Altered resting state attentional networks in diabetic neuropathic pain

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ABSTRACT

Background Chronic pain can be considered as a highly salient stimulus that continuously taxes the attentional and salience processing networks, thus interfering with cognitive abilities and, more specifically, consuming attentional resources. The aim of the paper was to explore whether and how diabetic neuropathic pain (NP) affects attentional networks.

Methods The authors sought to achieve this by investigating resting state functional connectivity (rsFC) in diabetic NP patients and comparing it with that of matched healthy controls.

Results NP patients showed a widespread reduction in connectivity in both the dorsal and ventral attentional networks, as well as in the dorsal anterior cingulated cortex (ACC), typically implicated in salience processing. The authors also found a generalised reduction in the length of functional connections in the NP group: in all the examined networks, the Euclidean distance between connected voxels was significantly shorter in patients than in controls.

Conclusion In diabetic NP, a parieto-fronto-cingulate network controlling attention to external stimuli is impaired. In line with previous studies, chronic pain can disrupt the synchrony of a common pool of brain areas, involved in self-monitoring, pain processing and salience detection.

INTRODUCTION

The nervous system is continuously bombarded by internal and extrapersonal stimuli. The priority is to identify the most relevant among these myriad of inputs. This capacity requires a system that can integrate highly processed sensory data with visceral, autonomic and hedonic markers.1 Pain is inherently salient, and it demands attention and cognitive resources, as it has to be evaluated in intensity and in other qualities. Thus, attention to a salient input such as pain can be viewed as the focussing of resources on a specific stimulus. While a growing number of studies have examined the relationships between attention and pain, and their neural correlates, few studies have addressed the issue of how pain engages and modifies attention. Indeed, the majority of studies to date have focused on the effects of attention on pain, while the effects of pain on attention are practically unexplored.

Lesion and neuroimaging studies employing non-painful stimuli have related attentional control to a network composed of parietal, frontal and cingulate cortical regions.2 Some studies have found similar patterns of cortical activation for both voluntary and involuntary attentional control mechanisms.3 Similarly to other attentional tasks, pain engages a common group of brain regions that includes the posterior parietal, prefrontal and anterior cingulate cortices.4 Sharing common cognitive resources and neural correlates, pain and attention systems are likely to interact. Indeed, it has been demonstrated that experimental pain can decrease cognitive performance and task-related activity.5 6 However, the interaction between pain and other functional networks has only recently started to be considered.7 8

We believe a promising perspective would be to consider the mechanisms underlying pain perception as a complex phenomenon that engages multiple cerebral areas acting together as a functional unit. Although not fully understood, such cognitive mechanisms have been shown to be impaired in patients suffering from chronic pain.9 10 Thus, patients with chronic neuropathic pain may represent a suitable population among which to investigate the effects of pain on cognitive functions and, more specifically, to shed light on how brain networks involved in attention systems can be modified by pain.

Resting state functional connectivity (rsFC) is a network analysis approach, based on temporal correlations between the activity in a seed area and the rest of the brain. It considers a set of brain cortices.

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interconnections among brain regions characterised by high baseline activity that decreases during attention-demanding cognitive tasks. Furthermore, Seminowicz and colleagues demonstrated that experimental pain can alter the functional connectivity evoked by an attentional task. Overall, these studies show that pain can alter the functional connectivity of networks involved in pain and homeostatic processing, and so they suggest that chronically taxed attentional networks can suffer and become impaired after years of continuous chronic pain. In the present study, we intend to investigate in more detail how and which attention systems can be affected by chronic pain, using the functional connectivity method.

Fox and colleagues demonstrated a bilateral dorsal attention system involved in top-down orientating of attention and a right-lateralised ventral attention system involved in reorienting attention in response to salient sensory stimuli. These two networks had previously been visualised in task-induced activation studies. The integrity of both Dorsal Attentional Network (DAN) and Ventral Attentional Network (VAN) rsfC has been explored in patients with spatial neglect, in whom a common disruption of specific areas of DAN and VAN was found. We thus considered these two attention systems and their possible modifications following chronic pain.

METHODS

For a more detailed description, see the supplementary online materials.

