

Fibromyalgia patients show an abnormal dopamine response to pain

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Abstract

Fibromyalgia is characterized by chronic widespread pain and bodily tenderness and is often accompanied by affective disturbances. Accumulating evidence indicates that fibromyalgia may involve a dysfunction of modulatory systems in the brain. While brain dopamine is best known for its role in pleasure, motivation and motor control, recent evidence suggests that it is also involved in pain modulation. Because dopamine is implicated in both pain modulation and affective processing, we hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission. Fibromyalgia patients and matched healthy control subjects were subjected to deep muscle pain produced by injection of hypertonic saline into the anterior tibialis muscle. In order to determine the endogenous release of dopamine in response to painful stimulation, we used positron emission tomography to examine binding of [¹¹C]-raclopride (D2/D3 ligand) in the brain during injection of painful hypertonic saline and nonpainful normal saline. Fibromyalgia patients experienced the hypertonic saline as more painful than healthy control subjects. Control subjects released dopamine in the basal ganglia during the painful stimulation, whereas fibromyalgia patients did not. In control subjects, the amount of dopamine release correlated with the amount of perceived pain but in fibromyalgia patients no such correlation was observed. These findings provide the first direct evidence that fibromyalgia patients have an abnormal dopamine response to pain. The disrupted dopaminergic reactivity in fibromyalgia patients could be a critical factor underlying the widespread pain and discomfort in fibromyalgia and suggests that the therapeutic effects of dopaminergic treatments for this intractable disorder should be explored.

Introduction

Although brain dopamine is best known for its role in pleasure, motivation and motor control, evidence is accumulating to suggest that dopamine in the basal ganglia may also be important for pain modulation. Results of animal studies using electrical stimulation of dopaminergic structures, such as the striatum, nucleus accumbens and ventral tegmental area, or administration of compounds leading to increased synaptic levels of dopamine (e.g. dopamine reuptake inhibitors), indicate that increased dopaminergic activity can attenuate nociceptive behaviour in animals (Chudler & Dong, 1995; Altier & Stewart, 1999; Magnusson & Fisher, 2000). Conversely, lowering endogenous dopamine release either by local anaesthetic microinjections into dopaminergic structures or selective neurotoxic lesions of dopaminergic neurons leads to hyperalgesia in animals (Saade *et al.*, 1997; Magnusson & Martin, 2002). Furthermore, animal data show that tonic noxious stimuli can lead to increased release of dopamine in the striatum (Gao *et al.*, 2001). These converging lines of evidence suggest an adaptive role for dopamine in the basal ganglia, whereby it can be released in response to noxious stimulation and lead to

endogenous antinociception. In accord with this, several positron emission tomography (PET) brain imaging studies in humans have documented that increased pain sensitivity is associated with an increased binding potential (BP) in the striatum of the exogenous radiolabelled ligand for the unoccupied D2/D3 receptors (Hagelberg *et al.*, 2002; Pertovaara *et al.*, 2004; Martikainen *et al.*, 2005; Scott *et al.*, 2006), which might reflect a reduction in tonic dopamine release, increases in receptor density or changes in receptor affinity. Some chronic pain patients show a reduced activity of the enzyme aromatic amino acid decarboxylase (Hagelberg *et al.*, 2003a,b; Wood *et al.*, 2007), indicating that alterations in the dopamine metabolism might indeed be related to clinical pain. Endogenous dopamine might respond dynamically to pain stress as suggested by a recent study showing that healthy individuals release dopamine in the basal ganglia in response to sustained experimental pain (Scott *et al.*, 2006). To date, no study has investigated the release of dopamine in response to a pain challenge in chronic pain patients.

Fibromyalgia is characterized by chronic widespread pain and bodily tenderness. The disorder, which occurs mainly in middle-aged women, is often associated with a variety of other symptoms including chronic fatigue, morning stiffness and affective disturbances. There is an increasing body of evidence to suggest that fibromyalgia may be related to dysfunctions of central inhibitory mechanisms (Clauw & Crofford, 2003). In particular, adaptation to

