

1 **Title: Relation of Dopamine Receptor 2 Binding to Pain Perception in Female**
2 **Fibromyalgia Patients with and without Depression – an [¹¹C] raclopride PET-study**

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36 **Abstract**

37 Dopamine D2/D3 receptor availability at rest and its association with individual pain perception was
38 investigated using the [¹¹C] raclopride PET-method in 24 female Fibromyalgia (FMS) participants
39 with (FMS+, N=11) and without (FMS-, N=13) comorbid depression and in 17 healthy women.
40 Thermal pain thresholds (TPT) and pain responses were assessed outside the scanner. We compared
41 the discriminative capacity, i.e. the individual's capacity to discriminate between lower and higher
42 pain intensities and the response criterion, i.e. the subject's tendency to report pain during noxious
43 stimulation due to psychological factors. [¹¹C] raclopride binding potential (BP), defined as the ratio of
44 specifically bound to non-displaceable radioligand at equilibrium (BP_{ND}) was used as measure of
45 D2/D3 receptor availability. We found significant group effects of BP_{ND} in striatal regions (left ventral
46 striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS- compared to
47 healthy subjects. Correlational analysis showed negative associations between TPT and D2/D3
48 receptor availability in the left caudate nucleus in FMS-, between TPT and D2/D3 receptor availability
49 in the right caudate nucleus in FMS + and positive associations between TPT and D2/D3 receptor
50 availability in the left putamen and right caudate nucleus in healthy controls. The response criterion
51 was positively associated with D2/D3 receptor availability in the right nucleus accumbens in FMS –
52 and negatively with D2/D3 receptor availability in the left caudate nucleus in healthy controls. Finally,
53 no significant associations between D2/D3 receptor availability and discriminative capacity in any of
54 the groups or regions was determined. These findings provide further support for a disruption of
55 dopaminergic neurotransmission in FMS and implicate DA as important neurochemical moderator of
56 differences in pain perception in FMS patients with and without co-morbid depression.

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58 Number of words = 283

59

60 **Introduction**

61 Fibromyalgia syndrome (FMS) is an idiopathic, diffuse soft-tissue pain syndrome with unclear
62 pathophysiology (Wolfe, 1990). Major depressive disorder (MDD) is the most frequent psychiatric
63 comorbidity in FMS (Fietta, Fietta, & Manganelli, 2007). A growing awareness of the role of
64 mesolimbic dopamine (DA) in pain perception, specifically in anti-nociception, has emerged in recent
65 years (Hagelberg et al., 2004; Jarcho, Mayer, Jiang, Feier, & London, 2012; Wood, 2008). Although
66 its precise function in nociceptive processes is only partially understood, DA regulation has been
67 shown to be disrupted in MDD and chronic pain (Epstein et al., 2006; Wood, 2008). Several Positron
68 Emission Tomography (PET)- studies demonstrated altered post-synaptic striatal DA
69 neurotransmission in chronic neuropathic pain syndromes including burning mouth, and atypical facial
70 pain, (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003; Wood,
71 Schweinhardt, et al., 2007) while an alteration of presynaptic DA transmission was evidenced in FMS
72 (Wood, Patterson, et al., 2007). Results of *in vivo* DA studies in MDD brought contradictory results
73 (recently reviewed by (Savitz & Drevets, 2013)). When differences were found they indicated a
74 reduced DA function in MDD that was however influenced by medication. However, postsynaptic DA
75 function has not been investigated so far in FMS and the role of depression in the DA changes
76 observed in chronic pain is not clear.

77 Moreover a positive correlation between individual pain sensitivity and striatal baseline raclopride
78 binding was observed in healthy volunteers (Hagelberg et al., 2002; Pertovaara et al., 2004; Scott,
79 Heitzeg, Koeppel, Stohler, & Zubieta, 2006). Pain sensitivity can be determined using the Signal
80 Detection Theory (SDT) that distinguishes two measures: the discriminative capacity, a measure of
81 neurosensory sensitivity, reflecting the subject's ability to discriminate between two stimuli of similar,
82 yet distinct, intensities. A low discriminative capacity is associated with relative insensitivity to
83 noxious stimulation and indicates an attenuation of neural activity in the sensory system (Clark &
84 Mehl, 1971). The response criterion is independent from discriminability and locates the person's
85 overall tendency to report pain; a high value indicates a stoical attitude (Clark & Mehl, 1971). The
86 response criterion and thermal pain threshold (TPT) were shown to be inversely correlated with the
87 D2/D3 Binding Potential (BP) in the right putamen in healthy volunteers, whereas the sensory

88 discriminative capacity was not significantly correlated with the D2/D3 BP in any striatal region
89 (Pertovaara et al., 2004). The association between measures of pain sensitivity with D2/D3 binding
90 has not been yet examined in chronic pain conditions.

