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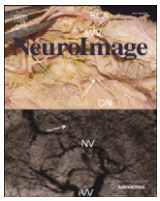

Repeated pain induces adaptations of intrinsic brain activity to reflect past and predict future pain

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ABSTRACT

Recent neuroimaging studies have revealed a persistent architecture of intrinsic connectivity networks (ICNs) in the signal of functional magnetic resonance imaging (fMRI) of humans and other species. ICNs are characterized by coherent ongoing activity between distributed brain regions during rest, in the absence of externally oriented behavior. While these networks strongly reflect anatomical connections, the relevance of ICN activity for human behavior remains unclear. Here, we investigated whether intrinsic brain activity adapts to repeated pain and encodes an individual's experience. Healthy subjects received a short episode of heat pain on 11 consecutive days. Across this period, subjects either habituated or sensitized to the painful stimulation. This adaptation was reflected in plasticity of a sensorimotor ICN (SMN) comprising pain related brain regions: coherent intrinsic activity of the somatosensory cortex retrospectively mirrored pain perception; on day 11, intrinsic activity of the prefrontal cortex was additionally synchronized with the SMN and predicted whether an individual would experience more or less pain during upcoming stimulation. Other ICNs of the intrinsic architecture remained unchanged. Due to the ubiquitous occurrence of ICNs in several species, we suggest intrinsic brain activity as an integrative mechanism reflecting accumulated experiences.

Introduction

Traditionally, functional magnetic resonance imaging (fMRI) studies have investigated changes of brain activity in response to sensory, motor or cognitive tasks that subjects performed in the MR scanner. Only recently, colleagues have revealed networks of distributed brain regions that are characterized by coherent ongoing activity in subjects at rest, in the absence of any observable behavior (Biswal et al., 1995; Greicius et al., 2003; Laufs et al., 2003; Damoiseaux et al., 2006; Fox and Raichle, 2007). These resting-state or intrinsic connectivity networks (ICNs) strongly resemble previously described task-activation patterns (Smith et al., 2009). However, the relevance of ICNs for human behavior remains a controversial issue.

ICNs transcend levels of consciousness and consistently occur in humans, monkeys and rats (Lu et al., 2007; Vincent et al., 2007; Greicius et al., 2008; Larson-Prior et al., 2009; Biswal et al., 2010). The ubiquity and robustness of the intrinsic functional architecture strongly supports the notion of ICNs reflecting underlying structural connectivity (Fox and Raichle, 2007; Hagmann et al., 2008; Honey et al., 2009). But there have also been reports of immediate variations in the coherence of ICNs associated with task performance of humans (Fox et al., 2007; Seeley et al., 2007; Albert et al., 2009; Lewis et al., 2009). We therefore hypothesize that at least portions of ICN activity continuously adapt with ongoing experiences and that intrinsic brain activity reflects past and anticipates future experiences.

In this study, we focused on repeated pain experiences and their relation to ICN activity before and after pain. More concretely, we asked whether recurring pain modulates functional connectivity (FC) within pain-relevant ICNs in a way that reflects recent pain and enables the prediction of future pain experiences. FC is a measure to quantify the strength of covarying activity between distributed voxels or brain regions. We derived ICNs by applying Independent Component Analysis (ICA) to resting state fMRI (rs-fMRI) data. Acute pain is

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consistently associated with neuronal activity in a distinct network of subcortical and cortical brain regions (Apkarian et al., 2005; Tracey and Mantyh, 2007). Among these, somatosensory cortices (SSC) process sensory aspects of pain, while the ventromedial prefrontal cortex (vmPFC) has been associated with its modulation (Koyama et al., 2005; Seymour et al., 2005). Despite our knowledge about activating these brain regions by acute pain, less is known about their role in encoding past and future pain. Yet, understanding how the brain processes pain beyond an immediate experience might help to explain the development of chronic pain conditions.

Materials and methods

Participants

Thirteen healthy male volunteers without any history of neurological, psychiatric or pain disease participated in this study. All participants received detailed information about the experimental procedures, were free to withdraw from the study at any time, and gave written informed consent. The Ethics Committee of the university hospital "Klinikum Rechts der Isar" (Technische Universitaet Muenchen) approved the protocols of the study. The data of an additional group of 16 healthy subjects that were scanned on the same scanner twice within a 14-day interval while participating in another study of our department were re-examined as a control group (Sorg et al., 2007).

Experimental design

Volunteers received a daily series of 8 painful and 8 non-painful alternating heat stimuli (40 s each, followed by 20 s baseline) on 11 consecutive working days. On the first and last day of the study we acquired resting-state functional MRI (rs-fMRI) data during 6 min before (PREpain) and after (POSTpain) painful stimulation. At the beginning of each fMRI session we collected an anxiety score (5-point Likert scale) from each subject in order to control for an overall level of arousal or anxiety to the study. The thermal stimulation protocol has previously been implemented in our group and described in detail (Valet et al., 2004). On the first day the pain threshold was assessed for each subject individually. Painful stimuli (1 °C above the pain threshold) were then applied via a thermode to the inner side of the right forearm in an undulating way and to one of three possible positions on the forearm to prevent skin sensitization. For each subject the stimulation temperature was kept constant during the 11 days of painful stimulation and the absolute temperature only varied slightly within the group (median: 44.0 ± 1 °C). After the stimulation period the volunteers rated the perceived pain intensity (PAIN) on an 11-point numerical rating scale (NRS). Differences in PAIN-ratings between days 1 and 11 were tested nonparametrically using the Wilcoxon signed-rank test ($p<0.05$).

