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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