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pain appears deficient in fibromyalgia patients, suggesting impairment of endogenous inhibitory mechanisms (Lautenbacher & Rollman, 1997). As dopamine seems likely to play a role in endogenous pain modulation as outlined above, we hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission. Indeed, a recent preliminary study suggested that the activity of the enzyme dopa decarboxylase is decreased in fibromyalgia (Wood *et al.*, 2007). With the present study, we investigated the release of dopamine in the basal ganglia in response to experimental muscle pain in female fibromyalgia patients and in age-matched healthy females. Endogenous dopamine release has been shown to decrease [¹¹C]-raclopride binding to brain dopamine D₂/D₃ receptors (Laruelle, 2000). Thus, we hypothesized that painful stimulation would lead to a decrease in [¹¹C]-raclopride BP in healthy subjects, caused by the release of endogenous brain dopamine, and that this response would be disrupted in fibromyalgia patients.

Materials and methods

Participants

Eleven female patients with fibromyalgia and 11 female healthy control subjects took part in the study. The two groups did not differ significantly with respect to age (healthy controls, 44.5 ± 9.3 ; fibromyalgia patients, 51.1 ± 10.5 years; $P = 0.13$). Exclusion criteria for both groups included smoking, use of recreational drugs, alcohol consumption of more than 3 units/week, pregnancy, and major medical, neurological or current psychiatric condition, including depression (DSM IV criteria). Patients could not be taking antidepressants or anticonvulsants and met the American College of Rheumatology criteria for fibromyalgia (Wolfe *et al.*, 1990), including at least 11 of 18 positive tender points. No healthy control subject met the criteria for fibromyalgia or had any other source of chronic pain. The protocol of the study was approved by McGill University Institutional Review Board. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

Stimulation paradigm

A fine needle (25-gauge) was inserted into the anterior tibialis muscle of the right leg and connected via tubing to an automated programmable infusion pump (Curlin Medical LLC, Huntington Beach, CA, USA). Subjects were told that they would receive two intramuscular infusions of saline solution, one that might be painful and one that might not be painful, and that the order of these two infusions was randomized across subjects. In fact, all subjects received the nonpainful normotonic (NT; 0.9% saline) infusion first, followed by the hypertonic (HT; 5.5% saline) infusion. This was done to minimize the risk of drop-outs while keeping the influence of expectation low.

Each infusion lasted for 20 min and consisted of a bolus of 30 mL/h in minute 1, 10.5 mL/h for minutes 2–6, a second bolus of 30 mL/h in minute 7 and 10.5 mL/h for minutes 8–20.

Psychophysical testing session

On a separate day prior to the imaging sessions, participants underwent a psychophysical session in order to familiarize them with the experimental paradigm and assess individual pain responses to the intramuscular infusions. At the beginning of the session, tender-point examination was performed in all subjects by an experienced

physician (P.W.). Tender-point examination assesses the presence of excess tenderness to manual palpation of 18 predefined muscle-tendon sites, which are scored from 0 to 4 (0, 'no pain'; 4, 'unbearable pain'). This yields a tender-point count (11 or more tender points are a diagnostic criterion for fibromyalgia) and the tender-point index. The tender point index is the sum of the pain scores of all examination sites.

Subjects then received the NT and the HT saline infusions at an interval of 30 min, according to the stimulation paradigm described above. Participants rated the pain intensity of the infusions continuously using a computerized visual analogue scale (COVAS; Medoc, Haifa, Israel) with two anchors ('no pain sensation at all' and 'the most intense pain tolerable'). In addition, subjects were asked after each infusion to verbally rate the maximum pain intensity and maximum unpleasantness using a numerical rating scale from 0 to 200 (0, 'no sensation at all'; 100, 'pain threshold'; 200, 'the most intense pain tolerable'; and -100, 'extremely unpleasant'; 0, 'neutral'; 100, 'extremely pleasant').

PET imaging sessions

Participants underwent two PET scans on separate days, during which they received either NT or HT saline infusion, respectively. As during the psychophysical session, the stimulus sequence was single-blind and all subjects underwent the NT session first, and scripted instructions were given to minimize patient expectations regarding the nature of each stimulus. Dynamic PET scans were obtained with a CTI/Siemens ECAT HR+ tomograph, operated in three-dimensional mode, yielding an image resolution of 4.2 mm full-width at half maximum (FWHM).