Patients

Eight right-handed patients suffering from peripheral Neuropathic Pain (NP) (four women and four men suffering from diabetic pain; age range = 51–78, mean age = 61 years) were enrolled from our multidisciplinary pain unit (table S1). This group of patients was also the subject of a previous study. All patients underwent a complete neurological and psychological examination as well as standard MR brain scanning by an experienced neuroradiologist (SD) to exclude structural/white-matter abnormalities on anatomical MR images. Patients suffering from significant central nervous disease and psychiatric disorders were excluded. All patients were assessed using standardised pain scales (visual analogue scale (VAS), numerical rating scale (NRS), McGill Pain Questionnaire (MPQ), Italian version). The spontaneous component of their pain syndrome was evaluated on the MPQ checklist. VAS readings were obtained from their clinical notes and both the day before and on the day of the study. In all cases, pain was restricted to the bilateral lower limbs. The duration of pain was >2 years in all cases. Patients were washed out of their medications at least 1 month before imaging (opioids or cannabinoids were never administered). Maximum care was taken to avoid situations that could actually trigger evoked pain during the imaging sessions.

Eight age- and gender-matched right-handed healthy volunteers (four women and four men; age range = 47–79, mean age = 59 years) acted as controls. None suffered from any neurological or psychiatric disorders, including chronic pain of any kind, nor had a history of drug or alcohol abuse. None were on medications known to alter brain activity.

All subjects gave their informed written consent, in line with the Declaration of Helsinki, and the study was approved by the local ethics committee.

Procedures

All subjects were instructed simply to keep their eyes closed, to think of nothing in particular and not to fall asleep. After the scanning session, participants were asked if they had fallen asleep during the scan; those who provided a positive or dubious answer were excluded from the study.

Data acquisition was performed on a 1.5 T INTERA scanner (Philips Medical Systems, Amsterdam, The Netherlands) with a SENSE high-field, high-resolution (MRIDC) head coil optimised for functional imaging. Resting state functional T2-weighted images were acquired using echoplanar (EPI) sequences; in the same session, a set of three-dimensional high-resolution T1-weighted structural images was acquired for each participant (see supplementary material for sequences’ details). Blood-oxygen-level-dependent (BOLD) imaging data were analysed using the Brain Voyager QX software (Brain Innovation, Maastricht, The Netherlands). In order to reduce artefacts, functional images were preprocessed as follows: (1) slice scan time correction; (2) 3D motion correction; (3) spatial smoothing (Gaussian kernel of 8 mm FWHM); (4) temporal filters (linear trend removals) were used to reduce cardiac as well as respiratory noise, and a band pass filter of 0.01–0.08 Hz was used, as several previous studies have found the frequency range (0.01–0.08 Hz) to have the greatest power in revealing the underlying connectivity. After preprocessing, each subject’s slice-based functional scan was coregistered with their 3D high-resolution structural scan and transformed into Talairach space. Functional connectivity was measured using a method similar to that described below.

ROIs for functional connectivity analyses of dorsal attention network (DAN) and ventral attention network (VAN) were determined from a meta-analysis of four previously published event-related fMRI studies of adults performing an attentional paradigm as previously suggested in the paper by He et al. The studies used for this meta-analysis were: Astafev et al and Corbetta et al. We defined eight ROIs (512 mm3 each) representing the DAN and five regions (512 mm3 each) representing the VAN. To further investigate the attentional system, we added a couple of supplemental ROIs (216 mm3 each) in the bilateral dorsal cingulated (dACC) cortex, selected according to Margulies et al. All selected ROIs are listed in table S2.

The first step in all rsfC analyses was to extract BOLD time courses from each ROI by averaging over voxels within each region. To compute rsfC maps corresponding to a selected seed ROI, the regional time course was correlated against all other voxels within the brain. The maps, representing the connectivity of a network (DAN, VAN) or dACC, were computed by conjunction analysis of the selected ROIs.

The individual participant multiple regression analysis (carried out using the general linear model (GLM)) resulted in a t-based map corrected for multiple comparisons with the false discovery rate (FDR q<0.05, cluster threshold K>5 voxels in the native functional resolution). Several nuisance covariates were included in our analyses to control for the effects of physiological processes and motion. Specifically, we included nine additional covariates that modelled nuisance signals from WM, cerebrospinal fluid (CSF) and global signal (GS), as well as six motion parameters.

