

PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION

Original Research Article

Changes in Clinical Pain in Fibromyalgia Patients Correlate with Changes in Brain Activation in the Cingulate Cortex in a Response Inhibition Task

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Abstract

Objective. The primary symptom of fibromyalgia is chronic, widespread pain; however, patients report additional symptoms including decreased concentration and memory. Performance-based deficits are seen mainly in tests of working memory and executive functioning. It has been hypothesized that pain interferes with cognitive performance; however, the neural correlates of this interference are still a matter of debate. In a previous, cross-sectional study, we reported that fibromyalgia patients (as compared with healthy controls) showed a decreased blood oxygen level dependent (BOLD) response related to response inhibition (in a simple Go/No-Go task) in the anterior/mid cingulate cortex, supplementary motor area, and right premotor cortex.

Methods. Here in this longitudinal study, neural activation elicited by response inhibition was assessed again in the same cohort of fibromyalgia patients and healthy controls using the same Go/No-Go paradigm.

Results. A decrease in percentage of body pain distribution was associated with an increase in BOLD signal in the anterior/mid cingulate cortex and the supplementary motor area, regions that have previously been shown to be “hyporeactive” in this cohort.

Conclusions. Our results suggest that the clinical distribution of pain is associated with the BOLD response elicited by a cognitive task. The cingulate cortex and the supplementary motor area are critically involved in both the pain system as well as the response inhibition network. We hypothesize that increases in the spatial distribution of pain might engage greater neural resources, thereby reducing their availability for other networks. Our data also point to the potential for, at least partial, reversibility of these changes.

Key Words. Pain; Fibromyalgia; fMRI; Executive Function; Response Inhibition

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread nonarticular pain, stiffness, and fatigue. Furthermore, cognitive complaints are reported to be present in more than 90% of patients with FM [1,2]. These complaints, known as “fibrofog” in patient parlance and “dyscognition” in the medical literature, add significantly to patients’ morbidity [3]. Performance-based tests of dyscognition in FM have found deficits in working memory, executive control, and attention [4–8].

Importantly, cognitive deficits have also been described in other chronic pain syndromes, such as chronic low back pain, neuropathic pain, and chronic pancreatitis [9,10]. A recently published meta-analysis concluded that chronic nonmalignant pain has a moderate, but significant detrimental effect on working memory performance [11]. The neurobiological mechanisms underlying these deficits are still poorly understood and further research is needed to unravel effects of pain (per se), concomitant disorders, such as depression and anxiety, and medication on cognition and brain function.

Modern brain imaging has provided some insights into the interaction between clinical pain, experimental pain, cognitive performance, and the neural correlates thereof [12]. Both painful stimuli as well as cognitive tasks (e.g., n-back, multisource interference task, Go/No-Go, etc.) robustly activate regions in the prefrontal cortex and superior parietal lobes, as well as the anterior cingulate cortex (ACC), mid-cingulate cortex (MCC), supplementary motor cortex (SMA), and the (anterior) insular cortex. Furthermore, it has been shown that painful stimuli can also modulate the executive attention network while engaged in a cognitive task [12,13]. These findings indicate that both pain perception and cognitive functioning partially rely upon overlapping structures and networks.

To date, most studies investigating the interaction between pain and cognitive functioning use experimental pain, enabling controlled application of various, well-defined pain intensities. Less is known about the neural correlates underlying the interaction between chronic pain and cognitive performance [14,15], one reason being the inability to modulate chronic pain in a controlled way in the scanner environment. One way around this drawback is to investigate pain patients longitudinally and to relate changes in clinical pain, either induced by therapy or just following a natural course, to changes in cognitive performance and related brain activation [16].

In a previous, cross-sectional study, we compared brain activity elicited by an inhibition task (Go/No-Go task) in a group of FM patients and healthy controls (HCs) [17]. The Go/No-Go task is a well-established neuropsychological test that requires the study subjects to suppress a certain motor response (for details, see below). The neural network underlying response inhibition has been investigated in a number of studies and is well characterized. The cortical brain areas most commonly associated with response inhibition include the premotor cortex, the right ventrolateral cortex, as well as several regions in the medial frontal wall (e.g., SMA, pre-SMA, MCC, and the dorsal ACC) [18–20], making up the inhibition network. Importantly, the simple Go/NoGo task (as applied in this study) is easy to perform, yielding high accuracies in both FM and HC. Accordingly, differences in brain activation during the task must be attributed to reasons other than performance. In the aforementioned study, comparing FM patients and HCs, a decreased blood oxygen level dependent (BOLD) response elicited by the inhibition task was found in FM patients in the medial frontal wall (i.e., dorsal

ACC/MCC and SMA) as well as in the right premotor cortex, despite equal performance (i.e., accuracy and reaction times). Our findings suggested that chronic pain in FM leads to a decrease in task-related brain activation in interface regions (i.e., regions that participate in the performance of multiple tasks and networks and possibly constitute regions of limited resources), which is in line with other studies investigating neural correlates of impaired executive functioning in FM patients [14].

In the present study, we aimed to investigate longitudinally changes in brain activity elicited by the same Go/No-Go task in the same cohort of patients and HCs [17]. In this longitudinal design, we compared brain activity during the task at baseline, to the activity found 12 weeks later. All FM patients and HCs took part in a larger clinical treatment trial investigating the effect of exercise, relaxation, and standard care on clinical pain, as well as perceived locus of control. A subset of patients and HCs took part in the Go/No-Go study to specifically investigate differences in task-related brain activation: 1) between groups; and 2) between groups over time (group \times time point interaction—current study). The latter approach specifically asked the question whether changes in pain over time would be associated, with changes in brain activation. We hypothesized that those patients, who had clinical improvement in terms of a reduction either in pain intensity or in percentage body area in pain (%BP), would show an increase in inhibition-associated BOLD response in regions previously shown to be hypo-responsive to the Go/No-Go task, such as the premotor cortex or the dorsal ACC/MCC region.

