluster threshold was k=89.

3. Results

3.1. Univariate analysis

The results of the univariate analysis in cohort two are presented in Fig. 2A and B. Fig. 2A depicts the main effect of emotional content (emotional vs. neutral stimuli). We observed activations in the medial prefrontal cortex (mPFC; superior frontal gyrus), the ventrolateral prefrontal cortex (vlPFC; inferior frontal gyrus), the anterior insula, the amygdala, the middle/superior temporal gyrus and the fusiform gyrus. The main effect of social relation vs. one person as depicted in Fig. 2B showed higher activations in posterior middle/superior temporal gyrus (including the temporo-parietal junction), the precuneus and the cuneus. The results are summarized in Tables S1 and S2. The results are consistent with our previous findings with this paradigm (Krämer et al., 2010).

Fig. 2C shows the regions which were selected for the subsequent network analysis. In cohort one, we found 202 regions showing a significant activation for either emotional or neutral stimuli compared

to object stimuli. The color-coding is arbitrarily used to best emphasize ROI boundaries. All brain regions which were activated in the contrasts testing for effects specific to emotional or social content in cohort two (Fig. 2A and B) are as well represented by ROIs derived from cohort one (Fig. 2C). This shows the consistency of the effects and the validity of our approach to identify relevant network regions in one cohort and apply this to data of the second cohort.

3.2. Connectivity between network modules

Applying Newman's spectral algorithm, the 202 brain regions were structured into four network modules based on data of cohort one (Fig. 3). Module one comprised regions in the middle and inferior frontal gyri (vl/dl PFC), inferior and superior parietal lobe and the precuneus. These regions encompass a fronto-parietal network (FPN) which is mostly associated with cognitive control functions (Dosenbach et al., 2007). Module two consisted of the calcarine and lingual gyrus, i.e. regions including the primary and secondary visual cortex. Module three comprised occipital and temporo-occipital brain regions, i.e. higher-order visual regions. In the following we refer to these modules as VN (visual network) 1 and 2, respectively. Module four finally included nodes in the medial prefrontal cortex, anterior insula, inferior frontal gyrus, posterior middle/superior temporal gyrus and the posterior cingulate cortex. Module four thus largely overlapped with brain regions typically associated with the mentalizing and empathy networks, but also with the default-mode network (Lieberman, 2007; Amft et al., 2014). We will thus refer to this module as extended default-mode network (eDMN) in the following.

We then tested in cohort two how experimental conditions modulate connectivity within and between modules. Performing ten statistical tests, we found three significant condition differences (p < 0.05; 0.05 FDR corrected; Table S3). Fig. 3 depicts how the functional connectivity was modulated by emotional stimuli, i.e. the main effect of emotional vs. neutral stimuli. The data is presented in form of chord diagram and the visualization was done using CIRCOS (Krzywinski et al., 2009). The individual brain network modules are represented by sectors on a circle. Blue lines indicate weaker connectivity for emotional stimuli, whereas red lines indicate stronger connections. Effects on the within module connectivity are indicated by blue and red colored sectors. Emotional relative to neutral stimuli increased connectivity of nodes within the eDMN. The nodes within VN2 (higher-order visual regions) showed weaker connectivity for emotional stimuli. Also the connectivity between VN2 to the FPN was decreased for emotional relative to neutral stimuli. The results are summarized in Table S3.

Our main focus was on the comparison between emotional and neutral stimuli but for completeness we also explored the main effect of social relation. We found an increased connectivity between the VN1 and 2 (0.05 FDR corrected; Table S4) for stimuli depicting social interactions. The increased connectivity between the two visual networks might be a consequence a larger complexity of the pictures involving two persons.