Following positioning in the scanner, a needle was inserted into an antecubital vein for the injection of [¹¹C]-raclopride, and a 25-gauge needle was placed in the right anterior tibialis muscle. After a 10-min transmission scan using a ⁶⁸Ge source, the respective infusion (NT or HT) was started according to the same protocol as in the psychophysical session. Ten minutes after the start of the intramuscular infusion, 10 mCi of [¹¹C]-raclopride in 10 mL of saline was injected over 120 s and dynamic acquisition of emissions scans was started. Twenty-six emission scan frames of increasing length were collected over a total duration of 60 min. At the end of the scan, subjects were asked to verbally rate the maximum pain intensity and unpleasantness using the numerical rating scale described above.

Magnetic resonance imaging

Each subject received a high-resolution T1-weighted magnetic resonance scan (3-D fast-field echo scans with 160 slices, 1 mm isotropic resolution, TR = 18 ms, TE = 10 ms, flip angle = 30°) for coregistration with PET images.

Analysis of behavioural data

The total COVAS ratings of the psychophysical session were integrated over time to produce an area under the curve (AUC) for pain ratings throughout the 20-min infusion period. The AUC scores and the pain and sensation ratings yielded by the poststimulation numeric rating scales were compared between the HT and the NT condition for each group separately using paired Student's *t*-tests (two-sided, $P < 0.05$). Unpaired *t*-tests (two-sided, $P < 0.05$) were used to compare ratings between fibromyalgia patients and healthy controls for the NT and for the HT condition.

Analysis of PET data

All emission scans were reconstructed using a 6-mm FWHM Hanning filter, producing an estimated final FWHM of 10–12 mm. PET frames were summed and coregistered with the corresponding magnetic resonance image (Woods *et al.*, 1993), and both images were transformed linearly into standardized stereotaxic space using the Montreal Neurological Institute template (Collins *et al.*, 1994). All transformed images were visually inspected to ensure that there were no alignment errors. Subsequently, all PET images were checked and corrected for motion (Perruchot *et al.*, 2004). Parametric BP maps were generated by calculating $[^{11}\text{C}]\text{raclopride BP}$ at each voxel ($\text{BP} = B_{\text{avail}}/K_D$, where B_{avail} is the density of available receptors and K_D is the dissociation constant), using a simplified reference tissue compartment model with cerebellar activity as the reference (Lammertsma & Hume, 1996; Gunn *et al.*, 1997). Voxel-wise statistical analysis followed techniques described by Aston and colleagues (Aston *et al.*, 2000) that allow for the incorporation of the dynamic information (separate time frames) in parameter estimates, and thus provide substantially more degrees of freedom than can be achieved when considering only final BP values for statistical testing. Using a search volume for the basal ganglia of 28 640 mm³, the threshold for statistical inference was set to $t = 3.8$ (corresponding to $P = 0.05$ corrected for multiple comparisons across the search volume; Worsley *et al.*, 2002). One statistical group map was calculated for each group to compare the BPs between the NT and HT conditions.

Region-of-interest (RoI) analysis

In order to incorporate psychophysical measures into the analysis, RoI analysis was performed in addition to voxel-wise analysis. We used six functional subdivisions of the basal ganglia as RoIs, as previously described (Mawlawi *et al.*, 2001; Martinez *et al.*, 2003), i.e. limbic striatum, associative striatum and sensorimotor striatum in the left and right hemispheres. To increase sensitivity, we only included voxels that showed a pain-related change in BP in the group statistical maps of HT vs. NT saline for either group using lenient thresholds ($t = 2.76$, i.e. $P < 0.01$ for one-sided tests). For each RoI, the mean BP was calculated. In addition, the percentage difference between conditions was calculated for each RoI [$(100 \times \text{NT saline}/\text{HT saline}) - 100$]. The differences in psychophysical ratings between NT and HT saline (AUC) were correlated with the percentage change in BP using linear regression analysis (Pearson's product moment correlation coefficient, two-sided test, $P < 0.05$). In addition, the BP during the NT condition was compared between groups (two-sided unpaired t -test, $P < 0.05$).

Previous reports have consistently found a relationship between raclopride BP at baseline and pain sensitivity in healthy volunteers in the right putamen (Hagelberg *et al.*, 2004; Scott *et al.*, 2006). We therefore delineated the right putamen as an additional RoI. Correlation analysis between BP in the right putamen in the NT condition and perceived pain intensity of the HT stimulation (AUC) was performed for the two groups separately. In the patient group, it was also tested whether the baseline BP in the putamen correlated with the tender-point index as a measure of their clinical pain (two-sided tests, $P < 0.05$).