Methods

Subjects

Initially we had investigated 18 individuals with FM and 14 HCs [17]. All study participants were taking part in a larger randomized controlled clinical treatment trial for FM. The second half of the study enrolled participants in this cognitive study. Participants (i.e., FM patients and HCs) performed a Go/No-Go task in the scanner [21]. Findings of brain activations associated with inhibition and differences in brain activations between both groups (cross-sectional study) have been previously reported [17]. Out of this group, 18 FM patients and 14 HCs underwent the same Go/No-Go task posttreatment (i.e., 12 weeks later).

All participants were females. The study was conducted in accordance with the Institutional Review Boards of the University of Michigan, and the Department of Defence (co-sponsor). To participate in the study, individuals with FM needed to: 1) fulfill the 1990 American College of Rheumatology research classification criteria for FM [22]; 2) be at least 18 years of age; and 3) be under the standard medical care of a physician for FM. Participants were ineligible if they had any of the following: 1) a severe physical impairment (e.g., complete blindness, or deafness, paraplegia) or coexisting physical injury (e.g., sprained ankle, neck injury, etc.); 2) comorbid medical

illnesses (e.g., morbid obesity, autoimmune diseases, cardiopulmonary disorders, uncontrolled endocrine or allergic disorders or malignancy within 2 years; 3) any present psychiatric disorder involving a history of psychosis, current suicide risk or attempt within 2 years of the study, or substance abuse within 2 years; and 4) a pending status associated with disability or the receipt of disability compensation for less than 2 years; as well as 5) standard exclusion criteria for magnetic resonance imaging studies.

Demographic and Clinical Data

The following clinical features were assessed: 1) demographics (i.e., age, education); 2) pain (i.e., average weekly pain intensity and percentage bodily pain distribution); and 3) mood (i.e., depression and anxiety).

Demographics—a standardized demographics form was used to record age and education as well as medical status.

Clinical Pain—pain was assessed using a patient experience diary, an electronic pain diary programmed to collect

pain ratings 6–8 times per day on a real-time random basis. Data were then aggregated to determine the weekly average pain rating ranging between “0” for “no pain” and “100” for “extreme pain” (the week before scan 1 and scan 2, respectively). Participants were also asked to complete a body mannequin similar to that used previously to assess the presence of chronic widespread pain [23]. The mannequin was partitioned into 70 body regions from which the percentage of body area in pain (%BP) could be assessed (Figure 1).

Mood—State depression and state anxiety were assessed using the Center for Epidemiological Studies—Depression Scale (CES-D [24]) and the State-Trait Personality Inventory state anxiety scale (STPI [25]), respectively. The CES-D is a 20-item self-report instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults in both clinical and normal populations. The CES-D has four separate factors: 1) Depressive affect; 2) Somatic symptoms; 3) Positive affect; and 4) Interpersonal relations. The questions are easily interpreted and address most of the areas included in the diagnostic criteria for