3.3. Connectivity modulated by emotional content

Next, we analyzed the main effect of emotional content (emotional > neutral stimuli) on connectivity between individual nodes within and between modules (or networks). We found 93 edges connecting 74 nodes (of 202 nodes; MNI center of mass coordinates in Table S5) which were stronger for stimuli with emotional content (p < 0.05 FDR corrected, Table S6). The results are depicted in Fig. 4 in form of chord diagrams. Fig. 4A shows all edges which connect nodes within modules, whereas Fig. 4B depicts all edges which connect nodes of different modules. We observed a higher connectivity between several nodes within the eDMN (Fig. 4A). This is consistent with the results shown in Fig. 3, namely a generally increased connectivity within the eDMN in
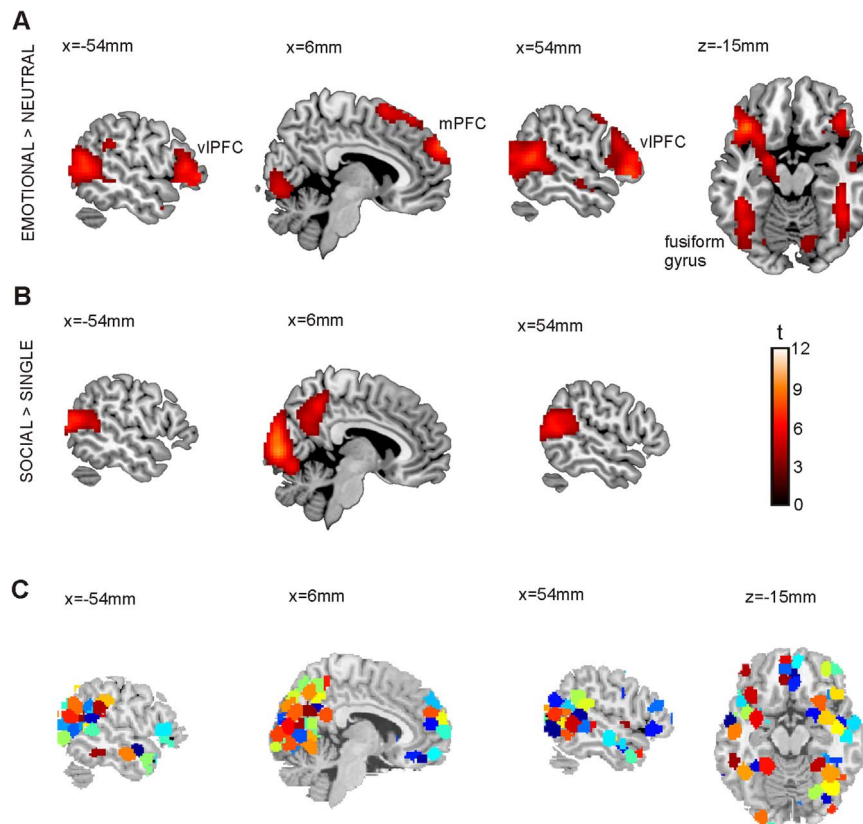
Fig. 2. Brain activity modulated by emotional content and social relation. A) Main effect emotional vs. neutral stimuli (emotional > neutral; cohort 2). B) Main effect social relation vs. single person (social > single; cohort 2). Statistical t-maps were assessed for cluster-wise significance using a cluster defining threshold of p=0.001 applying a topological q=0.05 FDR-correction. C) ROIs showing a significant effect for either emotional and/or social stimuli compared to objects (p < 0.01 uncorrected; cohort 1). These ROIs are used as nodes in the connectivity analysis. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

response to emotional relative to neutral pictures. Most prominent are stronger connections between posterior temporal and temporo-parietal brain regions and the medial PFC, the anterior insula and the amygdala. Whereas the analyses of connectivity on module-level revealed a relative decrease of connectivity within VN2 (see above and Fig. 3), no individual edge was significantly affected by emotional vs. neutral content (Fig. 4A). This suggests that the connectivity of edges within this module was generally slightly reduced during the emotion condition which yielded significance only when averaging across the whole module. On the other hand, we observed increased connectivity between few nodes in VN1 (lingual and calcarine cortex) in the emotion condition. Finally, within the FPN (cognitive control network), only one edge was significantly modulated by emotional content (superior frontal to medial frontal gyrus).

Fig. 4B shows all edges connecting different modules (between-module edges) which are significantly stronger for emotional stimuli. Increased connectivity between VN1, VN2 and the FPN are depicted in black, whereas connections between the eDMN and the other three networks are depicted in red, blue and purple. As can be readily assessed, emotional content mainly affected connectivity between nodes of the eDMN and nodes of the other modules. Regarding connectivity between the eDMN and the cognitive control network, we found the vlPFC and the dlPFC to be more strongly connected to the precuneus and the posterior cingulate cortex, but also to mediofrontal nodes. Regarding connections between the eDMN and VN2 (indicated by blue lines), we found especially a higher connectivity between temporo-parietal and mediofrontal regions to the fusiform gyrus. Also the precuneus was found to be more strongly linked to the inferior occipital cortex. Regarding connectivity between VN1 and 2, emotional content increased connectivity between the calcarine and lingual gyri of VN1 and the superior parietal and middle occipital cortex of VN2.

Emotional content did not affect connectivity of cognitive control network nodes and nodes of VN2 and only few edges to VN1 were modulated.