91 Here, we investigated the D2/D3 receptor availability at rest between FMS participants with (FMS+)
92 and without (FMS –) comorbid depression compared to healthy controls using the [¹¹C] raclopride
93 PET method to measure postsynaptic striatal D2/D3 receptor availability. We expected FMS patients
94 to show reduced [¹¹C] raclopride binding (measures as the ratio of specifically bound to non-
95 displaceable radioligand at equilibrium (BP_{ND}) in striatal regions compared to healthy controls,
96 reflecting a decreased postsynaptic availability of D2/D3 receptors in these patients as already
97 described at the presynaptic levels (Wood, Patterson, et al., 2007) and in agreement with findings for
98 neuropathic pain conditions (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al.,
99 2003). We expected the reduction to be more pronounced in FMS+ patients than FMS- patients.

100 Additionally, we aimed to test the association between pain sensitivity and striatal D2/D3 receptor
101 availability with regard to the role of comorbid MDD. We expected FMS patients to have decreased
102 thermal pain thresholds (TPT) and thermal pain tolerance (TOL), correlated to altered D2/D3 receptor
103 availability, but for pain responses to show no correlation with BP_{ND} in striatal regions. Together, we
104 believe that such evidence would indicate that the dopaminergic influence on pain sensitivity is
105 impaired in FMS.

106

107 **Experimental procedures**

108 **Subjects**

109 Given the predominance of women in FMS (Wolfe, Ross, Anderson, Russell, & Hebert, 1995) and to
110 reduce the heterogeneity of study samples, we decided to only include women in this study. A total of
111 24 female FMS patients were compared to 17 age- and gender-matched healthy control subjects.

112 Among the FMS patients 11 subjects were diagnosed with comorbid MDD. All FMS+ patients had the
113 onset of MDD subsequent to the FMS diagnosis. A description of clinical and demographic data
114 parameters for the FMS patients is provided in Table 1. FMS patients fulfilling the American College
115 of Rheumatology (ACR) classification criteria for Fibromyalgia (Wolfe et al., 1990) with decreased

116 pressure pain thresholds at a minimum of 11 of 18 specific tender points, located in 9 paired regions of
117 the body, were recruited from the Division of Rheumatology at the University Hospital Zurich. They
118 were recruited through flyers in medical practices, advertisements in newspapers, and advertisements
119 on websites associated with FMS. Controls were recruited through flyers on bulletin boards in public
120 places. Current and/or chronic medical conditions, current and/or lifetime psychiatric diagnoses, acute
121 or chronic pain and medication other than oral contraceptives were exclusion criteria for the controls.
122 All FMS patients had their FMS diagnosis confirmed by an experienced rheumatologist (HS) through
123 clinical examination, including measurements of pain thresholds at tender points using a digital
124 dolorimeter (LD 100 NRS, AC Engineering Basel, Switzerland). FMS subjects had a mean pain
125 duration of 13.46 years (SD=11.98), and a mean number of 16 tender points (SD=3.66). FMS subjects
126 were allowed to continue their SSRI (selective serotonin-reuptake inhibitors), TCA (tricyclic
127 antidepressants) and NSAID (non-steroidal anti-inflammatory drugs) medication during the study. A
128 total number of 12 FMS patients were taking antidepressant medication either for pain or depressive
129 symptoms. The use of opioids, neuroleptics, antiepileptics, and lithium was an exclusion criterion. All
130 subjects were tested for comorbid psychiatric disorders using the SCID (Structured Clinical Interview
131 for DSM-IV (First, 2002)). This instrument was also used to diagnose MDD in the FMS group. The
132 severity of depression was measured with the Beck Depression Inventory (BDI) , German version
133 (Hautzinger, Bailer, Worall, & Keller, 1995), and the Montgomery Åsberg Depression Scale
134 (MADRS) (Montgomery & Asberg, 1979). Anxiety was assessed using the State-Trait Anxiety
135 Inventory (STAI) (Laux, Glanzmann, Schaffner, & Spielberger, 1981). All participants were screened
136 for general MRI and PET exclusion criteria, pregnancy (pregnancy test on the day of scanning), and
137 breast-feeding. They were required to sign an informed consent which explained the procedures of the
138 study prior to information and testing. The study was approved by the Ethical Committee of the
139 Canton Zurich and the Swiss Federal Department of Health in accordance with the current version of
140 the declaration of Helsinki and the Swiss regulatory requirements.