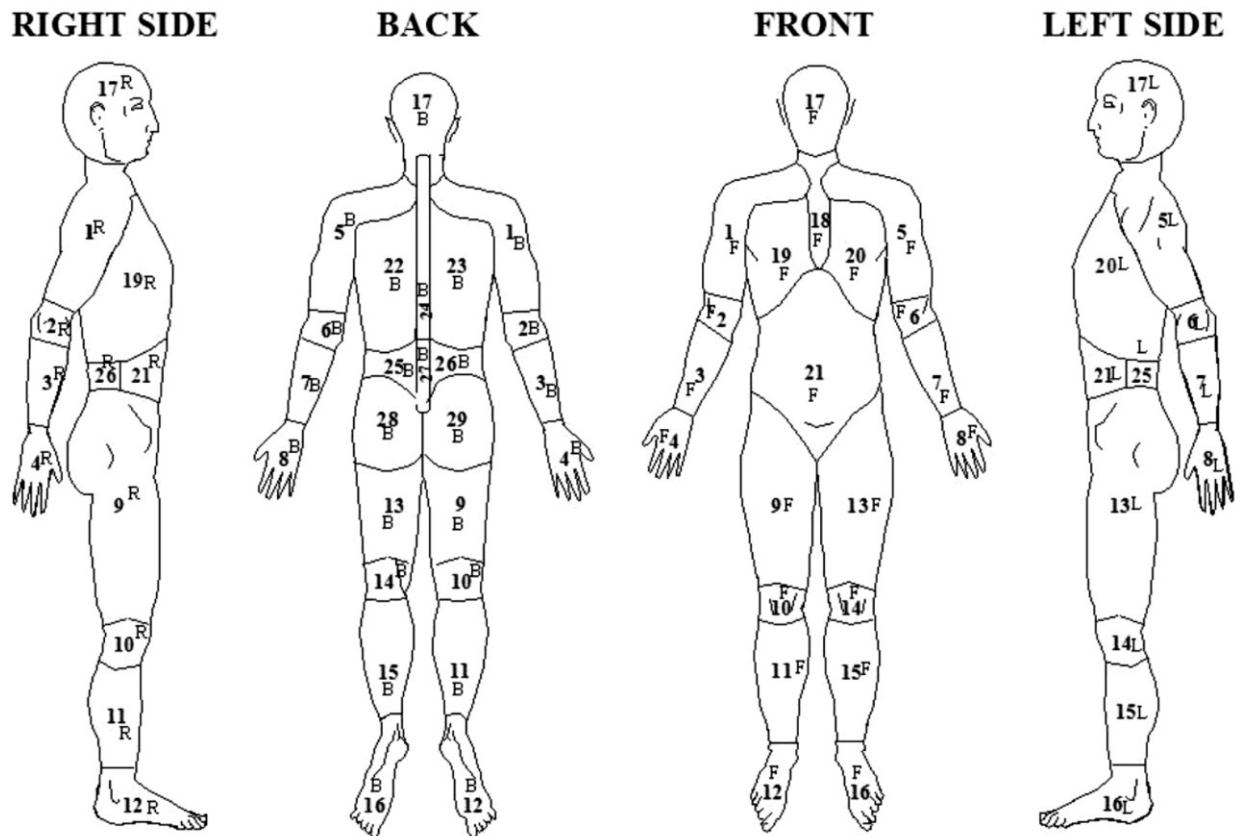


Figure 1 Mannequin with 70 body regions to assess percentage of body area in pain. Participants were asked to complete a body mannequin similar to that used previously to assess the presence of chronic wide-spread pain (modified version, [23]). The mannequin was partitioned into 70 body regions from which the percentage of body area in pain could be assessed.

depression. Most commonly, a single summary score is obtained with a cut-off of 16 used to indicate a high degree of depressive symptoms. The STPI is an 80-item self-report questionnaire with eight 10-item scales for measuring state and trait anxiety, anger, depression, and curiosity. For purposes of this study, a subset of 10 items were used that assessed state anxiety.

Data Acquisition and Analysis

fMRI Task

A simple Go/No-Go task was used to probe response inhibition, similar to previous studies by our group [21]. Participants were instructed to make a speeded response to target letters (i.e., letters other than X) by pressing a button (i.e., Go trials), but asked to make no response to infrequent nontarget stimuli (i.e., X; No-Go trials). There were no additional cues to increase time pressure. All stimuli, for Go and No-Go trials, were projected to the middle of the presentation screen; there were no differences with respect to color or font size. Stimulus duration was 500 msec, followed by a 3,500 msec screen with a fixation cross. There were five runs of 49 trials, each lasting 3 minutes 24 seconds, and containing 11, 12, or 13 No-Go trials (i.e., a total of 60 No-Go trials out of 245 total trials). No-Go trials were pseudo-randomized; the order of the stimuli remained the same across subjects and time points. Before scanning, all participants had a practice session of 49 trials on a desktop computer. False-alarm rate (i.e., responding to the No-Go signal) and reaction times (RTs) for correct responses were calculated as performance measures.

MRI Data Acquisition

Whole-brain BOLD functional images were acquired on a 3.0 Tesla GE Signa scanner (Milwaukee, WI, USA) using T2* weighted single-shot combined spiral in-out sequence with the following parameters: TR = 2,000 msec, TE = 30 msec, FA = 90°, FOV = 200 mm, matrix size = 64 × 64; in plane resolution = 3.12 mm × 3.12 mm, and slice thickness = 4 mm. Participants' motion was minimized using foam pads placed around the head along with a forehead strap.

Preprocessing and Statistical Analyses

Data were quality checked, preprocessed, and analyzed using Statistical Parametric Mapping (SPM) software packages, version 5 (Functional Imaging Laboratories, London, UK), running under Matlab 7.5b (Mathworks, Sherborn, MA, USA). Preprocessing steps included motion correction (realignment to the first image of the time series), normalization to the standard SPM-EPI template (generating 2 × 2 × 2 mm resolution images), and smoothing (convolution with a 6 mm full width at half maximum Gaussian kernel).

First-level analyses were performed using the general linear model implemented in SPM. Three regressors of

interest were: 1) all Go trials; 2) correct No-Go trials; and 3) failed No-Go trials (= false alarms). These were convolved with the canonical hemodynamic response function, with event duration of 4 seconds from stimulus presentation. Motion parameters were modeled as regressors of no interest. The main first-level contrast of interest was correct No-Go trials vs Go trials, as a model of inhibition (contrast image = $\beta_{\text{correct No-Go}} - \beta_{\text{Go}}$). This contrast has been described in previous studies [21]. First-level analysis was performed by linearly combining parameter estimates over all five runs of the task. Failed No-Go trials were not included in the analysis.

A random effect model was used for second-level analyses. The following analyses were performed:

Analysis 1: A correlation analysis within the FM group, correlating changes in clinical pain ($\Delta_{\text{clinical pain}}$) and changes in task-related activation pre- and posttreatment (difference image: contrast image_{time point 1} - contrast image_{time point 2}), to determine where in the brain (within the patients' group) changes in clinical pain were associated with changes in BOLD response. This was done for pain intensity (Analysis 1a) as well as for %BP (Analysis 1b).

Analysis 2: To corroborate the results from Analysis 1, the group of FM patients were divided via median split into "improvers" and "nonimprovers," yielding three groups overall (i.e., improvers, nonimprovers, and HCs). For the imaging data, this was done for %BP only, as the correlation analysis (Analysis 1) yielded significant results in a priori hypothesized regions only for %BP (see below). Improvers had a reduction of ≥20% of bodily pain. Repeated measures analysis of variance (ANOVA) was used to determine whether changes over time (pre- and posttreatment) in inhibition related BOLD response were significantly different between the three groups, specifically between improvers and HCs (Analysis 2a), as well as improvers and nonimprovers (Analysis 2b).

