NeuroImage 42 (2008) 845–849

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Changes in brain gray matter due to repetitive painful stimulation

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ARTICLE INFO

Article history:
Received 28 February 2008
Revised 24 April 2008
Accepted 14 May 2008
Available online 7 July 2008

Keywords:
Pain
Morphometry
Structural imaging
VBM
Cingulate cortex
Somatosensory cortex
Plasticity

ABSTRACT

Using functional imaging, we recently investigated how repeated painful stimulation over several days is processed, perceived and modulated in the healthy human brain. Considering that activation-dependent brain plasticity in humans on a structural level has already been demonstrated in adults, we were interested in whether repeated painful stimulation may lead to structural changes of the brain. 14 healthy subjects were stimulated daily with a 20 min pain paradigm for 8 consecutive days, using structural MRI performed on days 1, 8, 22 and again after 1 year. Using voxel based morphometry, we are able to show that repeated painful stimulation resulted in a substantial increase of gray matter in pain transmitting areas, including mid-cingulate and somatosensory cortex. These changes are stimulation dependent, i.e. they recede after the regular nociceptive input is stopped. This data raises some interesting questions regarding structural plasticity of the brain concerning the experience of both acute and chronic pain.

Introduction

Largely based on the abundant pain research of the past decade, the neurobiology of pain is increasingly understood as an integration of activity in distinct neuronal structures. Moreover, evidence of functional reorganization in chronic back pain and phantom pain patients supports the idea that chronic pain should not only be conceptualized as an altered functional state, but also as a consequence of central plasticity (Flor, 2003; Grusser et al., 2004). These functional changes comprise increased cortical activity and a shift of the cortical representation, which is interpreted as either an expansion or a shrinkage of the representational field of the affected part of the body (Maihofner et al., 2003; Pleger et al., 2004). These functional changes are dynamic, i.e. cortical reorganization recedes coincident with clinical improvement (Flor et al., 2001; Maihofner et al., 2004).

Until recently it has been thought that chronic pain states are attributed to abnormal nociceptive/antinociceptive function on different levels (Wall and Melzack, 2006) with a normal brain structure. However, any significant environmental change that requires a specific function, including learning a specific task, has the potential to alter brain structure (May et al., 2007). Given that the initiation of chronification of pain involves dynamic nociceptive input, one would expect that functional and structural changes would occur in modulatory areas of nociception.

Recently, we investigated how our central nervous system copes with repeated noxious stimulation and found that the phenomenon of habituation to pain is modulated by the rostral ACC (Bingel et al., 2007). Given that local morphologic alterations of the brain in areas ascribable to pain procession and pain modulation were detected in patients suffering from phantom pain (Draganski et al., 2006), chronic back pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006), fibromyalgia (Kuchinad et al., 2007) and frequent headaches (Schmidt-Wilcke et al., 2005; Schmidt-Wilcke et al., 2007), we aimed to investigate whether repeated noxious stimulation would not only alter the function (Bingel et al., 2007), but also the structure of the brain.

Using the design from our functional study, we investigated 30 healthy subjects who were stimulated with a pain paradigm over 20 min once every day for a time span of 8 days. To evaluate changes in brain structure over time, we performed structural MRI on day 1 and 8 of the experiment, as well as after 21 days and again 1 year ($n=14$) after the stimulation epoch of 8 days. We included the data after 1 year, as the functional changes following repeated pain experience (habituation of pain and increase in rACC activation) lasted for several weeks (Bingel et al., 2007 and unpublished data). We

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doi:10.1016/j.neuroimage.2008.05.044

hypothesized that repetitive painful stimulation would provoke structural changes in areas involved in the modulation of nociception. In line with this hypothesis, we decided to investigate healthy volunteers using a well-controlled experimental design to avoid the possible pathophysiological condition of patients suffering from chronic pain conditions.