In Fig. 4, the node degree centrality differences between emotional and neutral conditions are shown in form of histograms (inward connectivity in Fig. 4A and outward connectivity in Fig. 4B). Some nodes were highly connected during processing of emotional in comparison to neutral stimuli which is expressed by a high degree centrality (blue histograms in Fig. 4). These nodes are also depicted in Fig. 5, which shows the nodes with the highest within-module (Fig. 5A) and outward (Fig. 5B) degree centrality (one standard deviation above the mean). Nodes with high within-module degree centrality can be considered provincial hubs, whereas nodes with high between-module degree centrality can be considered connector hubs. Fig. 4C and D show the anatomical location of all nodes with a degree centrality one standard deviation above the mean. All provincial hubs but the lingual gyrus (VN1) belonged to the eDMN. They were located in the temporal and parietal cortex (bilateral angular and right supramarginal gyrus including the temporo-parietal junction), the dorsomedial PFC and the anterior insula. Connector hub regions were particularly the ventro-lateral PFC (FPN) and the posterior cingulate cortex (eDMN) (Fig. 5D). The ventrolateral PFC showed increased connectivity to multiple nodes in the eDMN and to nodes of VN1 in the emotional relative to neutral condition. The posterior cingulate cortex showed increased connectivity to nodes in the FPN (cognitive control network) and to nodes of VN2. Other regions like the ventromedial PFC (eDMN) and the fusiform gyrus (VN2) were also found to be connector hubs.
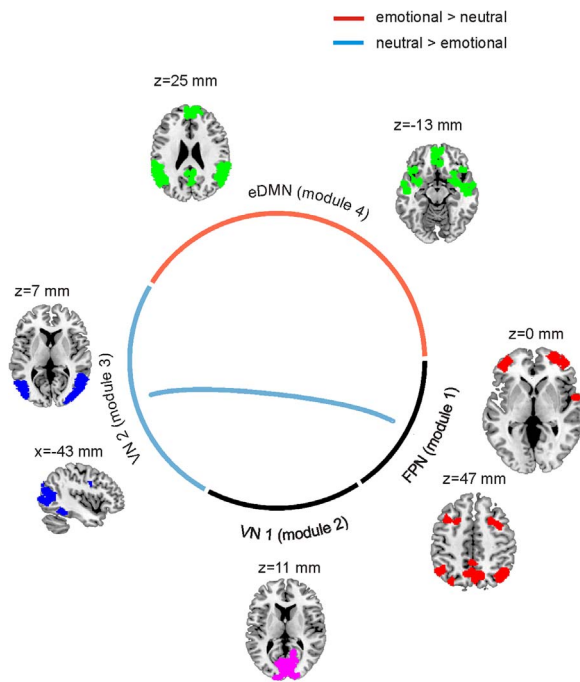
Fig. 3. Inward and outward brain network module connectivity modulated by emotional content. Shown are connections which are significantly different comparing emotional and neutral stimuli (p < 0.05 FDR corrected; cohort 2). The modular structure was derived from cohort 1. Red lines and sectors indicate outward and inward connections which are significantly stronger for emotional stimuli, whereas blue lines and sectors indicate weaker connections. Also shown are the brain regions comprising the network modules. Abbreviations: eDMN – extended default mode network; FPN – fronto-parietal network; VN – visual network. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

3.4. Comparison of emotion effects on connectivity and activation maps

Fig. 6 depicts all network nodes which showed a stronger connectivity during the emotional relative to neutral trials (blue; Fig. 4; Table S5) and voxels which showed higher activity (main effect of emotion). For the purpose of this comparison a relatively lenient threshold of p < 0.005 (uncorrected) with a cluster size of k > 20 was applied (see Fig. 2 for 0.05 FDR corrected data). As expected, there was considerable overlap between the two maps particularly in lateral and medial PFC, inferior temporal cortex and occipital cortex. Interestingly however, the posterior cingulate cortex and the precuneus showed changes in connectivity and a high degree centrality (Fig. 5B), but changes in activity comparing emotional and neutral stimuli were not significant even at lenient probability thresholds.

4. Discussion

We investigated the neural response to social-emotional stimuli from a network perspective using a graph-theory based analysis approach. Using a paradigm eliciting empathic responses to persons in emotionally charged situations, we assessed experimentally induced connectivity changes on intermediate and lower network levels.