In other words, the analyses comprised the following:

1. the calculation of differences in activation between correct No-Go and Go trials in each individual at time points 1 and 2 (= first level contrast images—2 per study subjects),
2. calculation of difference images between time points 1 and 2 (= 1 Δ image per FM patient),
3. correlation of Δ images with changes in clinical pain ($\Delta_{\text{clinical pain}}$): for $\Delta_{\text{pain intensity}}$ (Analyses 1a) and $\Delta_{\%BP}$ (Analysis 1b), and
4. performance of repeated measures ANOVA with contrast images comparing changes over time between FM—improvers and HC (Analysis 2a), and FM—improvers, and FM—nonimprovers (Analysis 2b).

All statistical maps (2nd level analyses) were corrected for multiple comparisons on the cluster level ($P < 0.05$), derived from an uncorrected $P < 0.005$ on the voxel level, with a cluster extent of 92 contiguous voxels, as estimated

by the AlphaSim application (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>), implemented in the Analysis of Functional NeuroImages (AFNI) software.

Results

Subjects and Behavioral Data

Due to missing data and/or poor quality of the images (e.g., motion parameters exceeding 2 mm in translation and/or 5° in rotation), only 17 FM patients (of originally 18 at baseline) and 12 HCs (of originally 14 at baseline) were included in this analysis. FM patients, both improvers and nonimprovers, had significantly more clinical pain ($P < 0.001$), as well as higher depression and anxiety scores than HCs ($P < 0.001$), pre- and posttreatment. Improvers did not differ significantly from nonimprovers on measures of depression and anxiety ($P > 0.2$), pre- and posttreatment. For details, see Tables 1–3.

Performance on the Go/No-Go Task

As shown in Table 1, there were, as expected, no significant differences between the FM group and the HC group in mean RT (552.8 vs 558 msec, respectively, $t_{(2,26)} = 0.16$, $P = 0.87$) and in mean false alarms (4.4 vs 2.7 false alarms, respectively, $t_{(2,27)} = 1.29$, $P = 0.21$) of the Go/No-Go task posttreatment, consistent with the pretreatment results previously published [17].

When looking at the FM patients, neither at time point 1 nor at time point 2 did the groups (improvers and nonimprovers) differ significantly in pain intensity and/or %BP. Not surprisingly, when looking at interactions, pain intensity improvers showed a significant decrease in pain intensity as compared with nonimprovers ($P = 0.003$); likewise, %BP improvers showed a significant decrease in %BP as compared with nonimprovers ($P < 0.001$, see Tables 2 and 3). When comparing improvers and nonimprovers (with respect to pain intensity), improvers had longer RTs than nonimprovers ($P = 0.025$) at time point 2 (Table 2); this was due to smaller SDs at time point 2 as compared with time point 1. Importantly, improvers even had a more pronounced decrease in RTs (Δ RTs: 48.2 ms) as compared with nonimprovers (Δ RTs: 22.4 ms); however, this interaction was not significant (group \times time point interaction, $P = 0.38$). When comparing improvers and nonimprovers (with respect to %BP), there were no significant group differences and interactions between false alarms and mean RTs, pre-, or posttreatment (Table 3). Error rates increased slightly, but not significantly in all four groups; there was a trend that pain intensity improvers had a less pronounced increase in error rates as compared with nonimprovers (group \times time point interaction, $P = 0.09$).

Correlations between Go/No-Go performance and symptoms of pain, depression, and anxiety were calculated. There were no significant correlations between RT or false alarms and any other variables during either time point 1 or time point 2.

Table 1 Demographics and performance on Go/No-Go task: patients (FM) vs healthy controls (HC)

	Time Point 1			Time Point 2		
	Group 1 FM Time Point 1 (N = 17)	Group 2 HC Time Point 1 (N = 12)	Descriptive Differences between FM and HC (t-tests)	Group 1 FM Time Point 2 (N = 17)	Group 2 HC Time Point 2 (N = 12)	Descriptive Differences between FM and HC (t-tests)
Demographics						
Age (years)	44.1 (9.9)	42.7 (12.2)	$t = .354$, $P = 0.726$	44.1 (9.9)	42.7 (12.2)	$t = .354$, $P = 0.726$
Pain						
PED	54.4 (16.4)	N/A	N/A	51.6 (14.9)	N/A	N/A
%BP	54.1 (21.6)	1.9 (4.7)	$t = 8.21$, $P < 0.001$	46.8 (24.7)	0.12 (0.41)	$t = 6.52$, $P < 0.001$
Allied symptoms						
Depressive symptoms (CES-D)	15.9 (9.4)	0.83 (1.3)	$t = 5.46$, $P < 0.001$	14.9 (9.5)	2.5 (3.3)	$t = 4.36$, $P < 0.001$
Anxiety (STPI)	18.6 (5.8)	10.7 (1.2)	$t = 4.64$, $P < 0.001$	17.5 (5)	11.6 (2.4)	$t = 3.83$, $P < 0.001$
Performance on the Go/No-Go Task						
Error rate (false alarm to No-Go signal)	2.1 (2.8)	3.4 (3.0)	$t = 1.24$, $P = 0.226$	4.4 (3.7)	2.7 (3.3)	$t = 1.291$, $P = 0.207$
Reaction time (to Go signal) (RT)	586.3 (151.4)	571.3 (158.4)	$t = 0.252$, $P = 0.803$	552.8 (60.6)	558.1 (113.9)	$t = 0.159$, $P = 0.875$

Summary of age, clinical pain, allied symptoms, and performance on Go/No-Go task.
 PED = average pain per day over last week (average pain each day/7); %BP = percentage of bodily pain distribution; CES-D = Center for Epidemiological Studies Depression Scale;
 STPI = State-Trait Personality Inventory; RT = reaction time.