Results

Sensations evoked by saline injections

Infusion of HT saline reliably provoked pain throughout the 20-min infusion period in both fibromyalgia patients and healthy controls.

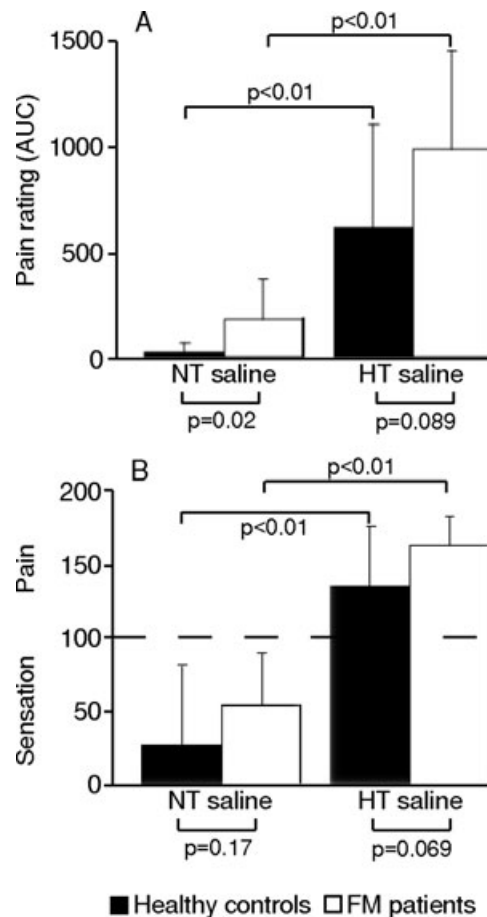


FIG. 1. Ratings of NT and HT saline infusion in fibromyalgia patients and controls. (A) AUC of continuous pain ratings in the psychophysical session. Infusion of NT saline was associated with significantly more intense sensations for fibromyalgia patients than for control subjects. Hypertonic saline infusion was associated with nonsignificantly more pain for the patients. (B) Post-infusion ratings in the PET session. HT saline infusion was significantly more painful than NT saline infusion for both groups. Normotonic saline infusion did not elicit frankly painful sensations in either group. Error bars represent SD.

Fibromyalgia patients rated the same physical stimulus as being nonsignificantly more painful than the control subjects (Fig. 1). Using the COVAS scale in the psychophysical session, both groups reported some sensation on the pain rating scale during the NT saline infusion, with fibromyalgia patients providing significantly higher ratings than controls (Fig. 1A). When subjects were given the possibility to differentiate pain from nonpainful sensations, neither group judged the NT infusion to be frankly painful (Fig. 1B). However, on the pleasantness/unpleasantness scale, fibromyalgia patients reported the NT infusion to be more unpleasant than did healthy subjects (mean \pm SD: patients, -29.6 ± 22.7 ; controls, -7.3 ± 14.2 ; $P = 0.012$).

PET $[^{11}\text{C}]\text{raclopride BP}$ in response to HT saline infusion

As predicted, healthy controls showed a reduction in raclopride BP within multiple areas of the basal ganglia in response to HT saline compared to NT saline, interpreted as a pain-evoked increase in dopamine release. Table 1 and Fig. 2 show regions in which the voxel-based statistical map revealed a significant reduction in BP during HT compared to NT saline infusion in healthy control subjects. Significant

TABLE 1 Regions of significant reduction in [¹¹C]-raclopride BP during HT compared to NT saline infusion in healthy controls

Region	Side	MNI co-ordinates			<i>t</i> -value	Corrected <i>P</i> -value	Cluster size (mm ³)	BP change (%)
		<i>x</i>	<i>y</i>	<i>z</i>				
Globus Pallidus	Left	-16	8	-2	5.12	< 0.001	248	-10.5 ± 8.1
Putamen	Left	-22	-2	10	4.50	< 0.001	288	-8.6 ± 11.6
Putamen	Right	30	0	10	5.01	< 0.001	864	-9.4 ± 14.9
Caudate Nucleus	Left	-12	4	20	4.93	< 0.001	656	-13.8 ± 11.2
Caudate Nucleus	Right	12	14	8	4.77	< 0.001	224	-9.3 ± 15.1

Mean values of BP change are ±SD. Significant decreases in [¹¹C]-raclopride BP (indicative of increased dopamine transmission) in the control group in the HT condition compared to the NT condition, based on the voxel-wise analysis. No significant decreases were observed for the fibromyalgia patients. The percentage change corresponds to the BP change at the peak co-ordinate of the cluster.