The stimulus material was designed to elicit heterogeneous categories of negative emotions. In a previous behavioral validation study, we verified that different negative emotions were elicited by the stimuli (for details see Krämer et al. (2010)). Although the empathic response to these different emotions might well vary to some extent (depending on the quality, intensity and complexity of the depicted emotion), these differences were not the focus of the present work. The focus was rather on the general empathic response to others' negative emotions. Also, we did not control to which extent affective or cognitive aspects of
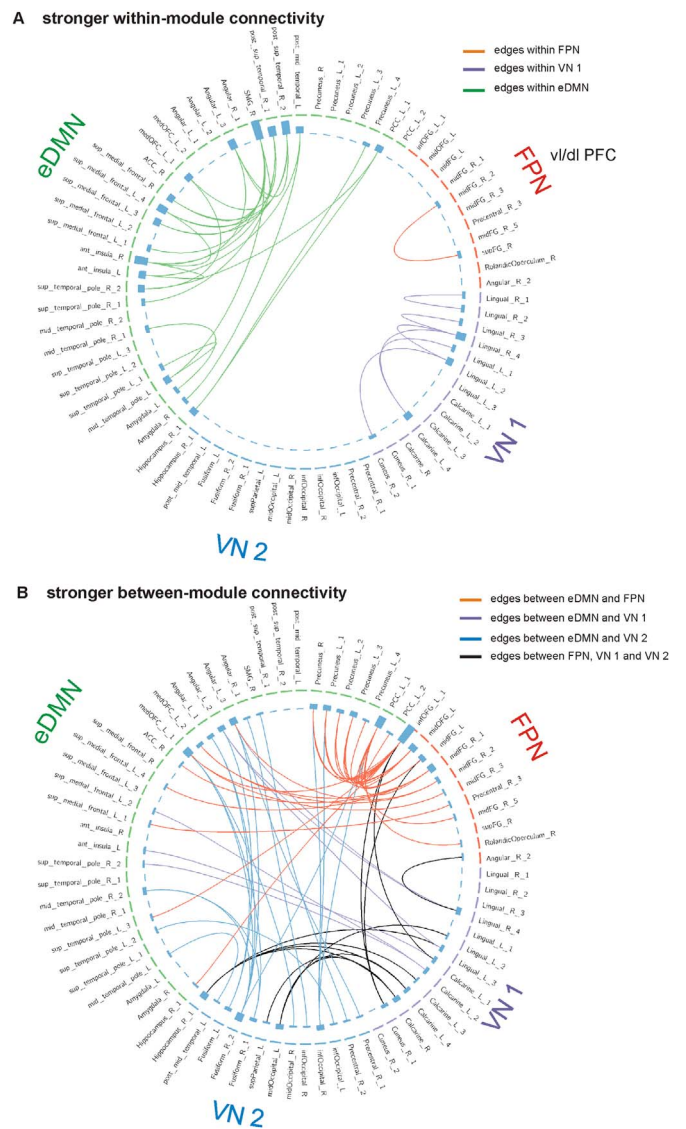

Fig. 4. Connections (edges) between network nodes which are significantly stronger for emotional vs. neutral stimuli. The network analysis was performed on cohort 2 using the ROIs derived from cohort 1 (Fig. 2C). A 0.05 FDR correction for multiple testing was applied. Network nodes are grouped according to the modular structure derived from cohort 1 (Fig. 3). A) Edges within modules showing increased connectivity. B) Edges between modules showing increased connectivity. Red: edges between eDMN and FPN; Purple: edges between eDMN and VN1; Blue: edges between eDMN and VN 2; Black: connections between FPN, VN1 and 2. The blue bars indicate the number of inward (A) and outward (B) connections which are stronger for emotional stimuli. Abbreviation: eDMN – extended default mode network; FPN – fronto-parietal network; VN – visual network. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

empathy were triggered by the stimulus material. Although it is reasonable to assume that both aspects play a role when viewing the pictures with emotional content we cannot make specific claims about involved cognitive and affective processes. As participants are not instructed to focus on any particular aspect of the stimulus material or their own affective response, the paradigm is especially suited to study participants' propensity to spontaneously engage in perspective-taking and empathizing. Future studies comparing different tasks (e.g. focusing on one's own vs. the other's emotions) will help to relate the reported network to specific aspects of empathy.

