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Coordinate-Based (ALE) Meta-Analysis of Brain Activation in Patients With Fibromyalgia

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Abstract: There are an increasing number of neuroimaging studies that allow a better understanding of symptoms, neural correlates and associated conditions of fibromyalgia. However, the results of these studies are difficult to compare, as they include a heterogeneous group of patients, use different stimulation paradigms, tasks, and the statistical evaluation of neuroimaging data shows high variability. Therefore, this meta-analytic approach aimed at evaluating potential alterations in neuronal brain activity or structure related to pain processing in fibromyalgia syndrome (FMS) patients, using quantitative coordinate-based "activation likelihood estimation" (ALE) meta-analysis. 37 FMS papers met the inclusion criteria for an ALE analysis (1,264 subjects, 274 activation foci). A pooled ALE analysis of different modalities of neuroimaging and additional analyses according functional and structural changes indicated differences between FMS patients and controls in the insula, amygdala, anterior/mid cingulate cortex, superior temporal gyrus, the primary and secondary somatosensory cortex, and lingual gyrus. Our analysis showed consistent results across FMS studies with potential abnormalities especially in pain-related brain areas. Given that similar alterations have already been demonstrated in patients with other chronic pain conditions and the lack of adequate control groups of chronic pain subjects in most FMS studies, it is not clear however, whether these findings are associated with chronic pain in general or are unique features of patients with FMS. *Hum Brain Mapp 37:1749–1758, 2016.*

Key words: fibromyalgia; pain; descending pain modulation system; meta-analysis; brain imaging; activation likelihood analysis

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Patients with fibromyalgia syndrome (FMS) suffer from chronic widespread pain in the musculoskeletal system and associated symptoms such as fatigue, sleep disturbance, and cognitive dysfunctions [Schmidt-Wilcke and Daniel J. Clauw, 2011]. The prevalence of fibromyalgia ranges from 2 to 8% and women are more affected with a 2:1 female to male ratio [Clauw, 2014].

The underlying etiopathogenesis is still unknown, but it has been hypothesized that fibromyalgia is a disorder of pain processing and pain modulation in the central nervous system due to dysfunctions of central pain inhibitory or intrinsic brain networks [Jensen et al., 2009]. Many studies have used neuroimaging to investigate neural activity in FMS patients. These studies showed differences in activation in response to experimentally applied pain stimuli in pain-related brain areas such as the insula, anterior and posterior cingulate, inferior parietal lobe, thalamus, cerebellum and primary and secondary somatosensory cortex (SI, SII) when compared with studies of pain processing in healthy humans [Apkarian et al., 2005]. There are further studies pointing to the presence of a significant imbalance of the intrinsic brain connectivity within the pain network and disrupted intrinsic connectivity within the default mode network (DMN) as well as hyperconnectivity between pain processing regions [Ichesco et al., 2014; Napadow et al., 2010].

However, despite the growing number of studies assessing brain activation no clear picture emerged from the existing literature considering the involvement of cortical and subcortical regions. The findings of FMS neuroimaging studies are inconsistent and hard to compare, as they included a heterogeneous group of patients, used different nociceptive stimuli, and different experimental designs which led to a variety of methods employed and obvious difficulties in generalization of the results. Given the inconsistencies in the studies, we aimed to clarify disease relevant brain alterations by performing a statistical coordinate-based meta-analysis of FMS neuroimaging studies using the "activation likelihood estimation" (ALE) method to investigate whether conclusions from existing reviews from different modalities can be corroborated. This meta-analytic tool enables detecting effects that may be weak, and hence went unnoticed in the original studies because they did not seem to be interesting according to the hypothesis, but are consistent across experiments [Eickhoff et al., 2009; Eickhoff et al., 2012]. The purpose of this study was therefore to test, in an exploratory fashion, which brain areas known to be important for pain processing in FMS were altered.

Abbreviations

ACC	Anterior cingulate cortex
ALE	Activation likelihood estimation
DMN	Default mode network
FMS	Fibromyalgia syndrome
FWHM	Full width at half maximum
MNI	Montreal Neurological Institute
PAG	Periaqueductal gray
ROI	Regions of interest
STG	Superior temporal gyrus
VOI	Volume of interest