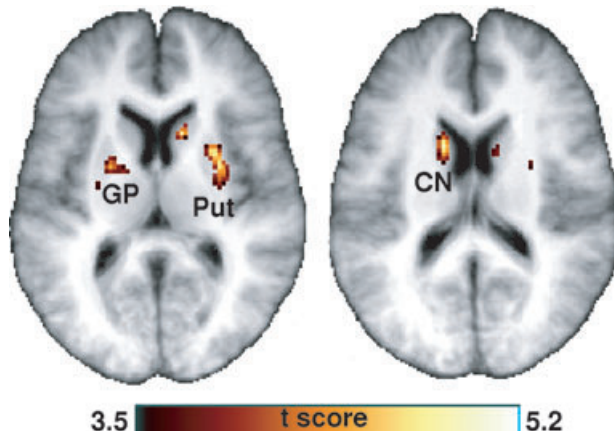


FIG. 2. Voxel-based statistical maps showing regions of significant reduction in BP during HT compared to NT saline infusion in healthy controls. No region showed a significant reduction in BP in the fibromyalgia patient group. GP, globus pallidus; Put, putamen; CN, caudate nucleus. The *t*-threshold was set to 3.5 for display purposes. Left side of brain is displayed on left.

differences were found in the globus pallidus, putamen and caudate nucleus. In contrast, no region in the basal ganglia showed a reduction in BP during HT saline in the fibromyalgia group.

Relationship between dopamine release and perceived pain intensity

Correlation analysis demonstrated that in healthy controls the magnitude of dopamine release (reflected by the percentage difference in BPs during NT and HT saline injections) and perceptual ratings of pain (equally the difference between the two conditions) were significantly correlated in three of the functional subregions and in the whole striatum (Fig. 3). Conversely, no significant correlations were demonstrated in patients with fibromyalgia (Fig. 3). Figure 3 also reveals that the change in BP in patients was more variable than in healthy controls. Some patients even showed an increase in BP in the HT condition.

Baseline raclopride BP

In order to further investigate the lack of dopamine release in response to pain in the fibromyalgia patients, we compared the BP during nonpainful saline infusion between the two groups. Fibromyalgia patients showed a lower raclopride BP than healthy controls in all functional subregions of the striatum (Fig. 4),

