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I KNOW THE PAIN YOU FEEL—HOW THE HUMAN BRAIN'S DEFAULT MODE PREDICTS OUR RESONANCE TO ANOTHER'S SUFFERING

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Abstract—Introspective and self-referential in nature, the human brain's default mode network (DMN) is presumed to influence our behavior in response to the environment in predictive manner [Raichle ME, Gusnard DA (2005) J Comp Neurol 493:167–176; Bar M (2009) Philos Trans R Soc Lond B Biol Sci 364:1235–1243]. In the current study, we hypothesize that the strength of DMN-connectivity contributes to distinct introspective psychological processes in every-day social life such as the intuitive understanding of other people through inner representation of their affective states −e. g. his or her pain. 19 healthy individuals underwent functional MRI scanning, which consisted of a resting-state-scan followed by the presentation of visual stimuli depicting human limbs in painful and non-painful situations. After scanning, participants were asked to evaluate the stimuli in terms of pain intensity perceived from the first person perspective. Independent component analysis (ICA) demonstrated that higher integration of the left medial orbitofrontal cortex (BA 32) into the anterior default mode network (aDMN) was associated with higher post-scan pain ratings. Furthermore, the exposition to the "Pain"-pictures led to relative increases of aDMN-activity compared to "No Pain"-stimuli which were also correlated with the subjective pain intensity. The behaviorally predictive functional architecture during a task-free period supports the notion that the DMN serves as a "memory of the future" [Ingvar DH (1985) Hum Neurobiol 4:127–136] in terms of a neuronal cache, storing "a priori scripts," which are recalled to deal efficiently with upcoming environmental events. In addition, our results suggest that an individual predisposition to identify oneself with another's pain influences the automatic response of the DMN during the observation of painful situations. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: default mode network, resting state, pain, emotion, introspection, proactive brain.

The human brain's resting state does not reflect random background noise, but represents a highly ordered neural "baseline" which comprises medial prefrontal cortex (mPFC), posterior cingulate, and precuneus as well as lateral parietal and temporal regions (Greicius et al., 2003). As spontaneous and continuous as heartbeat and breathing, BOLD-oscillations of this so-called default mode network (DMN) (Raichle et al., 2001) can be interpreted as a neural "self" in terms of a stable perspective of the individual in relation to its environment (Gusnard and Raichle, 2001). Thus, its functional architecture has often been presumed to reflect our individual disposition to feel and to think—and therefore to be predictive for our behavior (Raichle and Gusnard, 2005; Bar, 2009).

Being decreased by externally oriented attention, the DMN is active whenever the organism comes to focus on its own inner status −e. g, during a resting state, remembering the past, prospection and reasoning about the feelings of others which can be seen as introspective and self-projective in the broadest sense (Buckner and Carroll, 2007).

These processes are an every-day phenomenon in social interaction. Understanding other people relies heavily on the inner representation of their affective state, and this represents the first step towards human empathy (Decety and Jackson, 2004). However, this ability is developed to varying degrees in different individuals. Given the DMN as a stable distribution for perceiving our environment in relation to ourselves, the question emerges of whether the way we share our conspecifics' affective state is encoded in the functional anatomy of this circuit at rest.

Furthermore, the reduction of DMN-activity caused by exteroception is attenuated especially in medial prefrontal regions if the perception of an outer event elicits self-referential processes such as feelings and subjective judgments (Gusnard et al., 2001; Sheline et al., 2009). However, it remains unclear whether individually different DMN-connectivity during affective sharing can be linked to differences in the subjective perception of the emotionally laden outer event.

In this study, we focused on a specific and evolutionary fundamental introspective and self-referential trait in human social interaction—sharing others' pain. Critical to

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Abbreviations: DMN, default mode network; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; medOFC, medial orbitofrontal cortex; ROI, region of interest.

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survival, pain not only warns the suffering person by its physical threat value. Beyond that, it automatically attracts emotional attention leading to high affective contagion in potential caregivers (Craig, 2004) which makes an influence of the DMN very likely.

Using an established paradigm (Jackson et al., 2005, 2006), the primary aim of this investigation was to test if the DMN's functional architecture during a task free period would be predictive for the extent to which one shares another's pain measured by post-scan pain ratings. Furthermore, we hypothesized that observing others in pain would automatically lead to less task-induced decreases of DMN-connectivity than in response to non-painful situations. We presumed that this relative increase from the "No Pain"-to the "Pain"-condition would be correlated with the level of pain which one perceives when putting oneself into the painful situation.