141

142 **PET image acquisition**

143 [¹¹C] raclopride is an established *in vivo* method for estimating the availability of D2/D3 receptors in
144 the brain. The D2/D3 receptor antagonist [¹¹C] raclopride was produced on site according to Good
145 Manufacturing Practice (GMP) guidelines. PET scans were acquired using a PET/CT scanner with an
146 axial field of view of 15.3 cm in 3D mode (Discovery STE, GE Healthcare, Waukesha, WI, USA) at
147 the Department of Nuclear Medicine at the University Hospital Zurich. PET data were reconstructed
148 using filtered back projected segmented attenuation correction, for which a low dose CT scan was
149 acquired.

150 On the day of the PET study, subjects were asked to eat a well-balanced meal before the PET scanning
151 and not to consume too many liquids to ensure personal comfort during the scans. The PET
152 measurement took place in the same time frame (Monday afternoon from 3 pm to 5pm) for all
153 participants. [¹¹C] raclopride was injected as a slow bolus (260+/-20 MBq). Mean specific activity of
154 the tracer at time point of injection was (M=121.75GBq/μmol, SD=43.63). Dynamic scanning was
155 initiated at the time of tracer injection and continued for 60 min (31 frames of 4x15sec, 8x30sec,
156 9x60sec, 2x180sec, 8x300sec, total 60 min duration). Image data from 40-50 minutes were averaged
157 and exported for further processing in the PMOD software (Version 3.2, PMOD Technologies, Zurich,
158 Switzerland).

159

160 **Magnetic resonance imaging**

161 Each subject received a high-resolution T1 weighted magnetic resonance scan (3D fast-field echo
162 scans with 160 slices, 1mm isotropic resolution, TR= 18ms, TE= 10ms, flip angle= 30°) on a Philips
163 Ingenia Scanner for co-registration with PET images. All images were checked for structural
164 abnormalities and lesions by a clinical neuroradiologist.

165

166 **Determination of thermal pain threshold (TPT), pain tolerance threshold (TOL), and pain 167 modulation**

168 Standardized pain testing procedures were conducted by the same investigator on the same day as the
169 PET scanning with each subject in a separate session in a quiet room with constant ambient
170 temperature. Thermal pain threshold (TPT) and thermal pain tolerance (TOL) were determined using a

171 method of limits procedure (Hansen, Hopf, & Treede, 1996). Thermal cutaneous pain response was
172 measured by delivering heat stimuli to the thenar of the non-dominant hand with a 27-mm-diameter
173 thermal contact thermode (CHEPS, Medoc Ltd, Ramat Yishai, Israel). The CHEPS thermode has a
174 heating rate of 70°C/s and a cooling rate of 40°C/s. The same heating and cooling rate was applied
175 during the whole procedure. The CHEPS thermode has a subject response device that immediately
176 records the temperature once activated, and resets the thermode to the adaptation temperature in
177 preparation for the next trial. The area of the stimulus surface was 5.7. cm². TPT and TOL estimation
178 was based on five thermal stimuli starting at 32°C and rising linearly at a rate of 1°C/s until it was
179 stopped either by a button press or when the maximum temperature of 52°C was reached. To
180 determine TPT, subjects were asked to press the button on the response device when they experienced
181 pain for the first time. To examine TOL, subjects were asked to push the response button when the
182 sensation on their hand became intolerable or unbearable. The experimental paradigm for the pain
183 modulation was adapted and slightly modified from the study of (Pertovaara et al., 2004). Heat
184 stimulation started at 34.5°C and the temperature was increased linearly at a rate of 3°C/s to one of the
185 six predetermined temperatures (45.8, 46.3, 46.8, 47.3, 47.8, and 48.3°C) for a duration of 4s, after
186 which the stimulus temperature returned to baseline. The interval between successive stimulations was
187 15s. Each stimulus temperature was applied eight times and the order the stimuli were presented was
188 randomized across subjects. After presentation of each stimulus, the subject was asked to rate the
189 sensation evoked by the stimulus using a numerical rating scale ranging from 0 = no pain at all to 10 =
190 strongest pain imaginable. Before the actual testing sessions all subjects went through a brief training
191 session in which they were introduced to the experimental condition. The area of stimulation was
192 slightly varied by moving the thermode either to the left or right side for each trial to prevent
193 sensitization.