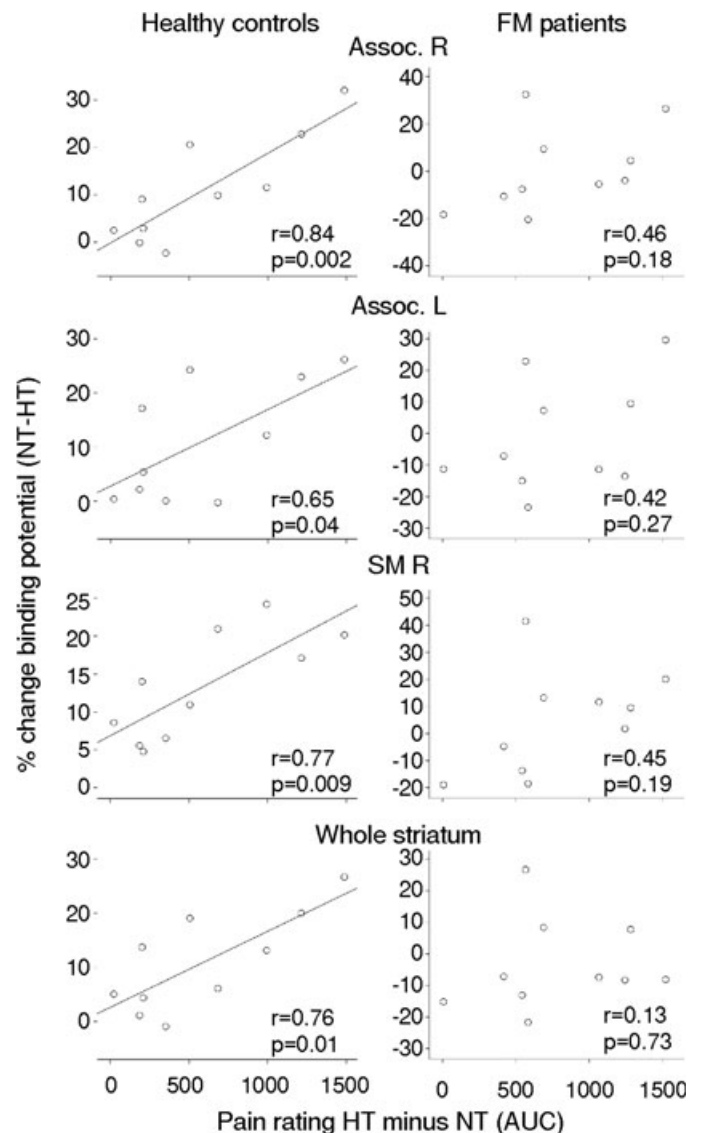


FIG. 3. The change in BP between the experimental conditions (NT – HT) was significantly correlated with the difference in the perceptual ratings between the HT and the NT condition in the control group. This relationship was absent in the patient group. Assoc, associative striatum; SM, sensorimotor striatum; L, left; R, right.

suggesting for example decreased dopamine receptor density or a greater release of dopamine in the NT condition in fibromyalgia patients.

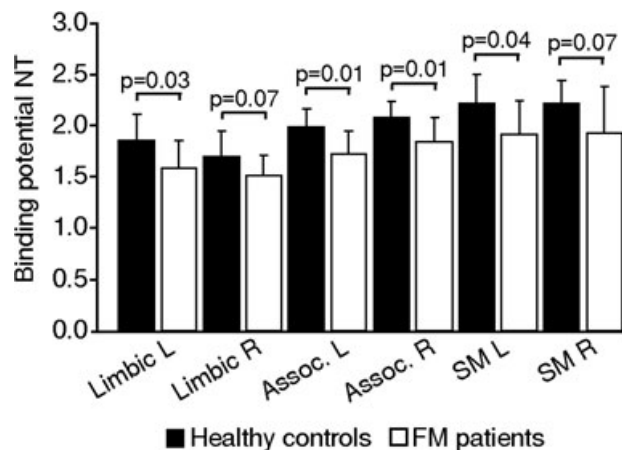


FIG. 4. Fibromyalgia patients displayed lower BP than healthy controls in all functional subregions of the striatum. NT, normotonic condition. Limbic, limbic striatum; Assoc, associative striatum; SM, sensorimotor striatum; L, left; R, right.

Baseline raclopride BP and pain sensitivity

Several previous studies have reported a positive relationship between pain sensitivity and baseline raclopride BP specifically for the right putamen in healthy volunteers (Hagelberg *et al.*, 2002; Pertovaara *et al.*, 2004; Martikainen *et al.*, 2005; Scott *et al.*, 2006). We investigated whether we would find a similar relationship in the right putamen in our sample and, in addition, whether this relationship would also be present in patients with fibromyalgia. Consistent with the previous studies, the healthy controls in our study displayed a significant correlation between the baseline BP and the perceived pain intensity of HT saline injection (Fig. 5). Despite the disruptions in dopamine reactivity in the fibromyalgia patients, they showed the same relationship between baseline receptor availability and pain sensitivity in the right putamen (Fig. 5). In addition, baseline BP in the right putamen in the fibromyalgia patients was positively correlated with a measure of their clinical pain, i.e. tender-point index ($r = 0.73$, $P = 0.01$).

Discussion

This study shows that healthy middle-aged women release dopamine in the basal ganglia in response to a tonic painful stimulus, thus supporting and extending recent findings in young healthy adult subjects (predominantly males; Scott *et al.*, 2006). We also observed a positive relationship between the amount of dopamine released in response to pain and the subjects' perceived pain intensity throughout the striatum, consistent with the results of Scott *et al.* (2006), who showed such a relationship in the caudate nucleus. Furthermore, we observed a positive relationship between the amount of pain caused by HT saline infusion and the baseline BP in the right putamen, which is equally in accordance with the findings of Scott *et al.* (2006), as well as of studies in which baseline BP was compared to pain ratings obtained in separate psychophysical sessions (Hagelberg *et al.*, 2002; Pertovaara *et al.*, 2004; Martikainen *et al.*, 2005). Thus, our observations in the healthy subjects strongly support the emerging idea on the adaptive role of striatal dopamine that can be released in response to noxious stimuli and determine individual sensitivity to pain.