Table 2 Demographics and performance on the Go/No-Go task: improvers vs nonimprovers—with regard to pain intensity

	Time Point 1		Time Point 2		Interaction (Greenhouse-Geisser Correction)
	Group 1 Improvers Time Point 1 (N = 8)*	Group 2 Nonimprovers Time Point 1 (N = 8)	Group 1 Improvers Time Point 2 (N = 8)	Group 2 Nonimprovers Time Point 2 (N = 8)	
Demographics					
Age (years)	43.5 (13.9)	44.5 (5.4)	43.5 (13.9)	44.5 (5.4)	$t = 1.89, P = 0.852$
Pain					
PED	61.5 (10.5)	47.2 (18.6)	50.8 (11.6)	52.4 (18.4)	$t = 0.204, P = 0.841$
%BP	69 (17.9)	39.8 (16)	52.1 (25.8)	44.1 (25)	$t = 0.634, P = 0.536$
Allied symptoms					
Depressive symptoms (CES-D)	15.5 (5.8)	17.5 (12.4)	13 (5.6)	18.5 (11.6)	$t = 1.197, P = 0.251$
Anxiety (STPI)	19.5 (6.4)	18 (5.8)	16.1 (4.7)	19.1 (5.4)	$t = 1.194, P = 0.252$
Performance in the Go/No-Go Task					
Error rate (false alarm to No-Go signal)	2.4 (3.9)	1.6 (1.7)	3.9 (3.4)	5.5 (4)	$t = 0.876, P = 0.396$
Reaction time (to Go signal) (RT)	629.5 (208.9)	535.6 (56.3)	581.3 (61.5)	513.2 (38)	$t = 2.532, P = 0.025$

* Of note there were missing PED data for one subject; accordingly, the FM group was split into two groups consisting of eight patients.

Summary of age, clinical pain, allied symptoms, and performance on Go/No-Go task.

FM = fibromyalgia; PED = average pain per day over last week (average pain each day/7); %BP = percentage of bodily pain distribution; CES-D = Center for Epidemiological Studies Depression Scale; STPI = State-Trait Personality Inventory; RT = reaction time.

Table 3 Demographics and performance on the Go/No-Go task: improvers vs nonimprovers—with regard to percentage of bodily pain distribution

	Time Point 1		Time Point 2		Descriptive Differences between Groups 1 and 2 (<i>t</i> -tests)	Interaction (Greenhouse–Geisser Correction)
	Group 1 Improvers Time Point 1 (N = 9)	Group 2 Nonimprovers Time Point 1 (N = 8)	Group 1 Improvers Time Point 2 (N = 9)	Group 2 Nonimprovers Time Point 2 (N = 8)		
Demographics						
Age (years)	40.2 (11.5)	48.5 (5.7)	40.2 (11.5)	48.5 (5.7)	<i>t</i> = 1.85, <i>P</i> = 0.085	
Pain						
PED	56.2 (14.5)	52.5 (18.9)	50.8 (11.8)	52.3 (18.2)	<i>t</i> = 0.441 <i>P</i> = 0.666	<i>P</i> = 0.53
%BP	59.7 (15.5)	47.9 (26.6)	35.2 (11.7)	59.8 (29.5)	<i>t</i> = 1.139, <i>P</i> = 0.273	<i>t</i> = 2.31, <i>P</i> = 0.035
Allied symptoms						
Depressive symptoms (CES-D)	16.4 (10.9)	15.3 (8.2)	13.4 (11.5)	16.7 (6.9)	<i>t</i> = 0.25, <i>P</i> = 0.804	<i>t</i> = .697, <i>P</i> = 0.496
Anxiety (STPI)	19.8 (6.6)	17.3 (4.8)	16.1 (4.8)	19.1 (4.9)	<i>t</i> = 0.89, <i>P</i> = 0.386	<i>t</i> = 1.28, <i>P</i> = 0.221
Performance in the Go/No-Go Task						
Error rate (false alarm to No-Go signal)	2.2 (3.4)	1.9 (2.2)	3.8 (3.3)	5.1 (4.3)	<i>t</i> = 0.246, <i>P</i> = 0.809	<i>t</i> = 0.73, <i>P</i> = 0.477
Reaction time (to Go signal) (RT)	553.1 (91.5)	623.7 (199.5)	560.7 (66.8)	542.6 (54.9)	<i>t</i> = 0.96, <i>P</i> = 0.35	<i>t</i> = 0.58, <i>P</i> = 0.571

Summary of age, clinical pain, allied symptoms, and performance on Go/No-Go task.

The group of FM patients were divided via median split into “improvers” and “nonimprovers.”

PED = average pain per day over last week (average pain each day/7); %BP = percentage of bodily pain distribution; CES-D = Center for Epidemiological Studies Depression Scale;

STPI = State-Trait Personality Inventory; RT = reaction time.