METHODS

Identification of FMS Brain Imaging Studies

A literature search was conducted using PubMed to identify relevant studies for inclusion in the ALE meta-analysis. All included articles were published in English or German language prior to March 2015. The search input was a combination of main keywords according to the disease terminology of fibromyalgia and either one of the general neuroimaging techniques [*(Fibromyalgia [Mesh] OR Fibromyalgia OR Fibrositis) AND (imaging OR Brain) AND (MRI OR Magnetic Resonance Imaging OR PET OR Positron Emission Tomography OR SPECT OR Single Photon Emission Computed Tomography)]* or the additional combination of specific terms according evoked pain paradigms [*AND (activation OR stimulation OR evoked)]*, resting or baseline brain activity [*AND (resting state OR baseline)]*, structural brain imaging [*AND (vbm OR voxel based morphometry OR dti OR diffusion tensor imaging OR tractography OR brain morphology OR cortical thickness)]*, spectroscopy studies [*AND (proton magnetic resonance spectroscopy OR Spectroscopy OR glutamate OR GABA OR Glx OR NAA OR neurotransmitter)]*, and electroencephalographic studies [*AND (EEG OR EP OR electroencephalography OR electroencephalogram OR evoked potential OR MEG OR magnetoencephalography OR magnetoencephalogram)]*.

Five-hundred studies including review articles were identified and were checked for the following criteria: (1) Articles must include results of brain imaging studies. (2) Single case reports were excluded. (3) Only papers reporting results from their own studies were included. The reference lists of identified review articles were screened manually for additional citations and one additional relevant publication was identified.

The 114 resulting articles were filtered for necessary inclusion criteria for ALE in a second step (Step 2): (1) Only studies which performed a statistical comparison were included. This implies that either patients with one or more control group or patients before and after treatment of any kind were statistically compared. (2) Studies needed to perform whole-brain analyses to also cover brain areas which were not in the subjective focus of the authors. Therefore, studies with only restricted regions of interest (ROI) or volume of interest (VOI) analyses were excluded. In studies that have also conducted ROI analyses in addition to a whole-brain analysis, only the results

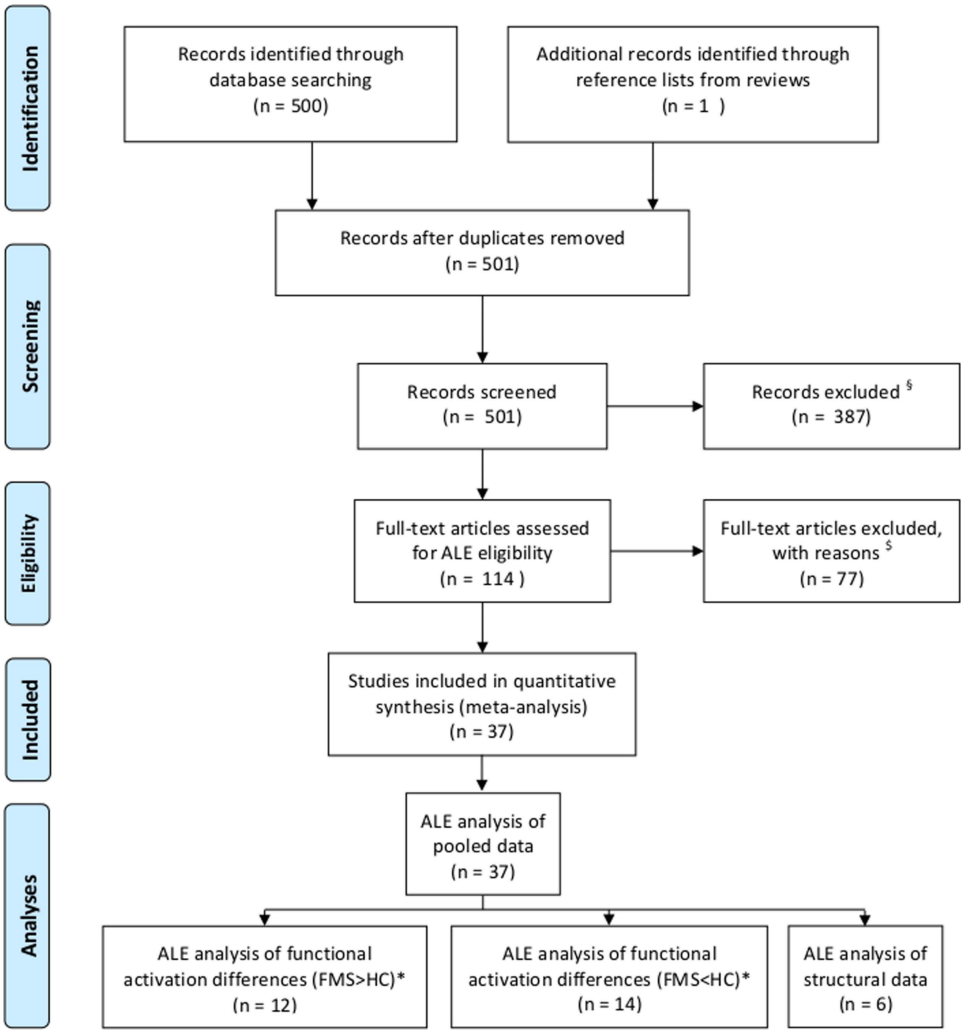

Figure 1.