Imaging data

We collected functional neuroimaging data on a 1.5 Tesla Siemens Symphony magnetic resonance system (Erlangen, Germany) using a gradient-echo EPI sequence (TE = 50 ms, TR = 3000 ms, flip angle = 90°, FoV = 230 mm^2, matrix = 64 x 64, 28 slices, slice thickness = 5 mm). Subjects were instructed to think of nothing particular and keep their eyes closed. Each rs-fMRI run comprised 117 functional volumes (~ 6 min) of which the first 3 volumes were discarded due to T1 saturation effects. Structural MRI data (TE = 3.93 ms, TR = 1500 ms, TI = 760 ms, flip angle = 5°, FoV = 256 mm^2, matrix = 256 × 256, 160 slices, voxel size = 1 × 1 × 1 mm^3) were acquired at the end of each session.

Processing of imaging data

Data preprocessing and ICA were performed as previously applied to rs-fMRI data in our group (Sorg et al., 2007).

Preprocessing

Functional MRI data were pre-processed using the SPM software package (SPM5, Wellcome Department of Cognitive Neurology, London) and in-house code for Matlab 7.1 (MathWorks, Natick, MA). Data were motion corrected, spatially normalized into the stereotactic space of the Montreal Neurological Institute (MNI) and spatially smoothed with an 8x8x8 mm Gaussian kernel. Before the volumes were entered into the ICA analysis we applied a voxel-wise z-transformation on the time-course data $y_{ijk}(t)$ by subtracting the mean $<y_{ijk}>$ and dividing by the standard deviation σ_{ijk}: $\hat{y}_{ijk}(t) = (y_{ijk}(t) - <y_{ijk}>)/\sigma_{ijk}$ (t being the time, indices i, j, k represent the three directions in space). The sensitivity of the multivariate ICA algorithm for correlation of variance between voxels, i.e. functional connectivity, was thereby rendered independent of the original BOLD signal magnitude across subjects.

ICA

We used the Group ICA toolbox (GIFT 1.3d; icatb.sourceforge.net) established for independent component analyses of fMRI data (Calhoun et al., 2001, 2009, 2004). The toolbox performed the analysis in four stages on a concatenated data set comprising the 4 rs-fMRI runs of all subjects: first the GIFT dimensionality tool estimated 18 independent components (IC) based upon the MDL criteria (Li et al., 2007). The aggregated data set was then reduced using principal component analysis (PCA) before the Infomax ICA algorithm (Bell and Sejnowski, 1995) calculated the ICs. For each individual GIFT finally reconstructed independent spatial maps of each rs-fMRI run (Calhoun et al., 2001) converted to z-scores. Hence individual maps are normalized with respect to variance in the component timecourse and the between-subject analyses are then performed on the maps of spatial weights (REF calhoun 2004). From the group spatial maps, we selected functionally relevant ICNs in a fully automated manner. On the basis of previous descriptions of brain regions covered by each ICN (Brodmann areas in Damoiseaux et al., 2008; Sorg et al., 2007), we created spatial templates representing each ICN using the marsbar toolbox (http://marsbar.sourceforge.net/). We then calculated the spatial regression of these templates against the ICA-derived maps as implemented in the GIFT toolbox and selected the best-fit ICNs from our analysis. From this set of ICNs we selected those networks that covered at least one brain region previously described in task-activation studies of pain processing in humans (Bingel et al., 2007; Gundel et al., 2008): primary and secondary somatosensory cortices, medial and lateral prefrontal cortices, insula, cingulate cortex and thalamus; see Table S2 for peak coordinates. Before we entered the individual's spatial maps into second-level statistics we reintegrated the initially calculated scaling factor σ_{ijk} into the data by voxel-wise multiplication in order to preserve each individual's profile of variance magnitude while leaving the normalized timecourse component unchanged (Sorg et al., 2007).

Second-level statistics

Group analyses were performed on the back-reconstructed spatial maps of all 13 subjects using SPM5 (Wellcome Trust Centre for Neuroimaging, UCL, London). We first evaluated the consistency of each ICN across sessions by calculating a repeated-measures ANOVA on the spatial maps of all 4 runs that we projected on a mean anatomical image of all subjects ($p<0.05$, FDR-corrected) (see Fig. S1). We then tested the five ICNs comprising pain related brain regions (maps B, C, F, G, J/K of Fig. S1) for plastic changes in response to the 11 days of repeated pain and entered the four spatial maps of each subject into within-subject ANOVAs (factors "subject,""session PRE/