Random-effect group-level analyses, controlling for age and gender effects, were conducted using the GLM and the ANCOVA analysis tool implemented in BrainVoyager QX. Corrections for multiple comparisons were carried out for each of the two networks and for the dACC using the FDR (q<0.05, cluster threshold>5 voxels in the native resolution). To test for significance of group-related differences, direct voxelwise group comparisons were performed using group-level contrasts. These contrasts produced FDR thresholded maps (q<0.05, cluster...
threshold K > 5 voxels in the native resolution) of those voxels that showed significant differences between the two groups. The resulting maps were then projected on a flattened representation of the brain using the BrainVoyager QX surface tool. Probabilistic maps were computed to evaluate the spatial consistency of functional connectivity patterns across subjects.

For each network (DAN or VAN), plus the dACC, and for each subject, we calculated the Euclidean distance between the centre of gravity of all centres of the respective ROIs and every other voxel that reached significance in the thresholded Z-score map of positive rsFC (cluster significance: p < 0.05, minimum cluster size k > 5 contiguous voxels). We examined group differences by performing a parametric analysis (t tests for independent samples, patients vs controls) for the total number of active voxels within 120 mm.

To test our results and demonstrate that our findings were not linked to some sort of overall effect in all the voxels of the patient group data, we calculated the rsFC of two more networks and compared the patient and control groups (see supplementary online materials and results).

RESULTS

Probabilistic maps
The spatial probability maps of the three rsFC networks showed good spatial reproducibility of individual subjects’ results (see figure S5 and tables S3, S4, S5) and very similar spatial distribution to that of previous rsFC studies of the same networks.21

Functional connectivity in DAN and VAN
The rsFC comparison of the two groups showed a reduced connectivity in the DAN as well as in the VAN for pain subjects. Voxelwise group comparisons revealed differences in both networks (see figures 1, S8, S9 and tables S9, S10); the cumulative voxel count (see figure S7) confirmed the prevalence of the rsFC mean number of voxels in the DAN and in the VAN for healthy subjects.

The dACC connectivity maps (see figures 1, S10 and table S11) replicated the evidence of reduced connectivity seen in the DAN and VAN; as expected, the cumulative voxel count (see figure S7) confirmed the results of the voxelwise analysis.

Overlapping between maps
To identify the degree of overlapping between all three rsFC subtraction maps, we performed an intersection analysis of the maps displayed in figures 1, S8, S9, S10 and summarised in tables S9, S10, S11. This yielded the areas of overlapping of the subtraction maps for two networks (DAN and VAN): in the bilateral middle temporal gyrus, bilateral superior temporal gyrus, bilateral cingulate gyrus (dACC), bilateral middle frontal gyrus (supplementary motor area and frontopolar area) and right cuneus and for three networks (DAN, VAN and additionally dACC): in the bilateral superior temporal gyrus, left cingulate gyrus (dACC) and right cuneus (see figures 2, S11, S12 and tables S7, S8).

To identify nodes that were common to both networks (DAN and VAN) and dACC, we performed a conjunction analysis between normal rsFC for all healthy subjects. Potential hub areas were found in the bilateral cingulate gyrus, right precentral gyrus, right supramarginal gyrus, left middle frontal gyrus (see figure S6 and table S8).

Voxel-distance differences
A significant decrease in the numbers of connected voxels was found in the patient group compared with the control group (see figure 3).

DISCUSSION
The present fMRI data suggest that in diabetic neuropathic subjects, there is a reduction in attentional network rsFC. The networks investigated in our study are superimposable on those described in previous papers.22 We found limited areas of overlapping between the networks being studied as described in a previous study by Fox and colleagues.21 The comparison of the DAN and VAN, respectively, in patients and healthy subjects, showed a widespread reduction in rsFC in both the attentional networks. These results seem to indicate a disruption of the attentional and salience processing networks.21
The paper by Seminowicz et al. indicates that pain can modulate a network involved in focused attention, suggesting a mechanism for the interference of pain on cognitive ability by the consumption of attentional resources. This interpretation is consistent with these data: chronic pain is a highly salient stimulus, continuously taxing the attentional and salience processing networks, and could modify the activity of those networks. This idea is supported by the findings of Baliki et al., who demonstrated that chronic pain has a widespread impact on overall brain function, suggesting that the disruptions of the DMN which they reported may underlie the cognitive and behavioral impairments accompanying chronic pain. These findings were confirmed by our recent study in which we observed reduced DMN connectivity in the bilateral primary sensorimotor areas and cingulated cortex, as well as left temporal and occipital cortices during resting states.

