Case Control Study

Neural Correlates of Maladaptive Pain Behavior in Chronic Neck Pain – A Single Case Control fMRI Study

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Chronic neck pain patients display functional impairments like decreased range of motion, decreased strength, and reduced sensorimotor function. In patients without structural damage, the reason for the persistence of pain is not well understood. Therefore, it is assumed that in chronic pain states, memory processes play an important role. We have now detected and tested a patient that might help us to better understand the neural correlates of maladaptive pain expectation/memory. This patient displays chronic neck pain and restricted unilateral motion of the cervical spine to the left. However, when the patient is distracted, she can perform head rotations without experiencing pain and without restricting her range of movement. Based on this observation, we asked her to imagine movements shown in a video: conscious, non-distracted head rotations (pain-provoking) versus distracted head rotations (pain-free) and compared these results with an age and gender matched control volunteer. Functional magnetic resonance imaging (fMRI) showed distinct brain activation patterns that depended on the side of rotation (pain-free versus painful side) and the kind of movement (distracted versus non-distracted head rotation). Interestingly, brain areas related to the processing of pain such as primary somatosensory cortex, thalamus, insula, anterior cingulate cortex, primary motor cortex, supplementary motor area, prefrontal cortex, and posterior cingulate cortex were always more strongly activated in the non-distracted condition and when turning to the left. The age and gender matched control volunteer displayed no comparable activation of pain centers. In the patient, maladaptive pain behavior and the activity of pain-related brain areas during imagined head rotations were task-specific, indicating that the activation and/ or recall of pain memories were context-dependent. These findings are important not only to improve the understanding of the neural organization of maladaptive pain behavior but also to reconsider clinical evaluation and treatment strategies. The current results therefore suggest that treatment strategies have to take into account and exploit the context in which the movement is performed.

Key words: Maladaptive pain behavior, pain memory, brain plasticity, motor control, neck pain, fMRI, action observation, motor imagery

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In chronic pain states, memory processes play an important role in maintaining symptoms and maladaptive behaviors (1-4). Plastic cortical alterations were shown in chronic low back pain (5), phantom limb pain (6), and complex regional pain syndrome (7). In chronic low back pain, shifted cortical representation (5), regional decrease in grey matter (8), altered structural connectivity (9), and activation of pain-related areas during visualization of painful experience (10) has been demonstrated.

However, in these studies, neural correlates of memory and the underlying associated maladaptive behavior processes are not well known. Therefore, it is impossible to differentiate whether cortical reorganization is maintained due to (undetected) structural changes of the pain-provoking structure or as a sign of persistent maladaptive pain memory associated with certain motor tasks. Thus, structural pathology and clinical presentation, i.e., pain, quality of movements, etc., are often not correlated

(11). Now, we have identified a neck pain patient that might help us to better understand the neural correlates of maladaptive pain behavior. Three years ago, the patient suffered from a cervical traumatic accident without any detectable anatomical damage in her magnetic resonance imaging (MRI) data. Physical examination revealed significantly restricted head rotation to the left (pain-provoking movement), whereas rotation to the right was unaffected (pain-free movement). Interestingly, in distracted situations the patient was observed with full rotation to the normally painful left side. Based on this observation we let her perform a motor task, in which the patient had to throw a ball over her head from the right to the left hand side. Thus, her main attention was on catching the ball rather than on the movement of the cervical spine. Nevertheless, the patient performed the task with movement restriction to the left side. However, when she made imprecise throws to the left hand side and, as a consequence, turned her head into full rotation to the pain-provoking side to visually follow the ball, she did not experience any pain. The aim of the present study therefore was to assess and compare brain activity of the pain-provoking movement (non-distracted head rotation) with brain activity during the throwing task (distracted movement). As it is not possible to measure brain activity by means of functional magnetic resonance imaging (fMRI) during actual head movements, we provided the patient and a control volunteer with videos of head rotations that were executed in a distracted and non-distracted context. Previous studies have shown large overlaps in brain activity during actual task execution and during observation of the same motor task with greatest effects when action observation was combined with motor imagery (AO+MI) (12). Furthermore, activity in brain centers representing pain perception is known to be apparent not only during the actual perception of pain but also when watching a painful scene (10). Therefore, we hypothesized that AO+MI of the pain-provoking, non-distracted movement should be differently processed by pain-related and expectation-related brain areas than the above-mentioned throwing (distracted) task. Furthermore, we hypothesized that differences between the affected and the not affected side should be apparent.

METHOD

A case control study with a matched control vol-unteer was performed at the University Hospital of Fribourg, Switzerland, in April 2012. After informed consent was obtained, initial physical examination was conducted one month prior to the fMRI investigation. The study was approved by the local ethics committee and adhered to the declaration of Helsinki.