194

195 **Determination of the subject's discriminative capacity and response criterion**

196 We chose the same components as (Pertovaara et al., 2004) derived from the Signal Detection Theory
197 (SDT) to determine the individual response characteristics to pain. Discriminative Capacity was
198 computed by the trapezoidal rule as the area below the Receiver Operating Characteristics (ROC)

199 Curve which is generated by cumulating probabilities of hits and false alarms for each response
200 elicited by the stimulus temperatures of 46.8° vs. 47.3° using PASW Statistics 21.0 (SPSS Inc.,
201 Chicago, Ill, USA). The exact description of the calculations of the response criterion is provided in
202 detail elsewhere (Pertovaara et al., 2004). Briefly, the criterion was defined as the rating scale criterion
203 where half the responses (to both stimulus intensities in each pair) are divided into higher response
204 categories and the other half into lower response categories. The response criterion was defined as
205 $C=0.5(Z_{SN}+Z_N)$. Within the calculation, the probability of rating a stimulus of 47.3° as painful (rating
206 categories 6-10 pooled together) was converted to a Z score (Z_{SN}) as described by Gescheider (1997,
207 pp.122-123 and Table A). The probability of rating a stimulus of 46.8° as non-painful (rating
208 categories 1-5 pooled together) was also converted to a Z score (Z_N).

209

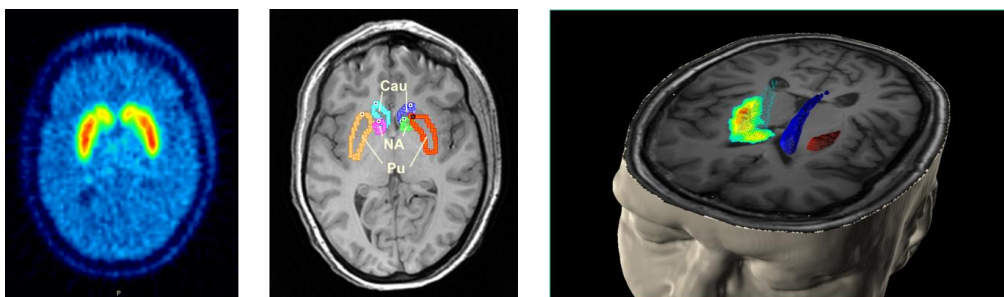
210 **Data analysis**

211 ***ROI analysis***

212 All PET emission scans were reconstructed using 3D filtered back projection including a 6mm FWHM
213 Hanning filter, producing an estimated final FWHM (full width at half maximum) of 10-12mm.
214 Corrections for subject motion during the 60 min PET acquisition were performed with a mutual
215 information registration of each image frame to a standard frame (0-8min after injection) before
216 attenuation correction. Based on the calculated motion, the transmission images were re-sliced and
217 projected for final attenuation correction, reconstruction and realignment. The realigned frames were
218 summed to generate an image that was co-registered with the corresponding MRI image using PMOD
219 software Version 3.2 (PMOD Technologies Ltd, Zurich, Switzerland). This was performed for the first
220 8 minutes of scanning, during which the radiotracer distribution was most sensitive to cerebral blood
221 flow (CBF), and thus for the cortical outlines to be sufficiently evident in order to guide image co-
222 registration. The PET frames were summed and co-registered with the corresponding magnetic
223 resonance image, and both images were transformed linearly into standardized stereotaxic space using
224 the Montreal Neurological Institute template. Mean tissue radioactivity concentrations were extracted
225 using MRI based regions of interest (ROI's), defined on a template MRI image using PMOD software
226 in the anteroventral striatum, putamen, nucleus accumbens, caudate nucleus and cerebellum after