Methods

Subjects

The subjects were recruited locally; most of them were medical students. 30 healthy male subjects, all right-handed, aged 21 to 43 years (mean 26±3) gave written informed consent to participate in the study, which was conducted in accord with the Declaration of Helsinki and approved by the local ethics committee. Due to difficulties in retrieving data for time point four (1 year follow-up), we were not able to obtain the structural MRI-measurement of 16 subjects. Our longitudinal analysis, including behavioral results and structural brain analyses is therefore restricted to the 14 subjects with complete data sets. These subjects participated in the above mentioned functional study on habituation which was recently published (Bingel et al., 2007). All subjects had normal pain thresholds at the site of stimulus application, no history of neurological or psychiatric disease, particularly no history of pain or headpain syndromes, and were free to withdraw from the study at any time. Given the known influence of depression on pain processing and perception, we made sure that our subjects were not suffering from depression and only included volunteers with a normal score on the Beck-Depression Scale. We also assessed any occurrences of minor pain events, including tooth-, ear-, headache or other contusions up to 4 weeks prior to and during the study period. The methods regarding subject's instruction and pre-experimental phase are described in detail elsewhere (Bingel et al., 2007). Pain thresholds were determined using the method of limits (Engen, 1971; Fruhstorfer et al., 1976) and lay within the normal range of an age matched sample of normative values (Bingel et al., 2007).

Experimental protocol

Our paradigm was designed to achieve tolerable yet effective nociceptive stimulation, which could be repeated over several days without damaging the individual. We therefore chose repetitive stimulation with a 48 °C thermode-induced heat stimulus, which inevitably activates nociceptive and mechanoreceptive peripheral afferents and evokes a moderate to intense painful sensation. The choice of stimulation parameters was based on a psycho-physiological pilot-experiment, in which we made sure that even if habituation takes place, the stimulation stays painful for the individual over the stimulation epoch of 8 days (Bingel et al., 2007).

The study phase consisted of an 8 day program of daily painful stimulation. On each day, the subjects were exposed to one session of painful stimulation, including pain ratings. These stimulation sessions, identical in- and outside of the scanner, consisted of 10 blocks of thermode stimuli with each block containing a series of six 48 °C stimuli (each lasting 6 s), resulting in a total number of 60 thermal stimuli. Thermal stimuli were applied to the left volar forearm and delivered by a 30×30 mm, peltier device (TSAII, Medoc, Israel). Five seconds after the sixth thermal stimulus of each pain block, the subject was prompted to rate his average sensation for the last 6 painful stimuli on a 0–100 visual analogue scale (VAS anchored at 0=first pain and 100=worst pain). To evaluate changes in pain processing, pain perception and brain structure over time, we collected psychophysical data (pain thresholds, pain ratings) and performed a structural MRI on days 1 and 8 of the experimental phase, as well as 3 weeks and 1 year after the stimulation epoch of 8 days.

Image acquisition

MR scanning was performed on a 3 T MRI system (Siemens Trio) with a standard headcoil. For each time point, days 1 and 8 of the experimental phase, as well as 3 weeks and 1 year after the experimental phase, a T_1 weighted structural MRI was acquired for each subject using a 3D-FLASH sequence (TR 15 ms, TE 4.9 ms, flip angle 25°, 1 mm slices, FOV 256×256).

Image processing and statistical analysis

Data pre-processing and analysis were performed with SPM2 (Welcome Department of Cognitive Neurology, London, UK) running under Matlab (Mathworks, Sherborn, MA, USA), described in detail elsewhere (Etgen et al., 2005). In summary, pre-processing involved spatial normalization, gray matter segmentation and 10 mm spatial smoothing with a Gaussian kernel. For the pre-processing steps, we used a previously described optimized protocol (Good et al., 2001) and a scanner- and study-specific gray matter template. A voxel by voxel repeated measures ANOVA was used in order to detect regional differences in gray matter over all four time points (day 1, day 8, day 22 and 1 year after the experimental phase). We tested for any regions that showed an increase or decrease in brain structure between the first time point (before the stimulation period) compared to the second (after 8 days) and third (after 22 days) time points (stimulation period), which showed a reverse behavior at time point four (1 year after the stimulation period). We applied a threshold of $p<0.05$ (corrected for multiple comparisons — family wise error, FWE) across the whole brain.

Results

The behavioral results and structural brain analyses are restricted to 14 subjects with complete data sets. However, the inclusion of all subjects ($n=30$; three time points in 16 subjects and four time points in 14 subjects) produced similar results.

Pain thresholds

Daily painful stimulation led to a significant attenuation of the pain ratings and pain thresholds. The mean heat pain thresholds for thermal pain increased significantly from 46.4 °C on day 1 to 47.5 °C on day 8 and 47.8 °C on day 22 (repeated measures ANOVA ($F(2,26)=5.7$, $p<0.05$). The mean heat pain thresholds for thermal pain decreased again to 46.1 °C 1 year after the experimental phase (paired T-test, $p=0.05$).

Neuroimaging results: morphometric changes over time

Comparing day 1 to day 8 or day 22, we found an increase ($p<0.05$, FWE corrected) in gray matter in the somatosensory