Patient

Physical Examination

A 21-year-old woman with 3 years of one-sided neck pain participated in the present study. Her case history began when she fell backwards with her occiput against a bar on her bed. Radiological imaging did not display structural damage directly after the accident or at the time of the present study. Since the accident, she has reported ongoing neck pain that was associated with head rotations to the left. The area of pain is located on the left side of the cervical spine and upper left trapezius side without radiation to the arm. She feels the pain deep inside and describes a dull aching scaled 6 out of possible 10 points on a numeric pain rating scale. Several visits to different physical therapy practices could not sufficiently improve her clinical state. She participated in manual therapy with mobilization of the cervical spine and upper thoracic spine, in training programs with the aim of restoring specific muscle functions such as activating the deep cervical flexors, and she performed sensorimotor exercises such as repositioning tasks with a laser pointer. However, none of these interventions considerably improved her symptoms.

The last examination was performed by a trained orthopedic manual therapist (IFOMPT Standard) with 14 years of professional experience. The results of the biopsychosocial assessment and the impairments of the sensorimotor system are presented in Table 1.

Apart from the clinical part of the physical examination, we asked the patient to perform a ball throwing task while seated. With the ball in her right hand next to her body, the patient was asked to throw the ball over her head to the left side of her body where she should catch the ball with her left hand. After catching the ball with the left hand, the patient threw the ball back to her right side. The patient usually tried to avoid head rotations which caused pain and therefore tried to throw the ball in a way that meant she could catch it with a head rotation to the left of only 20°. However, in situations where she threw the ball inaccurately she rotated her head without movement restriction and without pain. As she was not aware of her unrestricted

Table 1. *Results of sensorimotor and biopsychological assessments of the neck pain patient.*

Inspection	
Neutral head position	The Patient shows a deviation of the head about 10° in lateral flexion to the right perceived as neutral head position
Range of motion	
Rotation	Right 80° pain-free, left only 20° due to pain
Extension	70° with aberrant movement in middle cervical spine
Flexion	45°
Passive segmental motion	
Lateral flexion	Hypomobility in left lateral flexion at C0-C1
Extension	Hypermobility at C4-C5
	Hypomobility at C7-T1-T2
Sensorimotor performance	
Cranio cervial flexion task	24 mmHg on the craniocervical flexion task with augmented activity of sternocleidomastoideus muscle.
Balance	On average, 8 seconds in tandem stance with the right leg in front and 12 seconds in tandem stance with the left leg in front could be accomplished by the patient.
Cervical joint position sense	Relocation of the neutral head position shows both under- and overshoots of more than 5°.
Palpation	
PAIVM´s	Tenderness and increased movements in the middle cervical spine on Maitland Grad II Mobilisation. Stiffness and tenderness in the upper thoracic spine.
Painful muscles	Painful trigger points of trapezius, levator scapulae and the suboccipital extensors on the left side.
Assessments	
NPAD-d	55 points interpreted as moderately restricted.
FABQ	18 out of 66 points; Physical activity subscale: 6 points out of 24; Working subscale: 10 points out of 42. No noticeable fear avoidance behavior.
CES-D	1 point, indicating no depressive disorder

NPAD-d = Neck Pain Disability Index – German version; FABQ = Fear avoidance beliefs questionnaire; CES-D = Center for Epidemiological Studies Depression Scale – German version; PAIVM´s = Passive accessory intervertebral movements.