Show the sequence of the literature search and the process of inclusion or exclusion of articles according the PRISMA statement (see http://www.equator-network.org/reporting-guidelines/prisma/). §exclusion criteria = no brain imaging, single case reports, reviews. $exclusion criteria = no statistical comparison of groups, no whole-brain analysis, no standard stereotactic space coordinates (Talairach, MNI). * some articles show results of clusters with hyperactivation or hypoactivation. For each subanalysis these clusters were integrated separately. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of the whole-brain analyses were included. Furthermore, functional connectivity studies of a priori defined seed regions covering the whole brain or widespread cortical areas were included as well. (3) The results needed to be reported in a normalized standard stereotactic space, i.e., Talairach or Montreal Neurological Institute (MNI). The 114 studies and the respective reason for exclusion are listed in Supporting Information Table SI.

These criteria identified 37 papers for inclusion into the meta-analysis (Fig. 1, Table I). From these studies, the necessary parameters for an ALE analysis were extracted (Number of subjects, coordinates). We performed four independent ALE analyses:

We pooled data of different modalities [functional (fMRT, PET, SPECT, EEG), structural (VBM, DTI)] into one analysis. This approach gives information about the global changes in FMS independent of the implemented neuroimaging paradigm since each imaging modality, study design and data processing might bias the results in different directions. Therefore, a pooled functional and structural analysis compensates for such method-induced variance of data.

We analyzed the 18 functional studies only to provide information on the direction of activation changes of altered brain regions in FMS in (2a) an analysis with all brain regions showing greater activation ($n = 68$) in FMS