EXPERIMENTAL PROCEDURES

The study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Subjects

Nineteen healthy Caucasians (mean age: 48.79 yrs, SD 12.25, 13 females) gave informed written consent to participate in the experiment. No subject had any history of neurological, major medical, or psychiatric disorder as proved by SCID-I-Interview (Wittchen et al., 1997). All participants were right handed, as assessed by the Edinburgh handedness inventory (Oldfield, 1971).

Psychometric instruments

The occurrence of psychiatric disorders was assessed during a structured psychiatric interview (SCID-I, German version) (Wittchen et al., 1997) according to DSM-IV criteria (APA, 1994). The SCID assesses current (last 4 weeks before interview) and lifetime psychiatric status for major Axis I psychiatric disorders using criteria which are in accordance with the DSM-IV.

Picture stimuli

The visual stimuli has previously been developed and validated by Jackson et al. (2006) and were used with their permission. The stimuli consisted of a series of pictures showing human limbs in painful and non-painful situations. Various types of pain (mechanical, thermal, and pressure) were depicted in situations occuring in everyday life. The 120 pictures used in this study were selected from a larger sample and were grouped into four levels of pain (no, low, medium, high pain, 30 pictures each), on the basis of the pain intensity ratings of 20 independent subjects. Stimuli were presented within and outside the scanner with a computer running the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA; http://www.neurobs.com) to manage the timing and presentation of the stimuli.

Functional MRI resting state paradigm

Participants were asked to close their eyes and to relax, but to stay awake. This part lasted 370 s.

Functional MRI empathy paradigm

After the resting state session, participants were presented to the stimuli. Stimuli were grouped in 12 blocks, each of which consisted of nine stimuli chosen in randomized order from the same pain condition. Each stimulus appeared only once over the whole task. The presentation of each picture lasted 2 s followed by a 1 s blank screen, i.e., each block lasts for 27 s. Four further blocks of the same length were defined as a baseline condition, showing a blank screen with a centered fixation cross (for BOLD-timecourse, see Fig. 4). This led to a total set of 16 blocks (three blocks per pain condition plus four blocks baseline). The task was performed by choosing the blocks from this set in randomized order resulting in 432 s total task time.

Training and interview

Subjects underwent training outside the scanner immediately before the functional magnetic resonance imaging (fMRI) experiment in order to become familiar with the kind of stimuli and the procedure of post scan rating. Twelve stimuli not used for the fMRI paradigm were presented in randomized order (three from each of the four pain conditions). Participants were instructed to rate the pain intensity for each stimulus taking the self-perspective on a scale from 0 (no pain) −9 (strongest pain imaginable) by pressing the according key of a numeric keypad as quickly and as accurately as possible. The presentation of the stimuli was cycled until the subject got used to the rating procedure. Immediately after the fMRI part subjects underwent an interview outside the scanner. The stimuli were shown in the very same order as presented before in the fMRI task. Each stimulus was presented for 2 s (as in the scanner paradigm) followed by a blank screen.

The next picture was presented immediately after any of the target buttons was pressed. Again, the subjects were asked to answer as quickly and as accurately as possible. Ratings were recorded for each stimulus.

Data acquisition and fMRI procedures

Images were acquired with a 3T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands) with a standard 8-channel SENSE head coil. Thirty-two contiguous slices (no gap) with a steep angulation to leave out the eyes were acquired using a gradient echo-planar (EPI) sequence with the following parameters: 2000 ms repetition time (TR); 35 ms echo time (TE); 82 degree flip angle; 220 mm FOV; 4 mm slice thickness; 80×80 matrix; voxel size 2.75×2.75 mm; SENSE factor 2. Anatomical images were obtained using a T1-weighted turbo gradient echo sequence: 9 ms TR; 4 ms TE; 8 degree flip angle; 240 mm field of view (FOV); 240×240 matrix; voxel size 1 mm isotrop; 170 slices; no gap.

Image processing and data analysis—preprocessing. The entire data analysis was performed with SPM5 (Statistical Parametric Mapping software, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The first three images of each run were discarded to allow equilibration of longitudinal magnetization. The pre-processing steps were (1) realigning and unwarping the images to correct for movement artifacts and related susceptibility artifacts, (2) coregistration of the anatomical to the functional images, (3) segmentation and normalizing of the anatomical image to the standard stereotactic space (Montreal Neurological Institute, MNI, Quebec, Canada), (4) application of normalization transformation to the functional images, and (5) smoothing with a Gaussian kernel of 8 mm for group analysis.

Connectivity-analysis

We performed the independent component analysis (ICA) by using group ICA for fMRI toolbox (GIFT version 1.3e; http://icatb.sourceforge.net) established for the analysis of fMRI data (Calhoun et al., 2001).