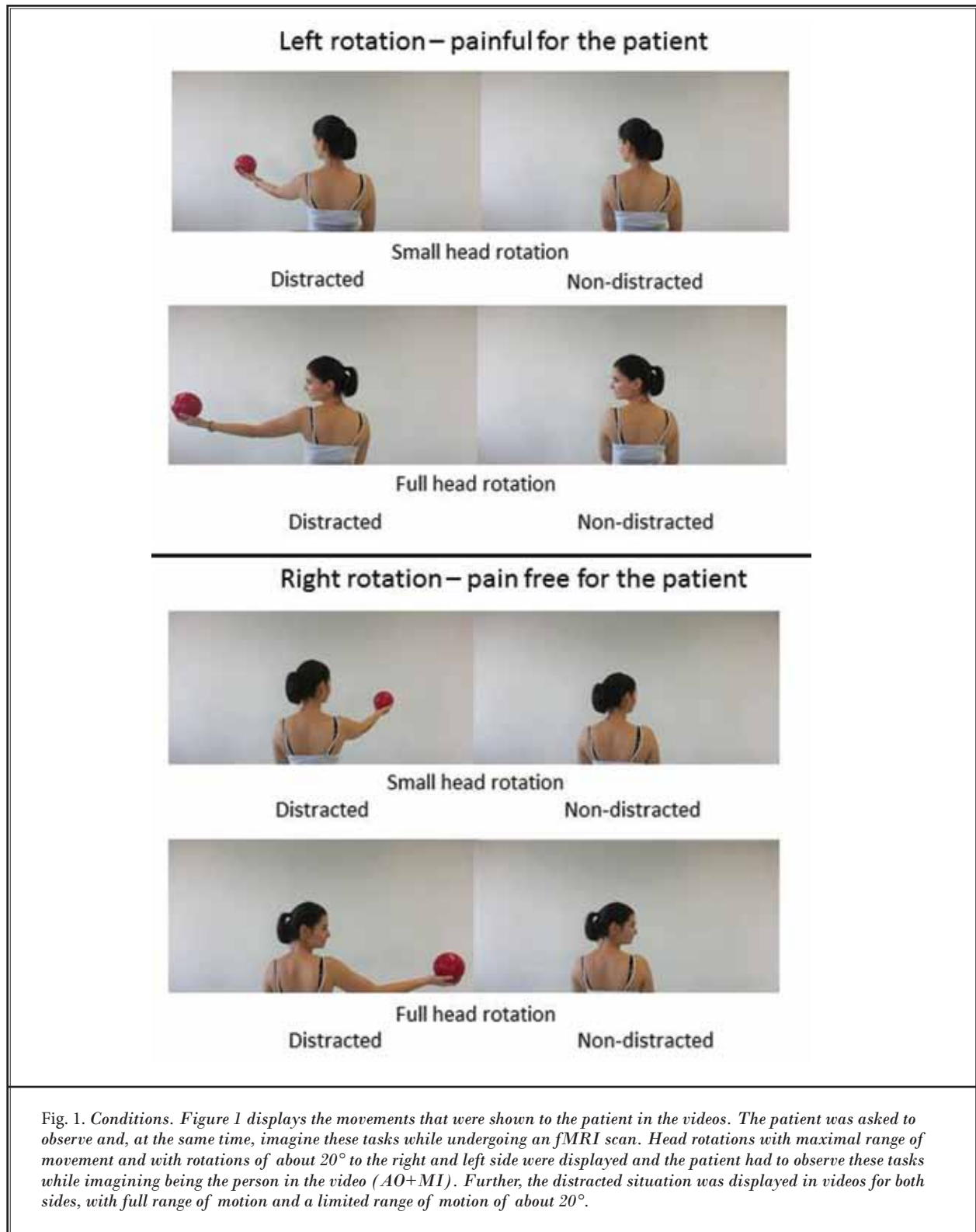movement behavior, we called this situation "distracted head movement/rotation."

Control Volunteer

One female volunteer, matched for age, body height, body mass, and sociocultural background without any history of neck pain, with normal range of motion and no further functional impairments served as control. The control volunteer was familiarized with the throwing task prior to the fMRI investigation.

fMRI Investigation

After informed consent was obtained, the patient and the control participated in an fMRI investigation in order to assess brain activity during AO+MI of 8 different head rotation tasks (Fig. 1). In the scanner, the patient was in supine position and cushions were used to reduce head motion. Presentation of visual stimuli appeared on an LCD screen (32" NNL LCD Monitor, Nor-

dicNeuoLab, Bergen, Norway). The patient regarded the screen through a mirror system with a visual angle of 17° for the height and 9° for the length. The videos were presented with E-Prime 2.0 software (Psychology Software Tools, Inc., www.pstnet.com/ PA, USA) at 60 Hz. Overall, brain activity was assessed in 8 conditions [2 ("non-distracted" vs. "distracted head rotation") x 2 ("left" vs. "right") x 2 ("small" vs. "large amplitude")] (Fig. 1). Thus, each video showed a certain combination of amplitude (20° vs. 80°), direction (left vs. right), and way of task execution (distracted vs. non-distracted). The patient observed the movements in the video and was asked to imagine at the same time being the person in the video performing the task. Thus, motor imagery (MI) was combined with action observation (AO) as this form of mental involvement (AO+MI) was previously shown to be superior to activate brain areas compared to motor imagery or action observation alone (12,13). All 8 videos lasted for 16 seconds and

Fig. 1. *Conditions. Figure 1 displays the movements that were shown to the patient in the videos. The patient was asked to observe and, at the same time, imagine these tasks while undergoing an fMRI scan. Head rotations with maximal range of movement and with rotations of about 20° to the right and left side were displayed and the patient had to observe these tasks while imagining being the person in the video (AO+MI). Further, the distracted situation was displayed in videos for both sides, with full range of motion and a limited range of motion of about 20°.*

were repeated twice in a randomized order. All videos were created with the same logic: each trial lasted for 2 seconds; one video consisted of 8 repetitions of one and the same trial. An auditory tone indicated the beginning of each movement. After each video, a resting period of 14 seconds was provided in which a white cross on a black screen was displayed. A 3T MRI scanner (Discovery MR750; GE Healthcare, Waukesha, Wisconsin USA) with a 32-channels standard head coil was used during acquisition at the Fribourg's Hospital in Switzerland (www.h-fr.ch/).