Our study also provides evidence that fibromyalgia patients exhibit an abnormal dopamine response to painful stimulation. In contrast to the healthy subjects, for the patient group there was no difference in

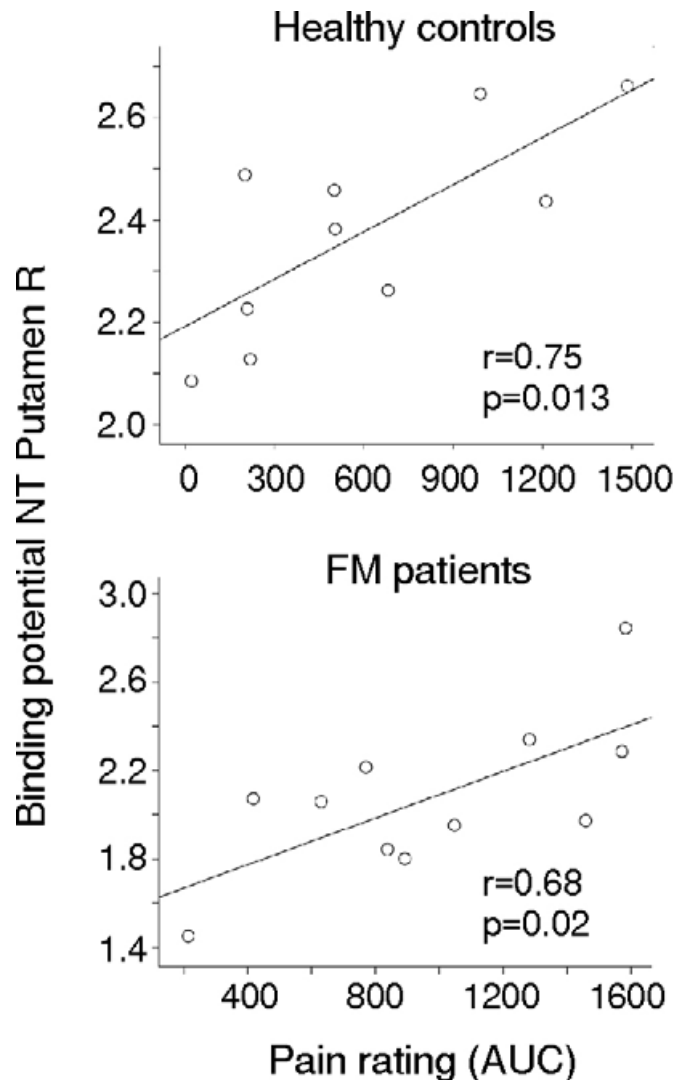


FIG. 5. The D2 BP in the NT condition was positively correlated with the amount of pain subjects experienced in response to HT saline infusion in both groups. AUC, area under the curve of the continuous pain ratings acquired in the psychophysical session.

dopamine release between the painful HT saline condition and the nonpainful NT condition. Further, an examination of individual subject data using RoI analysis revealed that the patients showed a heterogeneous behaviour: while some did indeed release dopamine in response to painful stimulation, others showed the opposite effect, i.e. increased D2 BPs in the HT pain condition compared to the NT condition (see Fig. 3). In addition, the positive correlation between the amount of released dopamine in the associative and sensorimotor striatum and the pain experienced, observed in healthy control subjects, was disrupted in all functional regions of the striatum in the patient group (Fig. 3). The relationship that was not disrupted in the fibromyalgia patients was the positive correlation between the amount of pain caused by HT saline infusion and the baseline BP in the right putamen (Fig. 5). Interestingly, the baseline BP in the right putamen of fibromyalgia patients was also related to their amount of clinical pain, as indicated by the tender-point index. These findings suggest the possibility that the right putamen is important for pain suppression, such that subjects with higher baseline D2 BPs in this region have a lower level of tonic pain suppression, leading to high pain sensitivity for both experimental pain and clinical pain.