Note that we investigated functional but not effective connectivity which would be an interesting future direction but which is challenging due the multitude of network nodes involved in processing socio-affective stimuli. The analysis of the network module structure revealed
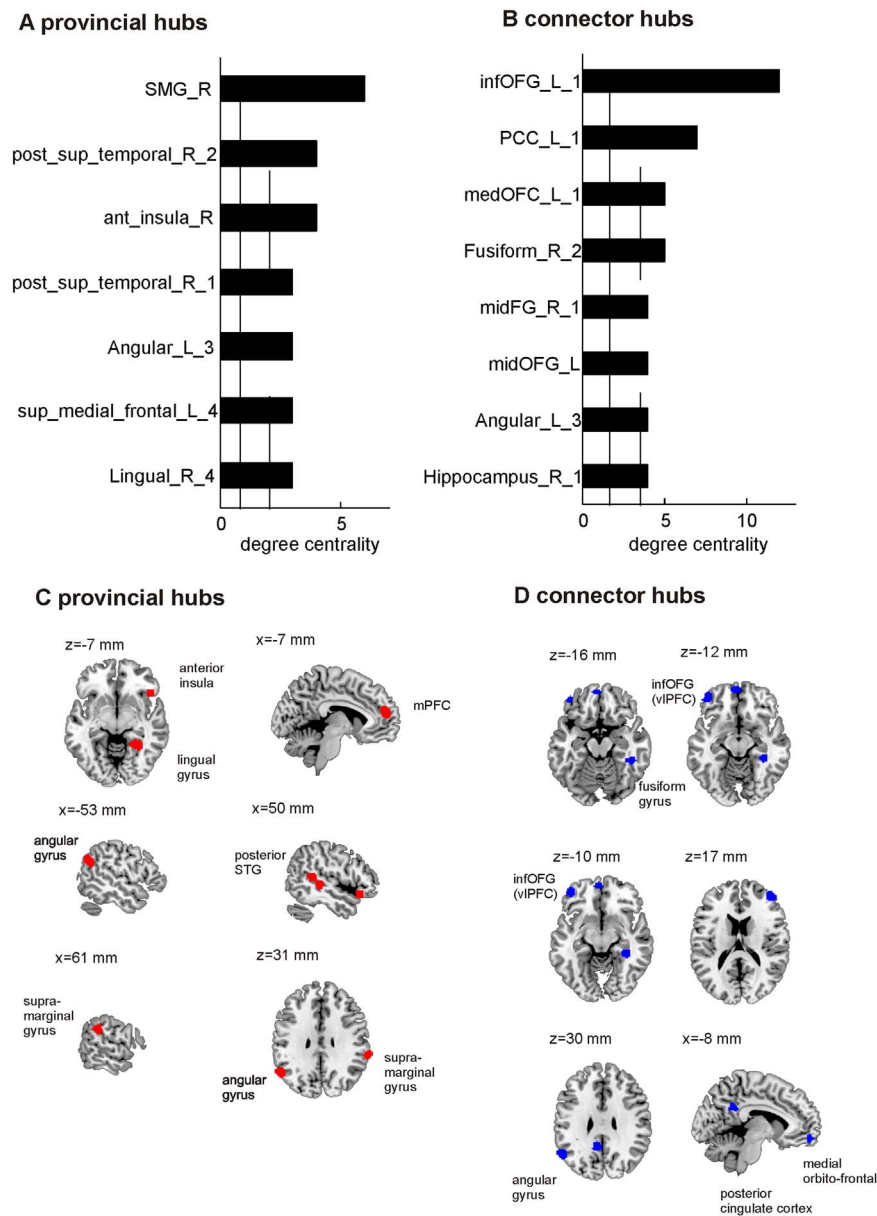
Fig. 5. Network nodes identified as provincial and connector hubs. A) Nodes showing a high within-module degree centrality (provincial hubs). B) Nodes with a high outward degree centrality (connector hubs). The solid lines indicate the mean degree centrality and the dashed lines indicate one standard deviation. Anatomical localization of (C) provincial and (D) connector hubs. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

an extended default mode network which showed increased within-module connectivity whereas visual and cognitive control modules showed reduced or unchanged connectivity. Within the eDMN, the emotional context increased connectivity especially between temporo-parietal areas and both dorsal and ventral mediofrontal areas as well as to the anterior insula. Moreover, precuneus and PCC showed increased connectivity to regions outside the eDMN, particularly to dorsal and ventral frontolateral regions. Hubs within the eDMN ("provincial hubs") were found to be the supramarginal gyrus, dorsomedial PFC, anterior insula and superior temporal cortex whereas hubs connecting different modules ("connector hubs") were identified as ventrolateral PFC, PCC and ventromedial PFC. In the following, we will first discuss the identified modular structure and then the observed connectivity changes both within eDMN and between eDMN and other modules.

4.1. Modular structure

The modular structure was identified based on activation maps in

an independent data-set which had been published previously (Krämer et al., 2010). The general effects of experimental conditions on brain activations were largely comparable between the two data-sets which can be assessed from Fig. 2 in the present work and Figs. 2 and 3 in the previously published paper. Specifically, comparing the emotional relative to neutral condition in our main data-set (Fig. 2) revealed activity in several brain regions related to empathy and social cognition (Zaki and Ochsner, 2012): anterior insula (AI), inferior frontal gyrus (IFG), medial prefrontal cortex (mPFC), ventrolateral prefrontal cortex (vlPFC), posterior part of the superior temporal lobe (pSTL), temporo-parietal junction (TPJ), amygdala and inferior parietal lobe (IPL). Similar activation patterns in both cohorts justify our approach to identify the network module structure in one data-set and apply it to the other data-set. This approach has the advantage that the network connectivity analysis is not biased by both identifying the module structure and investigating connectivity changes in and between these modules in the same data.

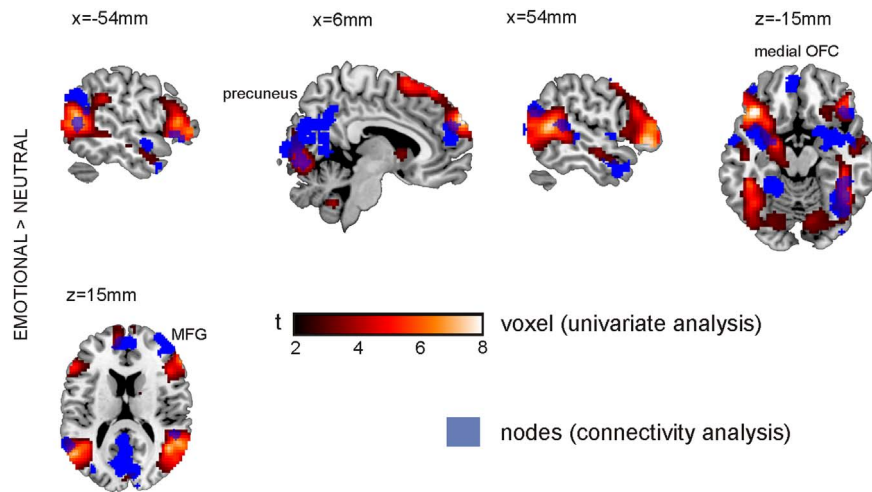We included in our module structure analyses all brain regions