Data Analysis

The Statistical Parametric Mapping SPM8 software (www.fil.ion.ucl.ac.uk/spm/) working on Matlab 2012b (MathWorks, Inc., www.mathworks.com/, MA, USA) was used to analyze the functional images. Please refer to Taube et al (13) for a further detailed description. Statistical parametric maps (SPMs) were assessed by the contrast (condition > baseline) to reveal the gen-

eral pattern of activation of each experimental condition (simple effects). To show differential patterns of activation between the painful and the healthy side for the patient and the control, contrasts were generated. These effects were displayed at $P < 0.001$ uncorrected with an extended cluster threshold of 60 contiguous voxels (P cluster < 0.05 uncorrected).

Results

Simple Effects

Non-distracted large head rotation to the painful left side versus resting baseline

The simple effects were calculated for activation patterns of the non-distracted movement with a range of motion of 80° compared to resting baseline. Activity in areas associated with processing and expectation of pain and movement were identified and involved S1, PFC, DLPFC, and PCC. Activity in motor areas involved
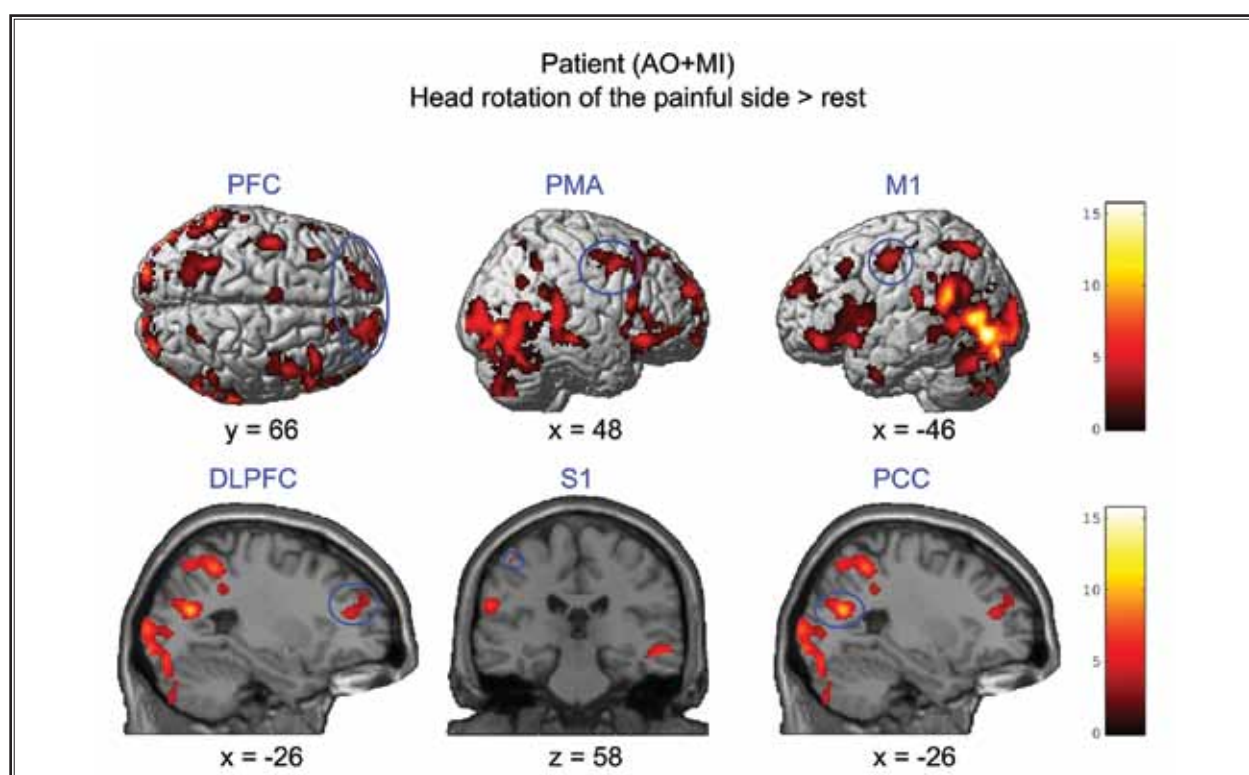
Fig. 2. *fMRI results – simple effects. Brain areas that were activated during combined motor imagery and action observation (AO+MI) of the pain-provoking movement to the left compared to the baseline (resting period). PFC, prefrontal cortex; PMA, premotor area; M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex; S1, primary somatosensory cortex; PCC, posterior cingulate cortex. fMRI results were displayed at P < 0.001 uncorrected with an extended cluster threshold of 60 contiguous voxels. Red-yellow colors highlighted the level of brain activation. (x, y, z) provides spatial coordinates in MNI space.*

activation in M1 and PMA (Fig. 2) for the patient. The control volunteer presented activity in the visual areas (BA 17, 18, 19), superior frontal gyrus (BA 10), insula, superior temporal gyrus (BA 22, 13), and in the cerebellum (declive).