Figure 2  Dorsal Attentional Network, Ventral Attentional Network and dorsal anterior cingulated cortex (ACC) resting-state functional connectivity group comparison. Two-sample t test q<0.05 false discovery rate-corrected, minimum cluster dimension K>5 voxels in the native resolution. Colours from red to yellow indicate increased connectivity. Colours from blue to green indicate reduced connectivity. All resting state functional connectivity maps were projected on a flattened representation of the brain using BrainVoyager QX.
Our study revealed a reduction or disruption of some resting state functional networks in the pathological population we examined. Of note, similar alterations of resting state network dynamics have been demonstrated in a number of neuropsychiatric disorders, including Alzheimer’s disease, depression, schizophrenia, clinical conditions characterised by impaired attention, such as attention-deficit/hyperactivity disorder and neglect. Although rsFC has been widely used, to date only one study has explored how a neuropsychological syndrome specifically involving attention (spatial neglect) is related to changes in attentional networks. This study, using a methodology similar to ours, found an acute disruption and disrupted connectivity in specific pathways in the dorsal and ventral networks that strongly correlated with impaired attentional processing across subjects.

To further investigate the attentional networks, we added two additional ROIs in the anterior cingulate cortex. In their study, Marguiles and colleagues placed a series of small ROIs in the anterior cingulate cortex and found a location positively correlated with regions typically implicated in attentional processes (e.g., dorsal and posterior inferior prefrontal cortices). This region has also been observed to be implicated in ‘salience processing,’ including the emotional aspects of pain. The dACC plays a role in the response to varied forms of salience, including the emotional dimensions of pain and empathy for pain. The comparison between patients and healthy subjects led to similar results for all the networks explored (DAN, VAN), and also to the observation of a significant superposition of areas with reduced rsFC. Several of those areas were also found to have reduced rsFC in a previous study exploring modifications in resting state functional connectivity subsequent to pain. The fact that all the networks examined in this work revealed a pattern of reduced connectivity and that this pattern is partially superimposable on the findings of previous studies on DMN rsFC suggests that chronic pain could disrupt the synchrony of a common pool of brain areas involved in self monitoring, pain processing and salience detection that can be explored using several different functional connectivity techniques. Chronic pain-induced cortical/subcortical reorganisation has been documented in animal models as well as in humans. More specifically, the reduced connectivity in the prefrontal cortex observed in our study is consistent with recent findings. Metz et al. found that in rodents, neuropathic pain leads to a rearrangement of the prefrontal cortex; Ploner et al. demonstrated that pain, in healthy controls, has the unique capability of disrupting the resting EEG rhythm on a large-scale spatial dimension (i.e., both α on the occipital areas and μ-rhythm on the sensorimotor areas).

The analysis of differences in voxel distances indicates a generalised reduction in connected voxels in the patient group in all the networks and in the dACC. That reduction is in line with several other results showing that a number of pathologies have a widespread impact on the brain network structure and efficiency (for a review, see Guye et al.). Our findings support a crucial role of the dorsal ACC in attentional network modulation. Fox et al. suggested that the prefrontal cortex (middle and inferior frontal gyri) may be a locus of functional interaction between the ventral attention system and the dorsal attention system. Our analysis of overlapping areas suggests that dorsal ACC may play a pivotal role in such an interaction. Gitelman and Mesulam hypothesised that spatial attention to external stimuli is supported by a large-scale network connecting not only the fronto-parietal cortices but also the cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli. Chronic pain could modulate the reduced activation of the parieto-fronto-cingulate network through the anterior cingulated cortex; such a network may support mental representation of motivational salience of external stimuli.

Several studies have shown that the ACC is a crucial area involved in the attentional modulation of pain, Bantick et al. found that subjects performing an attentional task (Stroop test) during painful stimulation showed reduced pain perception which was related to activation in areas of the ‘pain matrix,’ including the dorsal ACC. On the other hand, the crucial role of the ACC in affective modulation of pain is supported by several
Further research should explore the impact of chronic pain on DMN/attentional systems in other clinical populations: possible interactions with aetiology, concomitant symptoms, staging and grading of pain perception should be examined.

Limitations of the study and future research

This study enrolled only a limited number of patients, belonging to a specific neuropathic condition (patients with diabetes). Further research should explore the impact of chronic pain on DMN/attentional systems in other clinical populations: possible interactions with aetiology, concomitant symptoms, staging and grading of pain perception should be examined.

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Competing interests

None.

Patient consent

Obtained.

Ethics approval

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REFERENCES

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