Fig. 6. Comparison between activation and connectivity analyses. Shown are the network nodes which showed a stronger connectivity during the emotional trials (blue) and voxels which showed a higher activation. For the purpose of this comparison a p-threshold of p < 0.005 (uncorrected) with a cluster size of k > 20 was required. Corrected data is shown in Fig. 2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

which showed increased activity in any of the conditions involving socio-affective stimuli relative to objects. This reduces the number of brain network nodes from 773 to 202 regions which makes the analyses of a module structure more feasible and stable while preserving information about all relevant areas for (visual) social information processing. We determined the community structure in cohort one by applying Newman's spectral community detection algorithm to the group-mean correlation matrix. A proportional threshold of 25% was applied to the connectivity matrix. We chose this particular threshold as it led to a stable community structure, i.e. running the algorithm multiple times led to the same modules containing the same nodes. This was not the case for less stringent thresholds (tested 30% and higher in steps of 5%). Applying a threshold of 20% or less led to a disconnected network, i.e. single nodes were not connected to the network anymore. Since we wanted to characterize network nodes in terms of their role as provincial or connector hubs we aimed for a stable modular structure. No false positives enter the analysis by the choice of a certain threshold. Only the stability of the algorithm and the assignment of individual nodes to modules is affected. The choice of the threshold has a similar effect as changing the number of components in an Independent Component Analysis. The community structure was mainly used to group the nodes in such a way that the chord diagrams used to display the network are clearer as highly connected nodes are grouped together. The community structure also allows characterizing nodes and to identify provincial and connector hubs. This part of the analysis is purely descriptive and guides the interpretation of the results. The most relevant point for motivating our approach is that the modules resemble well known networks (visual, default mode, fronto-parietal network). Looking for provincial and connector hubs based on this community structure is thus very reasonable.

The analysis of the network community structure revealed four different network modules, of which one corresponded to an extended default mode network (eDMN). We use the term 'extended DMN' since module four contains brain regions which are not typically regarded as DMN regions, i.e. the anterior insula, the rostral temporal lobe and the amygdala. The DMN (Shulman et al., 1997) has been characterized as a 'task negative network' since the regions of the DMN decrease their activity during the execution of a task, e.g. motor tasks or visual stimulation (Gusnard and Raichle, 2001; Raichle et al., 2001). However, the DMN shows increased activity in social cognition tasks (Iacoboni et al., 2004; Uddin et al., 2005; Mars et al., 2012; Bzdok et al., 2013; Amft et al., 2014; Li et al., 2014; Bzdok et al., 2015; Eickhoff et al., 2016) or self-related processes (Gusnard et al., 2001; Wicker et al., 2003; Buckner and Carroll, 2007) as well as to episodic

memory (Greicius and Menon, 2004) and memory consolidation (Miall and Robertson, 2006).

In addition to the core DMN regions, the extended DMN included limbic and para-limbic brain regions as the anterior insula, the amygdala, hippocampus and the rostral temporal lobe which are known to be involved in emotional processing and empathy. This network largely coincides with a recent report of an "extended socio-affective DMN" which was based on meta-analytic connectivity modelling and resting-state analyses (Amft et al., 2014). The AI was not included in the work of these authors but has often been reported with respect to empathic responses to various emotions as pain, disgust or embarrassment (Jackson et al., 2005; Krämer et al., 2010; Krach et al., 2011; Zaki and Ochsner, 2012). Besides the extended DMN, three other modules were identified which reflected lower and higher-order visual perceptual processes (VN1 and VN2) and a network of fronto-parietal regions (FPN) typically associated with cognitive control, attention and emotion regulation (Dosenbach et al., 2008; Vincent et al., 2008; Banich et al., 2009; Power et al., 2011; Cole et al., 2013; Schweizer et al., 2013). Finally, brain regions which were specifically activated for emotional relative to neutral stimuli (Fig. 2) mostly belonged to the extended DMN but also to the cognitive control network (ventrolateral PFC) and higher-order visual network (fusiform gyrus). This shows the importance of identifying a network based on functional connectivity instead of mere co-activation patterns.