Brain Activation during Response Inhibition—Longitudinal Analysis

Correlation analyses within the FM group (including both improvers and nonimprovers) with changes in pain intensity and %BP were performed. There was a significant negative correlation between change in %BP and change in BOLD activation in the left dorsal ACC/MCC (cluster size: $k = 183$, $r(\text{cluster}) = -0.63$, $r(\text{peak voxel}) = -0.89$, $P < 0.05$, cluster level corrected). There were no significant correlations between pain intensity and BOLD response in this group. To exclude a regression to the mean effect, we performed the following analysis: a multiple regression with %BP at time point 1 and Δ eigenvariates of the activation cluster in the cingulate cortex as predictors and %BP at time point 2 as dependent variable. Adding Δ eigenvariates of the activation cluster significantly improved the model (significance F change 0.015). The model explained 60% of the variance ($P < 0.01$). For more detailed information on peak coordinates, r -values, and cluster sizes, see Table 4, Figure 2A and B. For a scatterplot (correlation of Δ clinical pain and Δ task related activation), see Figure 3.

Direct comparison of brain activation associated with inhibition (No-Go > Go) between the improvers and HCs (group \times time point interaction, Table 4) showed a trend for an *increased* activation in the improvers' group in the left dorsal ACC/MCC (cluster size: $k = 84$, $P < 0.1$ cluster level corrected; Table 4, Figure 2C and D). The same analysis (group \times time point interaction) with improvers and nonimprovers (No-Go > Go) showed a significant increase in activation in the improvers in the left cingulate cortex (cluster size: $k = 111$, $P < 0.05$ cluster level corrected; Table 4, Figure 2E and F).

Discussion

In this longitudinal study, we sought to relate changes in clinical pain to changes in brain activation elicited by

response inhibition in FM patients and HCs using a Go/No-Go task. As a main result, we report, as hypothesized, an increase in task-related BOLD response in the cingulate cortex (reaching into the SMA), a region that had previously been found to be "hyporeactive" in FM patients when performing a Go/No-Go task. This effect was only related to changes in %BP in pain, but not to pain intensity. To our knowledge, there is only one other study that investigated brain activation elicited by a cognitive task in chronic pain patients within a longitudinal study design. Seminowicz et al. reported an increase in cortical thickness of the left dorsolateral prefrontal cortex (DLPFC) in chronic back pain patients going along with a pain reduction and normalization of brain activation (in the DLPFC) during an attention-demanding cognitive task [16]. Our results are in line with this study, also describing an increase in brain activity, though in a different brain region, i.e., in the dorsal ACC/MCC, associated with a reduction in clinical pain.

Both acute and chronic pain affect cognition [26,27]. Cognitive deficits have been described in a number of chronic pain states such as FM [5,8,28], chronic low back pain (CLBP) [27], chronic regional pain syndrome [27], and chronic pancreatitis [10]. Both structural and functional brain imaging [15,29–32] have begun to shed light on possible mechanisms underlying these deficits. Using fMRI, Weismann-Fogel et al. investigated patients with temporomandibular disorder (TMD) and HCs performing a cognitive and emotional stroop task [33]. Despite nonsignificant differences in performance, TMD patients showed increased task-related activations in brain areas implicated in attention (lateral prefrontal cortex), emotional processing (amygdala, pregenual ACC), motor planning (SMA, primary motor cortex), as well as a diminished deactivation in the default mode network (DMN), specifically the medial prefrontal cortex and the posterior cingulate cortex, during task performance. A lack of deactivation in the DMN has also been reported by Baliki et al. in CLBP patients performing a visual attention task (despite equal performance) [31]. In a recently published

Table 4 Task-related brain activations: cluster sizes, z-scores/ r -values, and coordinates

Region	Cluster Size (Number of Voxels)	r Values (Peak Values)	z-score (Peak Value)	Coordinates (MNI)		
				x	y	z
Analysis 1—Negative correlation between %BR scores (time point 2 – time point 1) and BOLD response (FM group) (time point 2 – time point 1)						
L mid cingulate cortex	183	-0.89	4.43	-10	10	44
Analysis 2a: Improvers (time point 2 – time point 1) > Healthy controls (BOLD) (time point 2 – time point 1)						
L mid/anterior cingulate cortex	84*	n/a	3.26	0	28	24
Analysis 2b: Improvers (time point 2 – time point 1) > Nonimprovers (BOLD) (time point 2 – time point 1)						
L cingulate cortex	111	n/a	3.71	-8	10	44

* Cluster just misses the apriori defined cluster extent of 92 contiguous voxels to correct for multiple comparisons and is accordingly reported as trend.

Analysis 1: correlation analysis between changes in clinical pain ($\Delta_{\text{clinical pain}}$) and changes in activation (difference image: contrast image_{time point 2} – contrast image_{time point 1}); Analyses 2a and 2b: factorial design (repeated measures ANOVA), with group and time point as factors.

%BR = percentage body regions (in pain), MNI = Montreal Neurological Institute.