TABLE I. List of 37 studies included in the ALE analysis

Paper	Imaging method	Statistical comparison	Stat. threshold	*n* of included clusters
Functional studies FMS vs controls				
Brown et al. *Eur. J. Neurosci*. 2014;39:663–672.	EEG	16 FMS, 15 HC, 16 OA	corr. 0.05	14
Burgmer et al. *Psychosom. Med*. 2011;73:751–759.	fMRI	12 FMS, 14 HC	corr. 0.05	2
Burgmer et al. *Eur. J. Pain* 2012;16:636–647.	fMRI	17 FMS, 17 HC	corr. 0.05	3
Glass et al. *J. Pain* 2011;12:1219–1229.	fMRI	18 FMS, 14 HC	corr. 0.05	10
Gracely et al. *Arthritis Rheum*. 2002;46:1333–1343.	fMRI	16 FMS, 16 HC	corr. 0.05	14
Guedj et al. *Eur. J. Nucl. Med. Mol. Imaging* 2007a;34:130–134.	SPECT	18 FMS, 10 HC	corr. 0.05	18
Harris et al. *J. Neurosci*. 2007;27:10000–10006.	PET	17 FMS, 17 HC	corr. 0.05	4
Jensen et al. *Pain* 2009;144:95–100.	fMRI	16 FMS, 16 HC	uncorr. 0.005	2
Jensen et al. *Arthritis Rheum*. 2013;65:3293–3303.[a]	fMRI	26 FMS, 13 HC	corr. 0.05	1
Kim et al. *PLoS One* 2013;8:e74099.	fMRI	21 FMS, 11 HC	corr. 0.05	8
Loggia et al. *Arthritis Rheumatol*. 2014;66:203–212.	fMRI	31 FMS, 14 HC	corr. 0.05	25
Lopez-Sola et al. *Arthritis Rheumatol*. 2014;66:3200–3209.	fMRI	35 FMS, 25 HC	corr. 0.05	8
Maestu et al. *Clin. Neurophysiol*. 2013;124:752–760.	MEG	9 FMS, 9 HC	corr. 0.01	9
Martinsen et al. *PLoS One* 2014;9:e108637.	fMRI	23 FMS, 28 HC	uncorr. 0.001	7
Pujol et al. *PLoS One* 2009;4:e5224.	fMRI	9 FMS, 9 HC	corr. 0.05	14
Usui et al. *Arthritis Res. Ther*. 2010;12:R64.	SPECT	29 FMS, 10 HC	corr. 0.05	10
Wik et al. *Neuroreport* 2003;14:619–621.	PET	8 FMS, 8 HC	corr.	3
Wood et al. *J. Pain* 2007;8:51–58.	PET	6 FMS, 8 HC	uncorr. 0.01	14
Functional studies within FMS				
Boyer et al. *Neurology* 2014;82:1231–1238.	PET	16 FMS, 13 FMS	uncorr. 0.001	1
Guedj et al. *Eur. J. Nucl. Med. Mol. Imaging* 2007c;34:2115–2119.	SPECT	11 FMS, 6 FMS	uncorr. 0.001	3
Harris et al. *Neuroimage* 2009;47:1077–1085.	PET	10 FMS, 10 FMS	corr. 0.05	2
Jensen et al. *Pain* 2012;153:1495–1503.	fMRI	19 FMS, 15 FMS	corr. 0.05	1
Jensen et al. *J. Pain* 2014;15:1328–1337.	fMRI	21 FMS, 16 FMS	corr. 0.05	1
Schmidt-Wilcke et al. *Pain Med*. 2014;15:1346–1358.	fMRI	8 FMS, 8 FMS	corr. 0.05	1
Wik et al. *Eur. J. Pain* 1999;3:7–12.	PET	8 FMS (pre/post)	uncorr. 0.00	10
Structural studies				
Ceko et al. *Neuroimage Clin*. 2013;3:249–260.	VBM	27 FMS, 26 HC	corr. 0.05	9
Fallon et al. *Neuroimage Clin*. 2013;3:163–170.	VBM	16 FMS, 15 HC	corr. 0.05	4
Hsu et al. *Pain* 2009;143:262–267.	VBM	29 FMS, 29 HC	corr. 0.05	0
Jensen et al. *Arthritis Rheum*. 2013;65:3293–3303.a	cortical thickness	26 FMS, 13 HC	corr. 0.05	7
Kim et al. *Arthritis Rheumatol*. 2014;66:3190–3199.	DTI	19 FMS, 18 HC	corr. 0.05	1
Schmidt-Wilcke et al. *Pain* 2007;132 Suppl 1:S109–S116.	VBM	20 FMS, 22 HC	corr. 0.05	3
Connectivity studies				
Flodin et al. *Brain Connect*. 2014;4:587–594.	rsMRI	16 FMS, 22 HC	corr. 0.05	6
Harris et al. *Anesthesiology* 2013;119:1453–1464.	rsMRI	14 FMS (pre/post)	uncorr. 0.05	6
Ichesco et al. *J. Pain* 2014;15:815–826.e1.	rsMRI	18 FMS, 18 HC	corr. 0.05	8
Jensen et al. *Mol. Pain* 2012;8:32–8069-8-32.	fMRI	28 FMS, 14 HC	corr. 0.05	4
Napadow et al. *Arthritis Rheum*. 2010;62:2545–2555.	rsMRI	18 FMS, 18 HC	corr. 0.05	5
Napadow et al. *Arthritis Rheum*. 2012;64:2398–2403.	fMRI	17 FMS (pre/post)	corr. 0.05	2
Pujol et al. *Pain* 2014;155:1492–1503.	rsMRI	40 FMS, 36 HC	corr. 0.05	34

[a]*a*Study of Jensen included functional and structural analyses.
SPECT = Single Photon Emission Computed Tomography, PET = Positron Emission Tomography, VBM = Voxel-based morphometry, DTI = diffusion tensor imaging, fMRI = functional Magnetic Resonance Imaging, rsMRI = resting-state MRI, EEG = Electroencephalography, MEG = Magnetoencephalography, sr = seed regression, ICN = intrinsic connectivity network.

in contrast to controls and (2b) a separate analysis with all brain regions showing less activation ($n = 98$) in FMS in contrast to controls.

For purpose of testing the impact of structural changes in FMS we performed an additional explaratory analysis using clusters of structural studies ($n = 24$).

ALE Meta-Analysis

Statistical analysis of the studies was conducted using the revised ALE algorithm [Eickhoff et al., 2009] for coordinate-based analyses [Turkeltaub et al., 2002]. At first, a whole-brain modeled activation map (MA-map)

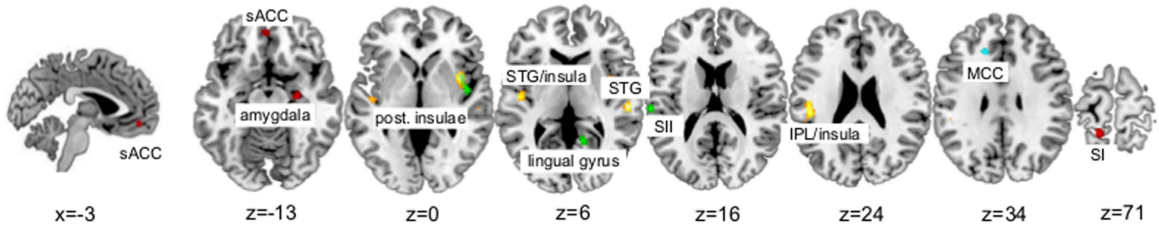

Figure 2.