Non-distracted large head rotation to the pain-free right side versus resting baseline

In the patient, the activation pattern of the 80° pain-free movement to the right side during AO+MI revealed activity in motor areas like PMA, the supplementary motor area (SMA), and the cerebellum. Furthermore, the insula was significantly activated. However, no activity was found in any other brain area associated with pain or the expectation of pain. Similarly, the control volunteer displayed activity in SMA, PMA, M1, caudate, thalamus, precuneus (BA 31), and superior and inferior frontal gyrus (BA 9, BA 10).

Non-distracted small head rotations to painful left side and pain-free right side versus resting baseline

The simple effects were calculated for activation patterns of the non-distracted head rotation of 20° compared to resting baseline. No activity was observed in pain-related and expectation-related brain areas for either the patient or the control irrespective of the side of rotation (left or right).

Contrasts

Non-distracted versus distracted large head rotation to the painful left side

Based on the observation that when the patient was distracted, she was able to fully rotate her head without pain, a contrast was defined to directly compare the non-distracted painful movement with the distracted movement (ball throwing task). AO+MI of the pain-provoking non-distracted movement revealed significantly higher activity in brain areas associated with the processing of pain such as S1, TH, and ACC, and compared to the distracted task. Furthermore, areas that are associated with the expectation of pain, such as the PFC and motor areas like M1, SMA, and the cerebellum, were more strongly activated in the non-distracted condition (Fig. 3). The control did not show significant cerebral differences between distracted and non-distracted conditions.

Differences between non-distracted and distracted large head rotations to the painful left side versus dif-

ferences between non-distracted and distracted large head rotations to the pain-free right side
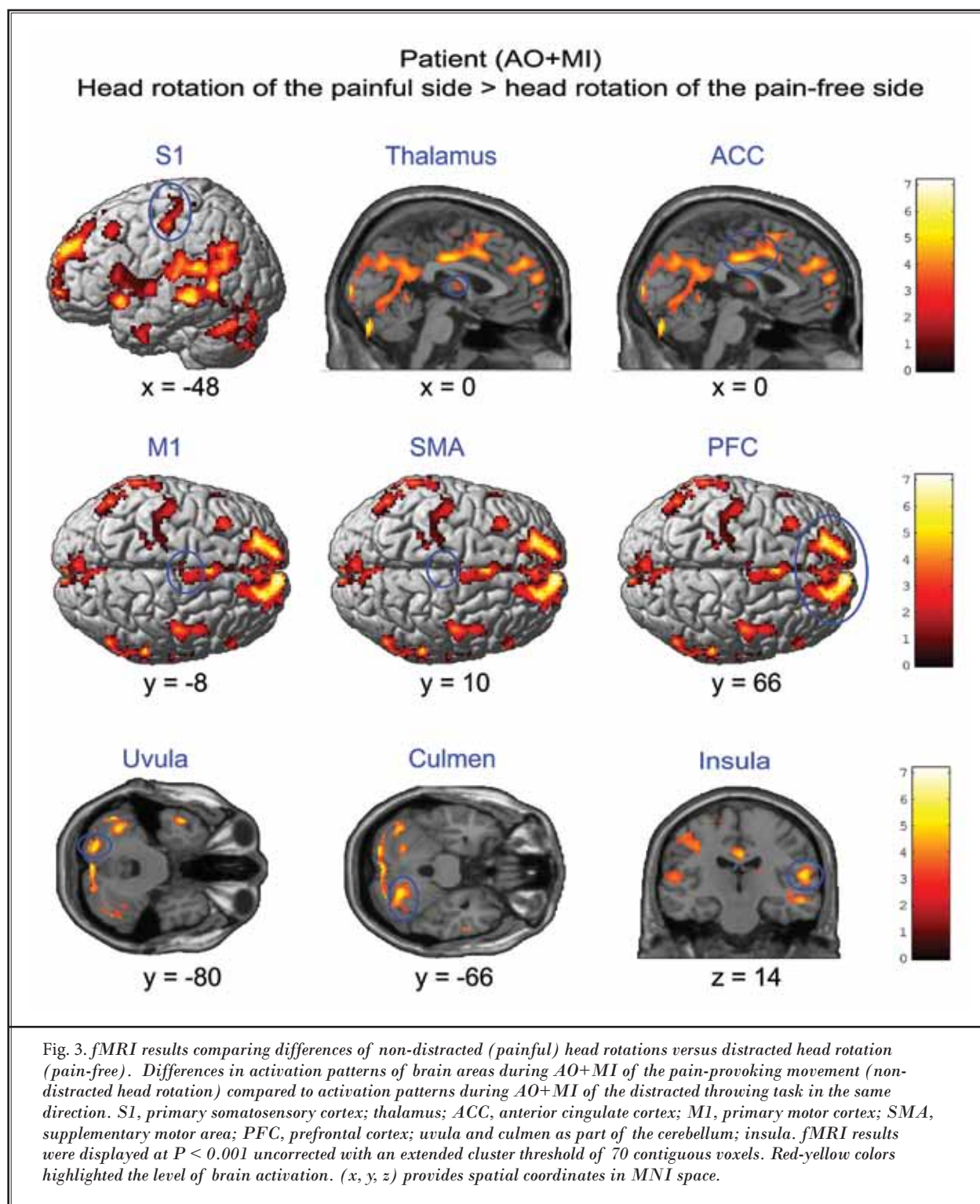
When comparing the differences of the pain-provoking non-distracted large head rotation (80°) and the distracted head rotation to the painful left side with the differences between the non-distracted pain-free movement and the distracted pain-free movement to the right side, extended activity was displayed in brain areas like ACC, PFC, and PCC. These areas are associated with the expectation of pain. Furthermore, the PMA was more strongly activated for the non-distracted painful left head rotation (Fig. 4). The control volunteer did not show significant cerebral differences between conditions.