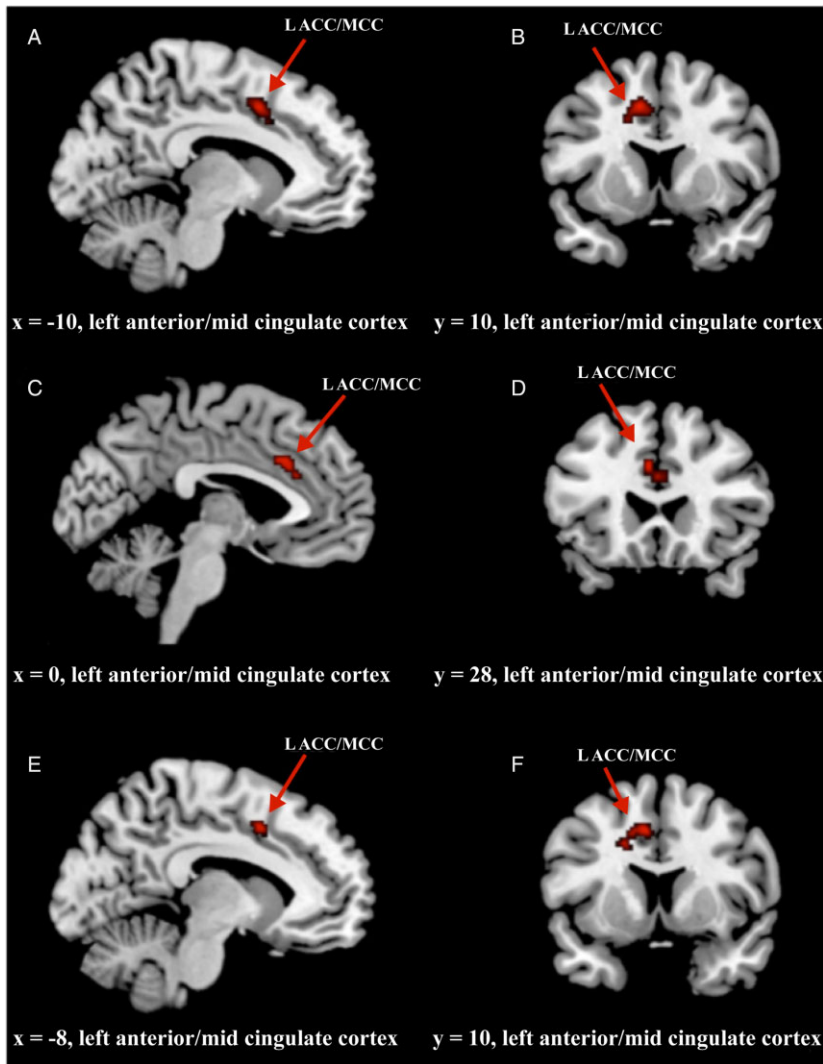


Figure 2 BOLD response related to inhibition—changes over time. (A and B) Analysis 1: correlation analysis between changes in clinical pain ($\Delta_{\text{clinical pain, \%BR}}$) and changes in BOLD response_{time point 2 – time point 1}. (C and D) Analysis 2a, improvers_(time point 2 – time point 1) > healthy controls_(time point 2 – time point 1). (E and F) Analysis 2b: improvers_(time point 2 – time point 1) > non-improvers_(time point 2 – time point 1); dACC = dorsal anterior cingulate cortex; L = left; R = right.

study, Seo et al. demonstrated decreased performance in FM patients as compared with HCs in a working memory task, associated with decreased task-related brain activation in the DLPFC, inferior parietal cortex, SMA, and ventrolateral prefrontal cortex [14], which is consistent with our previous findings reported by Glass et al. [17]. Interestingly, a hyporeactivity of the MCC and SMA has also been observed in FM patients in other cognitive contexts, such as expectancy of pain [34]. Overall, the literature is not yet conclusive and patterns of altered brain activation related to cognition might vary between pain syndromes and tasks, and might further depend on other factors such as pain duration, pain distribution, and existing comorbidities.

The medial frontal wall is reliably activated by both nociceptive stimuli, as well as cognitive tasks [35–37]. The cortical brain areas most commonly associated with response inhibition include the premotor cortex, the right ventrolateral cortex, as well as several regions in the medial frontal wall (e.g., SMA, pre-SMA, and the dorsal

ACC) [18–20], making up the inhibition network. Within this network, the cingulate cortex subserves different aspects of task performance; activation of the ACC has often been attributed to attention, as well as control and error detection [38], while the MCC and the SMA have been implicated in response selection and motor functioning. Importantly, with respect to pain and the interaction between pain and cognition, it has been hypothesized that the cingulate cortex is likely to be the most important component of the neural system that mediates the impact of pain-related distress on cognitive functions, (e.g., in terms of allocation of attentional resources) [39]. Interestingly, using VBM, Luerding et al. could show that in FM patients both clinical pain and cognitive performance correlate with gray matter density in neighboring regions in the medial frontal wall [29]. Furthermore, animal models using nerve injury to produce prolonged neuropathic pain have demonstrated structural micro- and macro-changes in the ACC/medial frontal wall associated with the induction of anxiety-like behavior and attention deficits [40–42]. It is unclear how these peripheral neuropathic pain models

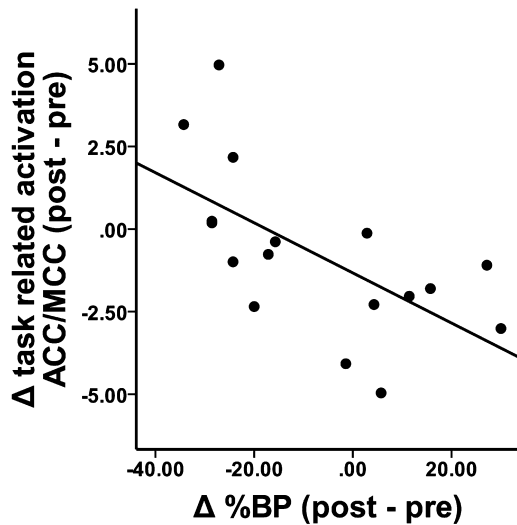


Figure 3 Correlation between changes in clinical pain and changes in task-related activation in the anterior cingulate cortex. Δ = difference between time points 2 and 1; ACC = anterior cingulate cortex; %BP = percentage body area in pain.

relate to chronic functional pain syndromes, like FM; however, these findings highlight the vulnerability of the medial frontal wall to a prolonged nociceptive input, mediating the effect of pain on higher cognitive functioning.