Two PET studies have examined the relationship between baseline raclopride BP and chronic orofacial pain (burning mouth syndrome and atypical facial pain; Hagelberg *et al.*, 2003a,b) and found that the chronic orofacial pain patients have a higher raclopride BP than matched controls, suggesting a lower dopaminergic tone contributing to chronic pain susceptibility. These findings contrast with our observation that fibromyalgia patients have a lower raclopride BP during the NT saline condition than do healthy controls. These observations may reflect an underlying difference in dopaminergic systems between fibromyalgia patients and those with chronic orofacial pain. Indeed, the deficiency of endogenous pain inhibitory mechanisms known to exist in fibromyalgia (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997) has not been described in burning mouth syndrome and atypical facial pain. Differences in raclopride BP may reflect different receptor density or baseline dopamine levels, or a combination of the two. Hence, lower baseline BP in fibromyalgia patients could be related to abnormalities of the dopaminergic system such as lowered receptor density or increased baseline dopaminergic tone.

An alternative explanation could relate to differences in the experimental paradigms. In our study, we chose to use as a 'baseline' an infusion of NT saline, in order control for nonspecific effects of the experimental situation (other than the pain caused by the HT saline infusion). In contrast, the studies of orofacial pain patients used a simple rest condition as 'baseline.' Because in our study the fibromyalgia patients found the NT saline condition to be unpleasant (although not painful), they may have released dopamine in response to that stimulus, as dopamine activity is considered to be involved in salient and arousing events (Horvitz, 2000).

Could the possible dopamine release in response to NT saline be the sole explanation for the disrupted dopamine response to HT saline? If dopamine is released during the NT saline condition, could further release in response to the frankly painful HT saline condition be too small to be detected? Although this is a possibility, evidence suggests that it is unlikely to be the unique explanation. The HT saline condition was significantly more painful than the NT condition, and the difference in perceptual ratings between the two conditions was at least as large for the fibromyalgia patients as for the healthy controls (see Fig. 1). Despite the large difference in perceptual ratings between the conditions, many fibromyalgia patients actually had lower raclopride BP during the NT saline condition than during the HT condition (see Fig. 3). In addition there was more variability in dopamine release for fibromyalgia patients than for healthy controls, with some patients showing increased raclopride BP during HT saline and others showing decreased BP. Given the range of the observed changes in raclopride BP, there is no reason to expect a ceiling effect in dopamine release, as pharmacological and nonpharmacological manipulations have produced larger effects (Pruessner *et al.*, 2000; Leyton *et al.*, 2002). Thus, our findings strongly suggest a disruption of normal dopamine release in response to pain for fibromyalgia patients. Nevertheless, additional studies are needed to clarify whether fibromyalgia patients have a similar or different disruption of striatal dopamine function at rest as observed in chronic orofacial pain patients.

The current study provides evidence for dysfunctional dopamine release in response to painful stimuli in fibromyalgia. Together with animal studies suggesting that the D2 receptor in particular is important for analgesia (Magnusson & Fisher, 2000), this implies that the abnormal pain processing in fibromyalgia patients could be explained by a reduction in postsynaptic dopamine D2 receptor activation by endogenous dopamine. Although further work is needed to fully understand dopaminergic neurotransmission in fibromyalgia,

our findings indicate that the cerebral dopamine system represents an important and physiologically relevant target for the treatment of fibromyalgia.

Conclusions

Our results demonstrate that the release of endogenous dopamine in response to tonic experimental pain in the basal ganglia is disrupted in fibromyalgia patients. In addition, fibromyalgia patients might show an abnormal release of dopamine in response to nonpainful stimulation. Dysfunction of dopaminergic neurotransmission may explain the primary clinical symptoms of fibromyalgia, i.e. chronic widespread pain and bodily tenderness. It remains to be determined whether other fibromyalgia symptoms stem from the same abnormality. Finally, our findings indicate that dopaminergic neurotransmission represents an important and physiologically relevant target for the treatment of fibromyalgia, although details regarding the pathophysiology of dopaminergic transmission in the disease remain to be clarified.

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Abbreviations

AUC, area under the curve; BP, binding potential; COVAS, computerized visual analogue scale; HT, hypertonic; NT, normotonic; PET, positron emission tomography; RoI, region of interest.

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