227 Drevets et al. (Drevets et al., 2001). Each individual MRI was registered to the template brain and the
228 ROI's were repositioned as needed to accommodate for individual differences in anatomy. The
229 anatomical accuracy and symmetry of each set of individual ROI's was verified by a neuroscientist
230 familiar with striatal anatomy (CMS). These ROI's were then back-transformed into the subject's
231 native MRI space and applied to the co-registered PET images (example in Figure 1). Simplified
232 reference tissue model (SRTM) (Lammertsma & Hume, 1996) was used for derivation of binding
233 potential (BP) using the cerebellum as reference region. The outcome measure was binding potential,
234 defined as the ratio of specifically bound to non-displaceable radioligand at equilibrium (BP_{ND}). BP_{ND}
235 can also be described as $BP_{ND} = f_{ND} * (B_{max}/K_D)$ where B_{max} is the concentration of D2/3 receptors,
236 K_D is the inverse of the affinity of the radiotracer for the receptor, and f_{ND} is the free fraction in the
237 nonspecific distribution volume of the brain. For each region, the BP_{ND} for patients and controls were
238 compared with those for FMS+ and FMS- patients and controls. Relationships between BP_{ND} and the
239 pain thresholds and measures were analyzed with the Pearson product-moment correlation coefficient.
240 A two-tailed probability value of $p < 0.05$ was chosen as the level of significance. Since age is known
241 to affect D2/D3 receptor BP, this factor was included in the analysis.

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242
243 **Figure 1:** ROI's placement. Transverse view Cau: Nucleus caudatus; NA: Nucleus accumbens; Pu:
244 Putamen

246 *Analysis of behavioral data*

247 PASW Statistics 21.0 software (SPSS Inc., Chicago, Ill, USA) was used for statistical analysis. Data
248 distribution was tested with the Kolmogorov-Smirnov test and by observing data histograms. The
249 results of normally distributed data are presented as mean +/- standard deviations. One way analysis of

250 variance (ANOVA) was used to assess differences in D2/D3 receptor availability between groups
251 (healthy, FMS-, FMS+) for each region of interest. Since age is known to affect D2/D3 receptor BP,
252 this factor was included in the analysis. Additional analyses included FMS duration, antidepressant
253 medication and BDI as factors. The difference between groups for experimental pain ratings (pain
254 threshold, discriminative capacity, and response criterion) of each group was tested using independent
255 samples t-tests and one-way ANOVA followed by post-hoc tests, where appropriate. $P < 0.05$ was
256 considered to represent a statistically significant difference.

257 Associations between D2/D3 receptor availability and psychophysical results (pain threshold,
258 discriminative capacity, response criterion) were determined using Pearson's coefficient of correlation.
259 $P < 0.05$ was considered as statistically significant.

260

261 **Results**

262 **ROI Analyses**

263 Mean BP_{ND} are summarized in Table 2. Analysis of postsynaptic D2/D3 receptor availability,
264 measured by [^{11}C] raclopride, demonstrated a significant group effects between healthy subjects, FMS-
265 and FMS+ patients in the left ventral striatum ($F(2,33)=5.3, p=0.01$), left caudate nucleus ($F(2,33)=$
266 $3.8, p=0.03$), and the left nucleus accumbens ($F(2,33)= 4.1, p=0.03$) after controlling for the effect of
267 age (see Table 3). The covariate age was significantly related to the BP_{ND} in the left ventral striatum
268 ($F(1,33)=19.9, p=0.01$). Simple contrasts revealed significantly less BP_{ND} in the left caudate nucleus
269 and left nucleus accumbens in FMS+ patients compared to healthy controls ($p=0.01$, resp. $p=0.02$) and
270 significantly less BP_{ND} in the left ventral striatum in FMS- than FMS+ patients ($p=0.02$). In additional
271 analyses with the covariates BDI, FMS duration and antidepressant medication no significant
272 correlations were found with BP_{ND} in any striatal regions ($p>0.1$).