Differences between non-distracted large and small head rotation to the pain-provoking side compared to the differences between non-distracted large and small head rotation to the pain-free side

In the patient, the comparison of differences between large and small head rotations to the left side with the differences between large and small rotations to the right side revealed augmented activity in pain expectation-related brain areas like the PFC and PCC. Furthermore, the PMA showed increased activity (Fig. 5). The control did not display significant differences in cerebral activity for this interaction.

Discussion

The current single subject study provides evidence that maladaptive pain behavior goes along with differences in activity patterns of the brain centers responsible for pain processing and the expectation of pain (S1, TH, In, ACC, PFC, DLPFC, PCC). First, during AO+MI of large head rotations, brain activity differed between the affected left (painful) and the non-affected right (pain-free) side, but no such differences were found for the control volunteer. Second, brain activity patterns for AO+MI of head rotations executed to the affected left side did not always provoke activity in pain-related brain areas. This means that when the head rotation was combined with a distracting motor task, in this case a ball throwing task, the patient showed significantly less activity in pain-related brain areas than in the non-distracted task execution. These results were confirmed by the behavioral data of the patient. The physical execution of the non-distracted head rotation to the pain-provoking left side was always restricted in range of motion due to pain, whereas a pain-free

Fig. 3. *fMRI results comparing differences of non-distracted (painful) head rotations versus distracted head rotation (pain-free). Differences in activation patterns of brain areas during AO+MI of the pain-provoking movement (non-distracted head rotation) compared to activation patterns during AO+MI of the distracted throwing task in the same direction. S1, primary somatosensory cortex; thalamus; ACC, anterior cingulate cortex; M1, primary motor cortex; SMA, supplementary motor area; PFC, prefrontal cortex; uvula and culmen as part of the cerebellum; insula. fMRI results were displayed at P < 0.001 uncorrected with an extended cluster threshold of 70 contiguous voxels. Red-yellow colors highlighted the level of brain activation. (x, y, z) provides spatial coordinates in MNI space.*