Because of the unknown relationship between spontaneous activity during rest and connectivity during an emotionally laden task, ICA-analysis was performed for resting state and task paradigm separately.

The toolbox uses a group ICA approach. First, the individual data were concatenated across time, followed by the computation of the subjectspecific components and time courses. For each of the conditions (resting state, task) the toolbox performed the analysis in three stages: (1) data reduction, (2) application of the ICA algorithm, and (3) back-reconstruction for each individual subject (Calhoun et al., 2001). In the first step (1), data from each subject underwent PCA, to reduce computational complexity was reduced. In doing so, most of the informational content of the data was preserved.

After concatenating the resulting volumes, the number of independent sources was estimated by the GIFT dimensionality estimation tool based on the aggregated data: 30 ICs for each of the both parts of the experiment. The final reduction step according to the selected number of components was achieved by PCA again. In the second stage of the analysis (2) we used the Infomax algorithm for running the proper IC analysis and a GM mask based on all subjects. In the final stage of back-reconstruction (3), time courses and spatial maps were computed for each subject. The resulting mean spatial maps of each group were transformed to z scores for display (Calhoun et al., 2001). The initially calculated scaling factor σ_{ijk} was reintegrated into the data by voxel-wise multiplication, before any statistics were applied to the individual subject maps.

Individual subject maps of the DMN were entered into random effects analyses in SPM5. Results were thresholded at $P<0.001$, corrected for false-discovery-rate (FDR) with cluster-extent-threshold of 50 voxels, and saved as masks which were used as functional region of interest (ROI) for the correlation analysis between functional connectivity and the pain ratings scores. Spatial correlation function of GIFT-toolbox was used to allocate corresponding networks over the different sessions.

Using temporal sorting, we compared the ICA-time course with the model's time course to explore the influence of the different types of interaction ("Pain", "No Pain," "baseline") on DMN-connectivity. The SPM5-design matrix which contains three regressors corresponding to the tasks was entered into temporal correlation analysis. Multiple linear regression sorting criteria were used to relate model-time course to ICA time course. This procedure led to a set of beta-weights for each regressor associated with each subject. Negative values represented the task-related decreases in activity, the degree of which were quantified by the absolute value of the beta-weight (e.g., Kim et al. (2009) used a similar approach). We compared the beta-weights of the different conditions using one-tailed paired *t*-tests on beta-weight statistics ($P<0.05$) to test if the the time course would be significantly different. Furthermore, we subtracted the beta-weights of "Pain" from "No Pain," "Pain" from "baseline" and "No Pain" from "baseline". These values reflect the strength of connectivity increases or decreases between the different conditions comparable to the GLM-approach used in neuroimaging studies.

Correlation analysis

To test our hypothesis that functional connectivity of the DMN during resting-state is correlated with the extent to which we share the pain of others, correlation analysis between the pain intensity participants attributed to the stimuli and the functional connectivity was performed. Because only cortical activity within the DMN is relevant in this study, the analysis was performed on a DMN-mask used as a functional ROI.

As level of significance, we applied $P<0.01$, corrected for multiple comparisons at the cluster level, with an underlying threshold of $P<0.01$ uncorrected at the voxel level. Person's correlation test was performed to illustrate the correlation between DMN-connectivity and the pain ratings ($R>0.1$, $P<0.05$).

To explore if the influence of the different types of stimulation ("Pain", No Pain', "baseline") on DMN-connectivity could be linked to the pain-ratings, we compared Pearson's correlation test between the beta-weights and the pain ratings ($R>0.1$, $P<0.05$).

RESULTS

After scanning, participants attributed on average 5.05 points (sd 1.12) to the pictures depicting painful situations on a pain-intensity scale from 0 to 9.

The ICA estimation led to 30 independent components for each condition (resting state and stimulation).

We identified two sub-units of the DMN (Fig. 1)