Depicts the results of the ALE-analyses on the Colin27_T1_seg_MNI template. Clusters of the pooled analysis are shown in yellow, clusters of the functional analysis are shown in green (FMS hyperactivation) and red (FMS hypoactivation), and the cluster of the structural analysis is shown in cyan. sACC = subgenual anterior cingulate cortex, STG = superior temporal gyrus, SI = primary somatosensoric cortex, SII = secondary somatosensoric cortex, IPL = inferior parietal lobe, MCC = middle cingulate cortex. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

describing the convergence of the assessed experiments is obtained by estimating activation probabilities for each voxel in the brain. The reported activation foci are treated as centers of a 3D Gaussian probability distribution, the width reflects an estimate of the spatial uncertainty of the foci of a given map and sample size of each experiment [Turkeltaub et al., 2012]. The full width at half maximum (FWHM) value and the null distribution of each voxel has been empirically determined. In the next step, a permutation test is used to distinguish true convergence of foci across different experiments from random spatial association (i.e., noise) by comparing the ALE scores to an empirical null distribution. The histogram of the ALE scores obtained under the permutation distribution is then used to assign *P*-values to compute the ALE map threshold [Eickhoff et al., 2012]. The resulting ALE maps were determined at a cluster-level Family Wise Error (FWE) rate-corrected threshold of $P < 0.05$ (cluster-forming threshold at voxel-level $P < 0.001$). For illustration, the ALE maps were imported into MRICron as overlay on a standardized anatomical MNI-normalized template (Colin_27_T1).

RESULTS

The pooled functional and structural meta-analysis included 37 studies with a total number of 1,264 subjects and 274 brain foci. Brain clusters in the right insula, areas of the transition between the parietal lobe and superior temporal gyrus (STG) to the insula, and the right STG were found (yellow clusters, Fig. 2).

The additional meta-analyses taking into account the direction of activation changes in FMS showed six brain regions. Patients with FMS presented hyperactivation in the right insula, the left postcentral gyrus (SII), and the right lingual gyrus (green clusters, Fig. 2). Hypoactivation in FMS was seen in the left postcentral gyrus (SI), the subgenual region (area 32) of left anterior cingulate cortex, and the right amygdala (red clusters, Fig. 2).

To test for the impact of structural alterations in FMS we performed an explaratory meta-analysis of the six studies investigating structural brain changes in FMS. An alteration was detected in the midcingulate gyrus around Brodmann area 32 (cyan cluster, Fig. 2).

Table II provides the respective coordinates, cluster sizes, and number of contributing foci of the related papers of all four analyses.

To control for a possible impact of the within-FMS studies (pre versus post intervention) on the result of the first pooled analysis, because these studies might represent the neural correlates of the treatment effect (in the context of FMS) but not the neural correlates of FMS itself, we performed an additional meta-analysis of the pooled data without these seven studies. This analysis confirmed our

TABLE II. Results of the global ALE analysis of FMS different modalities studies and ALE analyses of the functional studies with hyperactivation and with hypoactivation in FMS in contrast to controls

Label	Cluster size mm^3	Coordinates (MNI)			*N* foci contrib.
		X	*y*	*z*	
Global analysis (274 foci, 1264 subjects)					
Right insula	784	39	4	1	4
Left IPL/insula	888	−48	−27	24	6
Left STG/insula	672	−46	−12	5	4
Right STG	448	56	−23	5	3
FMS hyperactivation (68 foci, 383 subjects)					
Right insula	480	43	−2	1	3
Left SII	280	−62	−25	17	2
Right lingual gyrus	272	13	−55	7	2
FMS hypoactivation (98 foci, 503 subjects)					
Left SI	608	−15	−48	72	3
Left subgenual ACC	328	−2	48	−12	2
Right amygdala	304	27	−12	−15	2
Structural analysis (24 foci, 202 subjects)					
Left midcingulate gyrus	400	−17	30	31	2

Cluster-forming value = *P* uncorr.<0.001, cluster-level inference = *P* corr. <0.05, *N* foci contrib. = number of foci of the included studies which contributed to resulting cluster.

prior findings with little changes according the cluster localizations and sizes (see Supporting Information Table SII).