Fig. 4. *Differences between non-distracted and distracted large head rotations to the painful left side versus differences between non-distracted and distracted large head rotations to the pain-free right side. (A) The contrast revealed augmented brain activity in PMA, premotor area; PFC, prefrontal cortex; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex. (B) Graphics represent the contrast estimate from PCC (left plot) and ACC (right plot). Plots are based on a sphere of 10 mm around the (-6; -58; 28) voxel for PCC, and the (-12; 42; 8) voxel for ACC, red bars present the error with 90% of confidence interval. Non-distracted head rotation and distracted head rotation of the painful side (P-nd and P-d). Non-distracted head rotation and distracted head rotation of the pain-free side (Pf-nd and Pf-d). fMRI results were displayed at P < 0.001 uncorrected with an extended cluster threshold of 70 contiguous voxels. Red-yellow colors highlighted the level of brain activation. (x) provides spatial coordinates in MNI space.*
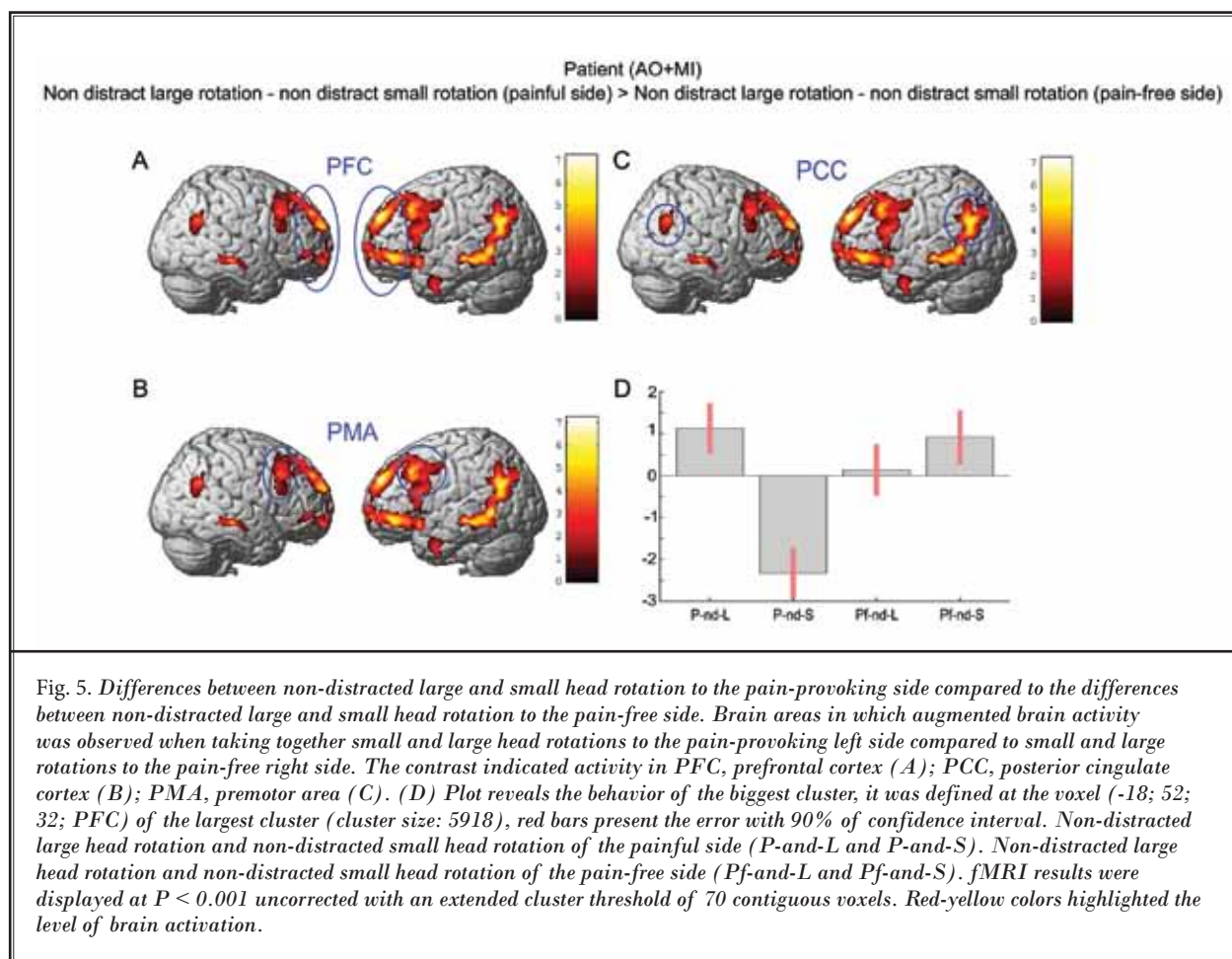
rotation was possible in the presence of a distractor. Therefore, the restricted painful range of motion in the absence of a distractor can be viewed as a conditioned pain response, displayed as maladaptive pain behavior.

Maladaptive pain behavior has been extensively investigated in chronic musculoskeletal pain by the fear avoidance model. Evidence supports the avoidance component as one key element in chronicity, especially in low back pain (14). However, the situation in chronic neck pain is less clear (15) and the present data do not point to this kind of mechanism. The patient did

not show fear, documented by a low score on the fear avoidance beliefs questionnaire (Table 1). Furthermore, at the neural level, there was no activity in the amygdala, which was previously demonstrated as a reliable marker for fear (16). Thus, the question of what the perpetuating factor is in this case remains speculative. As rotation of the head is a frequent everyday movement, the interrelation of pain and head rotation to the left might have been established in this patient in the early period after the accident. Furthermore, it was recently shown that even the mere intention to perform a pain-

Fig. 5. *Differences between non-distracted large and small head rotation to the pain-provoking side compared to the differences between non-distracted large and small head rotation to the pain-free side. Brain areas in which augmented brain activity was observed when taking together small and large head rotations to the pain-provoking left side compared to small and large rotations to the pain-free right side. The contrast indicated activity in PFC, prefrontal cortex (A); PCC, posterior cingulate cortex (B); PMA, premotor area (C). (D) Plot reveals the behavior of the biggest cluster, it was defined at the voxel (-18; 52; 32; PFC) of the largest cluster (cluster size: 5918), red bars present the error with 90% of confidence interval. Non-distracted large head rotation and non-distracted small head rotation of the painful side (P-and-L and P-and-S). Non-distracted large head rotation and non-distracted small head rotation of the pain-free side (Pf-and-L and Pf-and-S). fMRI results were displayed at P < 0.001 uncorrected with an extended cluster threshold of 70 contiguous voxels. Red-yellow colors highlighted the level of brain activation.*

ful movement can act as a covert conditioned stimulus inducing a fear response (17). Thus, this might have additionally or alternatively led to the maladaptive pain behavior. The contribution of this factor is supported by the fact that in our experiment, the mere mental simulation (AO+MI) to perform a head rotation to the left activated brain areas related to pain expectation, whereas no activation of pain related areas where found for the control.