4.2. Connectivity changes within the extended DMN

When applying the modular structure to the second data-set and examining connectivity changes caused by emotionally charged relative to neutral social stimuli, we found generally enhanced connectivity within the eDMN. This observation establishes the existence of a socio-affective network directly from functional connectivity and not from mere co-activation alone. This was found both on a module level (Fig. 3) and node level (Fig. 4), which showed emotion effects on connectivity mostly on the eDMN. On the node-level, we found stronger connectivity between posterior temporal lobe, angular and supra-marginal brain regions to limbic (amygdala, hippocampus) and para-limbic (temporal poles, TP) structures, the AI and mPFC. Within the eDMN, the supra-marginal and the angular gyrus node (both overlapping with the TPJ) and nodes in the posterior temporal lobe showed the strongest changes in connectivity as indicated by the highest condition effects on within-module degree centrality.

These temporo-parietal regions have been consistently reported in mentalizing or theory-of-mind studies (Castelli et al., 2000; Gallagher

et al., 2000; Narumoto et al., 2001; Vogeley et al., 2001; Calder et al., 2002; Heberlein et al., 2004; Gobbini et al., 2007; Carrington and Bailey, 2009; Bzdok et al., 2012) as well as in a range of other tasks unrelated to social cognition, such as audiovisual integration or biological motion perception (Saygin, 2007; Hein and Knight, 2008; Stevenson and James, 2009). The TPJ and adjacent brain regions have also been implicated in the attribution of agency to others (Farrer and Frith, 2002; Farrer et al., 2003). It has been proposed that the pSTG/TPJ implements detection and understanding of others' intentions and goal-directed behavior by integrating information from visual areas (Allison et al., 2000; Gallagher and Frith, 2003) and from brain areas relevant for evaluating socio-affective stimuli, such as amygdala, AI and mPFC (Li et al., 2014).

The increased functional connectivity between the pSTG/TPJ and mPFC in theory-of-mind and empathy related tasks has been reported in several seed-based functional connectivity analyses (Mason et al., 2008; Burnett and Blakemore, 2009; Atique et al., 2011; Baumgartner et al., 2012; Herve et al., 2012). In our data, the integrating function of the pSTG/TPJ is expressed by the high degree centrality, i.e. the increased connectivity to most brain regions of the extended DMN except for the PCC and precuneus. Also, nodes within the angular gyrus showed higher connectivity to areas outside the eDMN, namely the fusiform gyrus and the inferior/middle occipital cortex (VN2; see discussion below), reflecting its strong interrelation with areas involved in object and face perception. These nodes were not as strongly connected to other nodes within the extended DMN as to the pSTG/TPJ. On the other hand, PCC and precuneus showed an increased functional connectivity mostly to limbic and para-limbic brain regions, i.e. the hippocampus and rostral temporal lobe areas.

The bilateral anterior insula was also identified as a part of the extended DMN. This extends previous work where this brain structure was not reported as an integral part of the social-affective network (Mars et al., 2012; Amft et al., 2014). The anterior insula is frequently found to be activated in theory of mind and empathy studies (Carrington and Bailey, 2009; Craig, 2009; Menon and Uddin, 2010; Zaki and Ochsner, 2012). As reviewed by Craig (2009), the anterior insula is involved in interoception, experiencing emotional feelings, attention, cognitive control, performance monitoring and decision making. Menon and Uddin (2010) suggested that the anterior insula is a hub region which reacts to emotionally salient stimuli, facilitates access to attention and working memory when a salient event is detected, modulates via the posterior insula autonomic reactivity to salient stimuli and facilitates motor responses via its strong link to the anterior cingulate cortex. Supporting this view, Seeley et al. (2007) found that the anterior insula is part of both the executive-control and salience network. In the context of processing emotional picture stimuli, our data points to the anterior insula as a local hub region with strong connectivity to the medial PFC and the pSTG/TPJ (Fig. 4A). We did not observe stronger connectivity during the emotional condition to the fronto-patietal network (FPN). A stronger connectivity to the fronto-parietal network might be observed in paradigms where subjects actually have to respond to emotional stimuli.

To summarize, viewing emotionally charged social scenes increased connectivity generally within the extended DMN with the strongest effects on connectivity of the pSTG/TPJ regions and anterior insula with other DMN regions.