DISCUSSION

The aim of this ALE meta-analysis was to evaluate the potential structural or functional brain alterations in patients with FMS to gain a more detailed insight into the underlying pathophysiology of this chronic pain syndrome. Our analyses revealed differences in several brain regions critically involved in pain processing, including insula, amygdala, STG, lingual gyrus, and anterior/mid cingulate cortex. Because of the low number of included studies and foci ($n = 24$) in our structral analysis the obtained result should not be given the same weight as our other analyses und should be regarded with major caution. However, the mid cingulate cortex has been also reported in other pain and FMS studies [Amanzio et al., 2013; Ichesco et al., 2014; Schmidt-Wilcke et al., 2014].

In the following section, these regions will be discussed according to their specific functions in pain processing, as well as according to their potential involvement in a broader brain network for pain processing in FMS.

Insula

It has been recognized that the insula can be distinguished on the basis of anatomical and functional criteria. The role of the insula has been especially related to self-awareness, regulating emotion, and sensory motor and interoceptive processing as it occurs in pain. The anterior part of the insula is thought to coordinate the affective and emotional aspects of pain, whereas the posterior insula may play a greater role in sensory discriminative aspects of pain [Kurth et al., 2010]. Moreover, it has been described that chronic pain is associated with activation of the anterior insula, whereas experimental pain induces posterior insula activation, as in our results [Friebel et al., 2011]. Regardless of the stimulation technique used to elicit pain, neuroimaging studies have consistently shown a significant involvement of the insula [Apkarian et al., 2005]. In our meta-analysis of pooled data activation foci in the insula were detected mainly in the posterior part, which is in line with posterior insula activation in studies implementing experimental pain and the greater pain transmission in FMS.

The Anterior Cingulate Cortex (ACC)

The ACC plays a key role in regulatory and executive processes, and is responsible for expressing emotions especially associated with enhanced attention directed towards salient stimuli. Several studies have revealed a functional dissociation of this region during emotional processing [Bush et al., 2002; Paus, 2001]. Thus, it has been suggested that dorsal ACC is activated during experimental tasks eliciting a cognitive interference with non-emotional stimuli, whereas ventral ACC is rather involved in the modulation of emotional responses [Kanske and S. A. Kotz, 2011]. Cytoarchitectonically, the subgenual region of the ACC (sACC), as it was found in our functional meta-analysis showing hypoactivation in FMS, is more heterogeneous and seems to be particularly more related to cognitive and affective experiences than the pregenual (pACC) subregion [Palomero-Gallagher et al., 2015].

The ACC is involved in the processing of the affective component of pain, encoding unpleasantness and emotional memories, and regulating endogenous pain modulation [Fuchs et al., 2014]. In chronic pain, ACC hyperactivation has been interpreted as a deficit in emotional modulation and considered a possible underlying mechanism for the chronification [Kamping et al., 2013]. This view is also consistent with the hypothesis that opioidergic and neurotransmitter dysregulation of the ACC could play a significant role in insufficient pain inhibition [Martikainen et al., 2013].

Amygdala

The amygdala plays a central role in emotional learning, acquisition of emotional memories and emotional processing of sensory stimuli, especially fear and defensive behavior [Costafreda et al., 2008]. Neuroimaging studies have revealed a crucial role for the amygdala in the evaluation and the emotional processing of pain [Simons et al., 2014]. The pain modulatory role of amygdala is based on its projections to descending pain regions in the brain [Simons et al., 2014; Tracey and P. W. Mantyh, 2007], as well as on the fact that it is a relay station for both emotional-affective and cognitive processing of nociceptive and antinociceptive inputs including memories and expectations for pain [Bingel et al., 2006; Simons et al., 2014], which might be reason for the decreased activation in FMS in our functional contrast analysis.

The Superior Temporal Gyrus (STG)

The STG is typically associated with auditory perception and contains the primary auditory cortex and auditory association areas. Previous studies indicate that this region is also involved in the production, interpretation and self-monitoring of language, in the processing of social information, and in higher cognitive functioning [Howard et al., 2000; Pearlson, 1997]. Previous neuroimaging studies have suggested that the STG plays a role in the processing of pain-related unpleasantness and that its function seems to be affected in patients with chronic pain [Becerra et al., 1999; Duerden and M. C. Albanese, 2011; Smallwood et al., 2013]. However, the relation between STG activity, as it was found in our pooled analysis in FMS patients, and pain is so far not clear. Still, a number of recently published studies indicated that in FMS not only the

somatosensory system is affected, but that also other modalities are possibly involved. Some authors even hypothesize that FMS and other musculoskeletal diseases might be related to abnormal multimodal intergataion. As such the STG and the auditory cortex may also be of importance in abnormal pain processing [Lopez-Sola et al., 2014].