1. The anterior DMN which mainly includes areas of medial prefrontal cortex, medOFC, anterior cingulate and

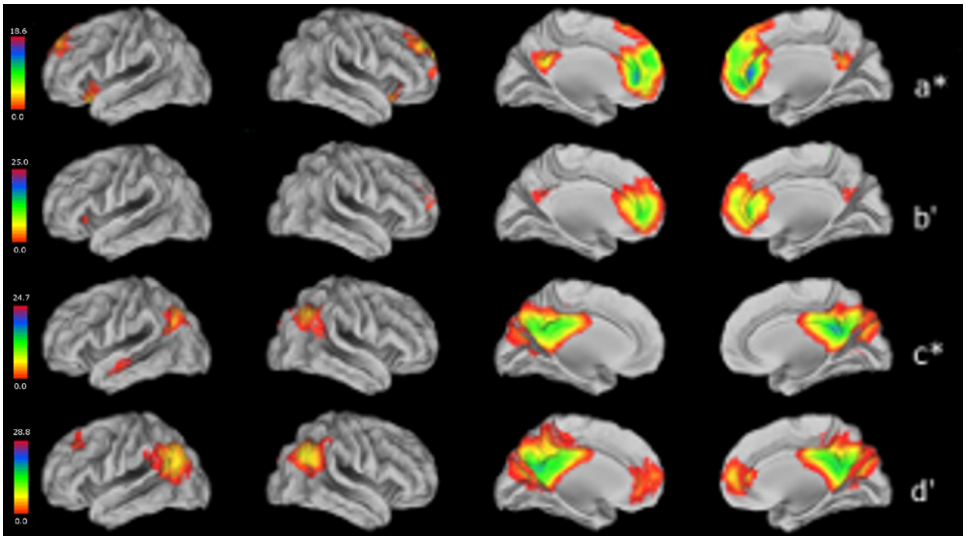

Fig. 1. aDMN (a, b) and pDMN (c, d) during rest (*) and stimulation (') ($P<0.001$ FDR-corrected, cluster-extent threshold$<$50 voxels). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

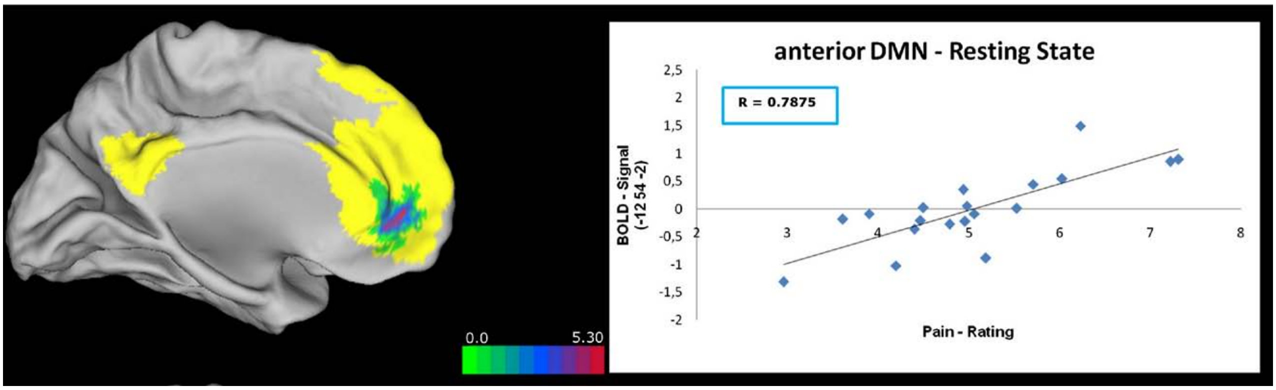

Fig. 2. Resting state: Positive correlation between post-scan pain ratings and functional integration of the medOFC (green, blue, red; −12 54–2, T=5.24, k=261, R=0.7857, $P<0.05$) projected on aDMN-architecture at rest (yellow). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

precuneus. During resting state, a cluster with its peak voxel located within left medial orbitofrontal cortex (medOFC) (BA 32, −12 54–2, T=5.24, k=261) and also including left pregenual anterior cingulate (BA 32) was positively correlated with the pain ratings ($R=0.7857$, Fig. 2).

Temporal correlation analysis revealed that the aDMN was deactivated by the "Pain" condition as well as by the "No Pain" stimuli compared to the baseline. During "No Pain," the decrease of connectivity was significantly stronger than during "Pain" (Figs. 3 and 4). The difference in connectivity between both conditions can be described as a relative increase from "No Pain" to "Pain" that was significantly correlated to the post-scan pain ratings (Fig. 3).

2. The posterior DMN which primarily involves the precuneus and the inferior parietal lobule. Additionally, small clusters within the medial prefrontal cortex were found during perception of the stimuli. No significant correlation between pain-ratings and resting state connectivity was detected. The pDMN was decreased less by the "Pain"-pictures than by the "No Pain"-stimuli but the difference was not significant.

DISCUSSION

In accordance with recent studies (Mantini et al., 2007; Calhoun et al., 2008; Damoiseaux et al., 2008), we found a dissociation of the DMN into a posterior located part (pDMN) and a more anterior anchored sub-network (aDMN). In particular, the different implications of the latter can be synoptically described as self-referential in nature (Gusnard et al., 2001; D'Argembeau et al., 2005; Buckner et al., 2008; Schneider et al., 2008), whereas the contribution of the pDMN was not found to be significant in our study.