4.3. Connectivity changes between the extended DMN and the cognitive control network

Although PCC and precuneus showed higher connectivity to limbic brain regions within the DMN, connections to other nodes within the extended DMN were not modulated by the emotional content. However, we found the PCC and the precuneus to be more connected to nodes of the FPN when emotional compared to neutral social stimuli

were presented. The FPN comprised brain-regions known to be involved in cognitive/executive control. Connections involving several nodes of the network, namely left vlPFC (IFG) and the right dlPFC, were modulated by the emotional content. The dlPFC has been implicated in top-down cognitive control and regulation of emotions (Ochsner and Gross, 2005; Herwig et al., 2007; Kanske et al., 2011; Aupperle et al., 2012; Silvers et al., 2015). Silvers et al. (2015), for instance, investigated the neural bases of uninstructed modulation of negative emotions. In their work, lower levels of self-reported negative affect evoked by aversive emotional stimuli were associated with recruitment of dorsolateral and dorsomedial PFC whereas higher levels of negative affect were associated with recruitment of the amygdala. Ohira et al. (2006) investigated the association of neural responses during voluntary suppression of emotions of both positive and negative valence. They found higher activation in the vmPFC and vlPFC during emotion suppression compared to attention. In a review article, Ochsner and Gross (2008) discussed sixteen articles investigating emotion regulation. All studies reported concurrent evidence for the implication of the vlPFC in emotion regulation independent of the actual strategy (suppression, reinterpretation or emotional dissociation).

The increased connectivity between the extended DMN and vl/dl PFC nodes (within the FPN) thus likely facilitates regulation of negative emotions. The PCC appears to be an important inter-modular connector hub in this process as it shows the strongest changes in connectivity to lateral PFC nodes and limbic/para-limbic brain regions during processing of emotional stimuli (Fig. 4). The role of the PCC in cognition and its strong integration within the DMN and its functional connectivity to the fronto-parietal cognitive control network at rest is well-established (Leech et al., 2011, 2012; Leech and Sharp 2014). The PCC has been shown to be activated by emotional stimuli, independent of positive or negative valence (Maddock et al., 2003). It is also a brain region which is consistently found to be activated in TOM/empathy tasks (Carrington and Bailey, 2009; Bzdok et al., 2012; Zaki and Ochsner, 2012) as discussed earlier in the context of the DMN. Importantly, the PCC is part of a brain network including lateral and medial PFC regions and temporal brain regions which is implicated in emotion generation and regulation via reappraisal (Ochsner et al. 2004; Otto et al., 2014). This emphasizes the role of the PCC in integrating emotion and cognition and explains its connectivity to the cognitive control as well as limbic brain regions in the context of emotional processing and its appearance as connector hub within the brain network. The important role of the PCC as a central hub within the brain network is also evident from structural data using diffusion tensor imaging (DTI) (Hagmann et al., 2008). The PCC is a structural core region, i.e. a region with high degree centrality constituting a connector hub that links all major structural brain network modules.

Interestingly, the PCC did not show a higher activation during processing of emotional stimuli (main effect of emotion; Figs. 2 and 6) but significant changes in functional connectivity. This emphasizes both the importance of the PCC in processing emotional stimuli and the strength of the functional connectivity analysis complementing the univariate analysis investigating the brain activations only.

Apart from showing a stronger connectivity to the PCC and the precuneus, the lateral PFC (FPN) was found to be strongly connected to the angular gyrus, medial PFC brain regions and limbic brain regions including the hippocampus (Fig. 4B). The left vlPFC (IFG) showed the highest outward-degree centrality (Fig. 5B and C). The vlPFC has been associated with the expectation and evaluation of emotional stimuli (Hynes et al., 2006; Bender et al., 2007), with decision making (Rolls, 2000; Kringelbach and Rolls, 2004), behavioral inhibition (Rubia et al., 2003; Aron et al., 2004; Goldstein et al., 2007) and emotion regulation (Ohira et al., 2006; Ochsner and Gross, 2008). The left vlPFC appears as a crucial connector hub (high outward degree) which integrates information from a multitude of DMN regions. Future studies might examine altered connectivity between lateral PFC and the extended

DMN during empathic responses in psychiatric patient populations (e.g. anxiety disorders, obsessive-compulsive disorder) using a similar network approach expanding on previous seed-based connectivity studies (Fitzgerald et al., 2010; Harrison et al., 2013; Arnold Anteraper et al., 2014; Posner et al., 2014) or resting-state network analyses (Göttlich et al., 2014).

5. Conclusions

The investigation of functional connectivity between nodes activated by socio-emotional visual stimuli led to new insights into the neural mechanisms underlying empathy. We show that the common approach to assign co-activated brain regions to a single network is not valid and that brain regions responding to socio-affective information can be assigned to several sub-networks or modules. The extended DMN is specific for processing emotional stimuli, whereas the other networks related to visual processing and cognitive control/attention (fronto-parietal network) are not. Looking at the data from the network perspective revealed a stronger functional connectivity within the extended DMN in response to emotionally charged social stimuli. Within the extended DMN, the posterior STG/TPJ region and the anterior insula proved to serve as provincial hubs. Our data also suggested an interaction between the extended DMN and the FPN (cognitive control) likely reflecting emotion regulation. Crucial connector hubs between the two network modules were the posterior cingulate cortex (DMN module) and the left ventrolateral PFC (FPN).

Conflict of interest

None.

Acknowledgements

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2016.12.044.

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