The Lingual Gyrus

The lingual gyrus is a part of the visual association cortex and plays a relevant role in the analysis of visual memories [Bogousslavsky et al., 1987]. Studies with depressed patients have also shown functional and structural abnormalities in the lingual gyrus [Veer et al., 2010]. The lingual gyrus is also considered as part of the so-called DMN, a network playing a central role in emotional self-awareness, social cognition, creativity, and ethical decision making [Boyatzis et al., 2014]. Moreover, hyperactivation of lingual gyrus has been associated with augmented sensitivity to pain [Loggia et al., 2011], as it was found in our functional meta-analysis.

The Postcentral Gyrus (SI and SII)

The SI has been implicated in the spatial coding and sensory-discriminitive aspects of pain such as anticipation, quality, intensity and localization processing [Apkarian et al., 2005; Bushnell et al., 1999; Schnitzler and M. Ploner, 2000]. The SII seems to be involved in relaying nociceptive information to the temporal lobe limbic structures. Functionally, the SII has been involved in the detection, recognition, learning, and memory of painful stimuli [Schnitzler and M. Ploner, 2000]. Studies have shown significant decreases in gray matter of the somatosensory cortex of chronic pain patients [Schmidt-Wilcke et al., 2006]. Chronic pain patients show reduced brain processing of the physical properties of somatosensory information (e.g. SI, SII), together with an enhanced activation of brain regions involved in the processing of cognitive, emotional and introspective aspects of pain [Apkarian et al., 2005; Williams and R. H. Gracely, 2006].

HOW DO WE EVALUATE ABNORMALITIES IN PAIN REGIONS IN FMS?

The ALE-findings seem to indicate that FMS might be associated with structural or functional changes in brain regions which are altered in other chronic pain disorders as well. Previous studies in FMS have explored different hypotheses to explain these alterations in FMS, such as pathological pain augmentation responses to experimental pain stimuli [Gracely et al., 2002], alteration of neurotransmitter function [Harris et al., 2007], impairment of the descending pain inhibitory network [Jensen et al., 2009], or altered resting state networks [Napadow et al., 2010].

One of the most discussed mechanisms in FMS has been an impaired descending pain inhibition [Jensen et al., 2009]. It is known that the periaqueductal gray (PAG), as part of the descending inhibitory pathway, receives inputs from cortical and subcortical regions such as the PFC, ACC, insula, and amygdala, thus modulating nociceptive information processing within the rostroventral medulla and the dorsal horn of the spinal cord [Tracey and P. W. Mantyh, 2007]. Moreover, the ACC and the insula are key regions involved in processing of affective pain components [Cifre et al., 2012]. Affective and cognitive factors, such as anticipation, attention, anxiety, or depressive states could modulate pain perception by alterating the normal function of these areas. Thus, the observed hypoactivation of the ACC and amygdala in FMS in our functional meta-analysis, together with hyperactivation of the insula might support the idea of a dysfunction of the system of descending pain modulation in FMS [Jensen et al., 2012]. However, in the context of these ALE meta-analyses, it cannot be answered whether the interaction of these brain regions is altered as a network or if the alterations might occure independend of their network function.

Another interesting perspective in the study of brain dysfunction in FMS is provided by the dynamics of resting-state brain networks. In this context, the observed hyperactivation in FMS of the lingual gyrus in our functional meta-analysis, as part of a so-called DMN are highly relevant [Boyatzis et al., 2014]. This network is typically deactivated during a variety of externally focused tasks [Buckner et al., 2008]. Whereas DMN deactivation is induced during acute pain in healthy subjects, distrupted DMN connectivity or DMN-insula have been observed in multiple chronic pain conditions [Baliki et al., 2008; Napadow et al., 2010; Seminowicz and K. D. Davis, 2007]. It is speculated that an altered intrinsic DMN connectivity may characterize a common mechanism in chronic pain, rather than being specific to FMS. In this sense, these alterations of the DMN should be interpreted as a consequence of the chronification of pain. However, these brain regions have also other functions and are involved in other brain networks. Our pooled structural and functional ALE meta-analysis does not consequently imply that an associated brain network is specifically dysfunctional or even involved in FMS.

There have been other meta-analyses utilizing the ALE approach in order to decipher commonly activated brain areas of the pain matrix and its modulation. In chronic neuropathic pain increased activation in the left secondary somatosensory cortex, ACC, and right caudal anterior insula was shown when compared to experimentally induced pain [Friebel et al., 2011]. Another meta-analysis examined brain activation in response to different types of painful stimuli in healthy volunteers and thereby provided positive evidence for the involvement of SI, SII, ACC, insula, prefrontal cortex (PFC), thalamus, and basal ganglia in processing of nociceptive stimuli [Duerden and M.