Our data suggest that the neural underpinnings of inter-individual behavioral differences in affective sharing are detectable not only during presentation to a task. During a relaxed stimulus-independent status with closed eyes, the integration of the medOFC into the aDMN was positively correlated with the subjective post-scan pain

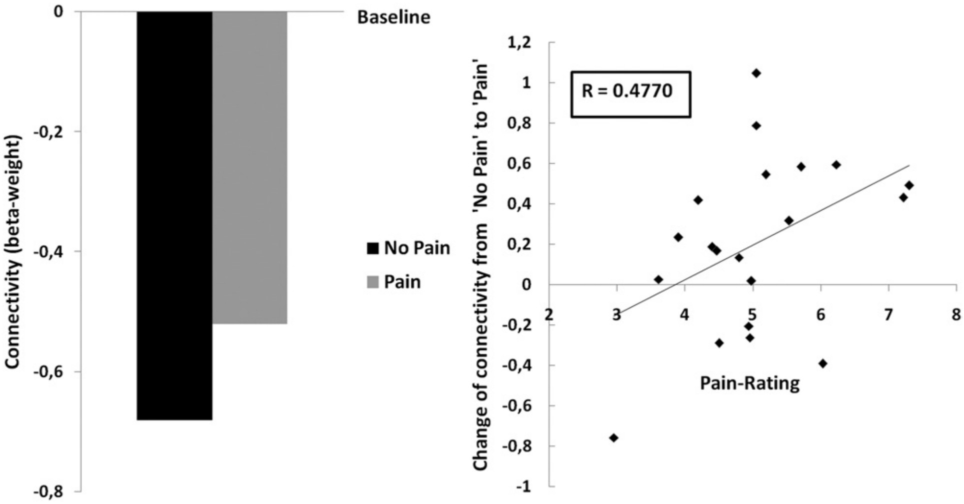

Fig. 3. Visual pain perception: The relative increase of aDMN-connectivity from "No Pain" to "Pain" (beta-weight statistics, paired t-test $P<0.05$) was positively correlated with post-scan pain ratings (R=0.4770, $P<0.05$).

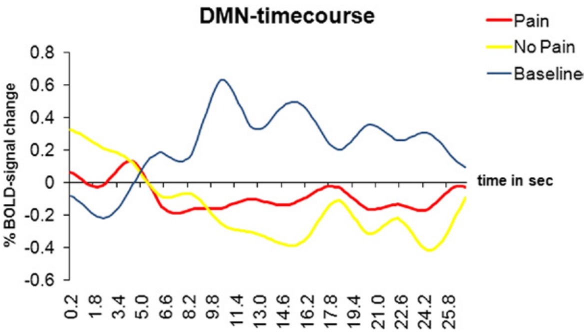

Fig. 4. Visual pain perception: Event averaged ICA-timecourses for "Pain", "No Pain" and "baseline". For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

ratings. This region is involved in the evaluation of the positive and negative aspects of a situation (Ochsner et al., 2002; Lamm et al., 2007a,b), in decision making (Elliott et al., 2000), in monitoring the associations between stimuli and outcomes (Amodio and Frith, 2006), and contributes to self-referential processing (Schneider et al., 2008). The connectivity pattern detected here provides further evidence for Ingvar's idea of a "memory of the future" (Ingvar, 1985) and the "proactive brain" (Bar, 2009), which posits that human behavior is at least to a certain extent driven by neural "a priori scripts" which are stored in the brain's resting state and which encode our response to environmental stimuli. Specifically, we presume that the tendency to refer specific aversive stimuli to oneself relies particularly on its functional architecture during a task-free period.

In response to the picture-stimuli, aDMN as well pDMN were decreased supporting former evidence for down-regulation during a cognitive demanding task (Raichle et al., 2001; Greicius et al., 2003; Fox et al., 2005; Mayer et al., 2010).

In a similar way to the findings of Sheline et al. (2009), aDMN-connectivity was found to be less decreased during aversive painful picture stimuli than when subjects were perceiving neutral painless events. The dimensional nature of this relative increase from the "No Pain"-condition to the "Pain"-condition was correlated with the subjective pain-intensity participants attributed to the stimuli after scanning. From this finding, we infer that a more intense contagion by another's affective state is accompanied with less reduced aDMN-activity in response to emotionally laden outer events compared to a baseline.

LIMITATIONS

Our study is limited by the absence of attentional measurement during scanning and by the assumption that participants attended to the stimuli inside the scanner according to the instructions given in the prescan training.

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