Brain activity in pain-related areas during head rotations to the affected and non-affected side

It was recently demonstrated that not only the execution, but also the observation of movements that are associated with pain, activate brain centres such as In, TH, PCC, and motor areas in patients with chronic lower back pain (10). Therefore, the results of the present study showing differential activity of these brain areas depending on the side of head rotation are well in line

with this previous finding. In general, non-distracted large head rotations to the left (painful side) were accompanied by activity in S1, PFC, DLPFC, and PCC. Furthermore, activity in motor areas involved activation in M1 and PMA, whereas rotation to the right did not display significant activation of any of these areas (simple effects). When calculating contrasts, significantly larger activity was seen in ACC, PFC, PCC, and PMA when turning the head to the left rather than to the right. Importantly, the control did not show such side-dependent differences in activation. Our results are therefore well in line with previous reports from chronic low back pain patients (10), in whom the visualization of movements that were associated with painful experiences like carrying heavy luggage resulted in enhanced brain activity in the TH, In, SMA, PM, PCC, and cerebellum. In this previous study, it was suggested that the former experience of back pain may sensitize patients so that they activate part of the pain matrix, also during observa-

tion of potential harmful postures or movements. Our results confirm and extend these findings by showing that memory retrieval of unpleasant experiences can be highly task-specific, i.e., only the rotation to the left was associated with activation of pain-related brain areas but not head rotations to the right. Furthermore, the current results demonstrate that the activation of brain areas related to the processing of pain is scaled based on the amplitude of the rotation. Large rotations caused greater activity in PFC, PCC, and PMA than small rotations. This result also fits well with the clinical presentation of the patient where the execution of small rotations was associated with little or no pain.

Brain activity in pain-related areas during head rotations with and without a distracting secondary motor task

The clinical evaluation of our patient demonstrated painful restricted head rotation to the left side. However, in distracted situations, full range of motion of the cervical spine was possible without any pain. The behavioral data were complemented by brain activation patterns obtained in the fMRI-scanner when contrasting these 2 tasks (non-distracted head rotations versus distracted head rotations): While AO+MI of the non-distracted movement revealed extended activity in S1, TH, In, ACC, PFC, M1, cerebellum, and SMA, such activity was absent in the case where the same head rotation to the left was observed in a different, distracted context (throwing task). The selective activation of the pain matrix and the selective perception of pain indicate maladaptive pain behavior in our patient as the control volunteer did not show such differential activation patterns. Further, the potential protective nature of pain can be refuted in this case, because within the distracted task, less activation of areas responsible for pain expectation was found. The analgesic effect of distraction is widely recognized (18). However, to our knowledge it has never been shown before that distraction may serve to deactivate the pain matrix, so that movements that are usually associated with pain can suddenly be performed without discomfort.

Looking in detail at the non-distracted and distracted head rotation, one may argue that although the head rotations were comparable, the 2 motor tasks clearly differ. The throwing task was undoubtedly the more demanding task, and it is well established that increases in task difficulty enhance activity in motor centers (13,19). Thus, we would have expected to see greater activity in the distracted head

rotation task than the non-distracted task, at least in motor centers. This imbalance in motor-related brain areas may also be responsible – at least in part – for the impaired ability of neck pain patients to relocate their head in predefined locations (20). However, even more importantly, the current results show that activation of pain memories depend on the context. Therefore, we can conclude for this case that distracting the attention away from the pain-provoking movement prevents the perception of pain, enhances physical performance, and leads to entirely different brain activity, i.e., no activation of pain-related areas. It may therefore be argued that a certain level of attention has to be dedicated to the affected neck in order to activate the pain matrix. This may be a crucial point for the therapy of maladaptive pain memory/behavior. For neck pain patients, it was recently demonstrated that a balance training intervention proved to be efficient with regard to reducing pain and improving sensorimotor function of the cervical spine (21). It may be speculated that during balancing, head movements are executed but attention is primarily allocated to keep and/or restore postural equilibrium. Thus, balance exercises and the throwing task may be characterized as motor tasks involving the cervical spine without paying attention to the cervical motion itself. Instead, the focus is set on higher demands such as postural control or catching a ball probably preventing the activation of the pain matrix.

Relevance of the Present Findings

Although the current results display only the situation of one single patient with chronic, one sided neck pain so that the results cannot be generalized, they may nevertheless be important not only to improve the understanding of the neural organization of maladaptive pain behavior but also to reconsider clinical evaluation and treatment strategies. From a clinical point of view, examination of chronic neck pain patients must clarify, whether symptoms and movement behaviors serve to protect tissue or whether they display maladaptive pain associated movement behavior, related to the expectation of pain. For this purpose, it is important to keep in mind the differentiation of distracted versus non-distracted test-situation that we have provided by the ball throwing task (distracted) and the conscious head rotation task (non-distracted). Closely related to that, our results suggest that treatment strategies have to take into account and exploit the context in which the movement is performed.

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