C. Albanese, 2011]. Moreover, another ALE analysis suggest that there are distinct, but overlapping neuronal networks, such as in the insula, ACC, PFC, SII and thalamus in different types of stimulus-evoked pain (hyperalgesia, allodynia), clinical neuropathic and experimental pain [Lanz et al., 2011]. During placebo analgesia in paradigms using experimental noxious stimulation, increased activity in the ACC, insula, thalamus and hypothalamus as well as in the PAG was observed. Results were interpreted in favor of a true antinociceptive effect underlying placebo analgesia, in addition to assumed modulation of cognitive evaluation of pain intensity [Amanzio et al., 2013]. Results from all these meta-analyses [Amanzio et al., 2013; Duerden and M. C. Albanese, 2011; Friebel et al., 2011; Lanz et al., 2011] are compatible with our findings, i.e., they show different activation patterns of commonly activated regions underlying nociception.

ARE THE REPORTED REGIONS THE MAIN AREAS THAT FUTURE STUDIES IN FMS SHOULD FOCUS ON?

Comparable alterations in pain processing areas have also been observed in patients with other chronic pain conditions including low back pain, and irritable bowel syndrome [Apkarian et al., 2005]. Therefore, it remains unclear whether brain alterations of our results apply only to patients with FMS, or might reflect a general brain alteration linked to chronic pain itself. In our opinion, one of the major problems of the existing neuroimaging literature in FMS is the lack of adequate comparison groups with chronic pain or other relevant comorbid conditions, like depression. In our pooled meta-analysis only one study included a pain control group. Therefore, it is clearly possible that FMS and other chronic pain disorders share overlapping central mechanisms, and show similar features and common neural correlates of pain. Our meta-analysis summarizes previous findings and indicates possible differences of identified areas in patients with FMS. Further studies are needed to provide both a specific and general view on dysfunction of pain processing in this disease. From our perspective future studies should keep the following recommendations in mind, to improve the quality of neuroimaging research in FMS:

- To avoid false positive or negative results or a reporting bias every study should always include a whole-brain analysis and report the corresponding results. A restricted analysis of special ROI like areas of the pain network should be the second choice of analysis only and must be reserved to test restricted hypotheses or to explore detailed statistical information like the temporal characteristics, particular sizes and directions of effects, or correlation of effects with behavioural data. But it is important that the whole-brain approach is the only basis to give better and unbiased information on the possible underlying neurobiological processes in FMS.
- To control the specifity of results, studies must integrate a group of patients suffering from a chronic pain disorder with an underlying and identifiable organic reason as a control population. Otherwise results cannot beviewed as being specific to FMS.

LIMITATIONS

It should be also noted that besides studies during resting state conditions, which indirectly investigated clinical pain in FMS as well, no direct contrast between clinical and experimental pain conditions has been examined in FMS so far. The central representation of experimentally induced and spontaneously ongoing FMS pain might be different such that the current analyses do not provide the clinically relevant abnormalities and neuronal correlates of spontaneous clinical pain in FMS. Therefore, results of these studies should be generalized with some caution in understanding the pathophysiology of FMS.

Coordinate-based meta-analyses include studies with different statistical thresholds and there is no possibility (other than excluding studies) to control this possible bias. As shown in table I, only seven studies with 43 clusters of our analysis reported results with uncorrected statistical thresholds. In face of 274 analyzed clusters in total we feel safe that including these studies with a certain risk of false positive results is more appropriate than neglecting them altogether.

Another limitation of our pooled ALE-analysis might that even with strict inclusion criteria, the included studies still varied on a large number of variables. The data were derived from heterogeneous paradigms (resting state or task-oriented), experimental methods (functional or structural modalities), different statistical power and control comparisons (patients vs. healthy controls or after vs. before treatment with different treatment methods). By using the statistical ALE-approach however, the risk of false positive results is greatly reduced and results which are not typical for the majority of the studies will not show significant results. The current pooled analysis aimed to investigate consistent regions of alteration in FMS across modalities and type of task, rather than identifying correlates of alteration in specific tasks and modalities.

CONCLUSION

The aim of this meta-analysis was to explore brain alterations in FMS patients using the statistical power of the ALE-meta-analytic approach. The prevailing hypothesis in previous literature that FMS is characterized by brain abnormalities of pain processing is consistent with the

present ALE analysis. Nevertheless, since these alterations have been also demonstrated in patients with other chronic pain conditions (e.g. irritable bowel syndrome, low back pain), the specifity of these findings must be regarded with some caution. The lack of positive control groups of patients with other chronic pain conditions in almost all of the reviewed studies makes it difficult to assess whether these changes are associated with chronic pain in general or are unique features of patients with FMS. Therefore, further neuroimaging studies are required comparing FMS and other chronic pain disorders to answer the question of disorder specificity.

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