Several conceptually different, but by no means exclusive, approaches have been taken to provide a theoretical framework for dyscognition in chronic pain [26], one of which, here referred to as the *network concept* (or *concept of competing demands*) highlights the fact that the pain system interacts with other neural systems, such as the executive attention network, the salience network and the DMN. According to this concept, a hyperactive pain system, due to ongoing pain perception (or pain anticipation/vigilance to pain), takes up neural resources, no longer available for other networks, and/or leads to a malintegration of other brain networks into the pain system [43], and subsequently to their malfunctioning. The executive attention network (including the inhibition network), the salience network, and the pain system access the medial frontal wall, which might reflect a common effect the corresponding stimuli have on the brain, (e.g., related to attention and/or decision-making). On the other hand, the same region might just provide neural resources for different networks with the ability of network switching, depending on the present task. It is also conceivable that the cingulate cortex serves as an interface region enabling information flow between different networks. Overall, it is still a matter of debate whether emotion, pain, and cognitive control are functionally segregated in distinct subdivisions of the cingulate cortex or whether they share overlapping regions such as the anterior MCC constituting a hub where information about

reinforcers can be linked to the motor system responsible for expressing affect and executing goal-directed behavior [39]. In either scenario, our data highlight both the centrality and functional dynamics of this region in the interaction between (clinical) pain and executive functioning.

Overall, our data not only support an important role of the cingulate cortex in different tasks, but also suggest that the degree of activation and the degree of integration within different networks can support dynamic alternations depending on environmental conditions/demands (i.e., our data suggest functional reorganization associated with pain improvement). Strictly speaking, the term “functional reorganization” describes the recruitment of neural tissue previously not at all (or only to a lesser degree) involved in a specific task, associated with a shift in the cognitive process [44]. Against this background, our findings should better be referred to as redistribution rather than (true) reorganization, as we found changes (increases) in regional brain activity, having been shown active before without a shift in the underlying cognitive process [44].

Limitations

Several limitations of this study need to be addressed. First, the sample size is relatively small with 17 patients in the correlation analysis, and 8 vs 14 (improvers vs HCs) and 8 vs 9 (improvers vs nonimprovers), respectively, in the repeated measures ANOVAs. This small study sample also hampers treatment-specific analysis, i.e., patients’ brain activation was only analyzed with respect to pain and changes thereof, but not with respect to the interventions applied. One might argue that different interventions possibly have different effects on task-related brain activation and indeed future studies will have to investigate larger sample sizes, especially when interested in treatment-specific effects on brain activation.

Second, the relation between perceived dyscognition and test-based deficits requires further investigations. For FM, Glass could demonstrate that the perceived degree of dyscognition exceeds the actual deficits seen in the neuropsychological tests, implying either an exacerbation by comorbidities, such as anxiety and depression, and/or alterations in meta-cognitive processes [45] (i.e., the process of reflecting over and judging one’s own performance [and the certainty with which one has performed]). An interesting question that arises is whether, at a certain stage, altered task-induced brain activation is more closely related to perceived dyscognition rather than to the performance itself. This would imply that the lack of activation, for example due to limited resources, induces altered self-perception (of the brain’s activity), leading to the feeling of dyscognition, while the actual test performance is still within normal ranges. In this study, no meta-cognitive data, e.g., questionnaires about the degree of perceived dyscognition and perceived performance, had been collected. Future studies should take these aspects, i.e., task complexity, task relevance, and meta-cognition,

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into account when further disentangling neural correlates of pain-associated dyscognition.

Finally, pain-related changes in brain activation in the cingulate cortex were only related to %BP in pain, but not to pain intensity. The usual focus in pain measurement in FM is primarily pain intensity, and secondarily functional constructs such as pain interference, followed by temporal features such as pain duration. Although inherent to the concept of FM, “widespreadness” of pain has only recently become as important as measuring the intensity of pain in understanding the potential mechanisms driving the pain complaint in FM [46]. The presence and extent of widespread pain suggest an enhanced involvement of central nervous system processes in the development and maintenance of chronic pain [47,48]. A leading hypothesis regarding the importance of pain distribution posits that impaired antinociception plays an important role in the genesis of chronic in FM [49,50]; however, strictly speaking, impaired antinociception would explain phenomena like hyperalgesia, but not necessarily spontaneous pain. Given that altered proprioception (eventually misinterpreted as pain) also plays a role, one could argue that the extent of pain distribution correlates with the extent of proprioceptive signal gaining access to the ACC/MCC, i.e., salience/pain network and undergoing misinterpretation. In this sense, pain distribution might be an even more sensitive clinical marker than pain intensity to the underlying pathophysiological process.

Summary and Outlook

In this longitudinal study, we demonstrated that FM patients whose clinical pain improved showed an increase in task-related BOLD response in the cingulate cortex and SMA, (i.e., that a preexisting regional hypoactivation is, at least to some degree, reversible), and secondly, that the extent to which pain decreases correlates with the increase in task-related BOLD response. We hypothesize that chronic pain takes up neural resources, which are then no longer available to other networks. However, this seems to be a reversible process, such that a decrease in pain is associated with functional reorganization, in terms of a normalization in task-related brain activity. As cognitive deficits have also been found in other chronic pain states, such as CLBP [30,51,52], it will be interesting to see whether the conceptual approach put forth by this study is also valid for other chronic pain states or whether it is specific to FM. Furthermore, it would be of interest whether the integration of a “shared” region into a nonpain network can actually be used to improve clinical pain, (i.e., whether it is possible to use cognitive load to reduce the ability of pain to involuntarily capture attention) [53,54].

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