273

274 **Experimental pain ratings (TPT, TOL, response criterion, discriminative capacity)**

275 Table 3 represents the mean values of all experimental pain ratings.
276 An independent samples t-test was conducted to compare TPT and TOL between all FMS patients
277 ($n=24$) and healthy controls ($n=17$). FMS patients showed a significantly lower TPT ($m=41.1,$
278 $SD=4.5$) compared to healthy subjects ($m=45.0, SD=4.4; t(39)=2.8, p=0.01$). Also the TOL was
279 significantly lower in FMS patients ($m=44.7, SD=3.7$) compared to healthy subjects ($m=47.7, SD=3.7;$
280 $t(39)=2.5, p=0.02$). One-way ANOVA considering 3 groups of subjects showed significant effects for
281 TPT ($F(2,38)=4.34, p=0.02$) and TOL ($F(2,38)=3.7, p=0.03$). A post-hoc Gabriel test indicated that
282 FMS+ patients reported a significantly lower TPT ($p<0.02$) and TOL ($p<0.03$) than healthy subjects.
283 The FMS- group did not significantly differ from the other two groups. The index of response bias
284 (response criterion) and the discriminative capacity did not differ significantly between the three
285 groups ($F(2,35)=0.61, p>0.94$, resp. $F(2,16)=1.18, p>0.33$ for discriminative capacity). The response
286 criterion was not significantly correlated with TPT (healthy subjects $p>0.6$, FMS- $p>0.07$ and FMS+
287 $p>0.9$) or TOL (healthy subjects $p>0.3$, FMS- $p>0.3$, FMS+ $p>0.09$). Discriminative capacity was not
288 associated with TPT (healthy subjects $p>0.3$, FMS- $p>0.4$, FMS+ $p>0.2$) or TOL (healthy subjects

289 $p>0.4$, FMS- $p>0.7$, FMS+ $p>0.2$) in any of the groups. FMS duration, antidepressant medication or
290 BDI were not significantly correlated to TOL or TPT ($p>0.1$).

291

292 **Correlation of D2/D3 receptor availability with pain responses**

293 *Thermal Pain Threshold (TPT)*

294 In FMS+ patients, striatal D2/D3 receptor availability in the right nucleus caudate was significantly
295 correlated with TPT ($r=0.65$, $p=0.03$) (see Figure 2). In FMS- patients, striatal D2/D3 receptor
296 availability in the left caudate nucleus was significantly correlated with TPT ($r=0.66$, $p=0.02$), (see
297 Figure 3).

298 In healthy subjects, striatal D2/D3 receptor availability in the left putamen ($r=0.56$, $p=0.01$) and right
299 caudate nucleus ($r=0.513$, $p=0.05$) were significantly associated with TPT (see Figure 4).

300

301 *Thermal Pain Tolerance (TOL)*

302 No significant correlations between striatal D2/D3 receptor availability and TOL were found in any of
303 the three groups ($p>0.2$).

304

305 *Response criterion*

306 Healthy subjects showed a significant correlation of the response criterion with the D2/D3 receptor
307 availability in the left caudate nucleus ($r=-0.645$, $p=0.001$) (see Figure 5). FMS- showed a significant
308 correlation of the response criterion with the D2/D3 receptor availability in the right nucleus
309 accumbens ($r=0.67$, $p=0.03$) (see Figure 6). No significant correlations of the response criterion with
310 the D2/D3 receptor availability in any striatal region could be determined for FMS+.

311

312 *Discriminative capacity*

313 The index of the subject's discriminative capacity, the area under the ROC curve, varied over a wide
314 range between the subjects and did not differ significantly between the three groups ($F(1.38)=2.1$,
315 $p=0.15$). Correlations of the discriminative capacity with the D2 receptor availability were not
316 significant ($p>0.17$) in any of the three groups.

317

318 **Discussion**

319 The major innovation of the present study was that it examined the link between striatal D2/D3
320 receptor availability and individual pain perception in FMS patients, both with and without comorbid
321 MDD, compared to healthy subjects using the [¹¹C] raclopride PET method. To our knowledge, this is
322 the first study investigating the link between striatal D2/D3 receptor availability and individual pain
323 responses in FMS that differentiated between individuals with and without depression.

324 In line with our expectations, we found significant group differences in BP_{ND} in striatal regions (left
325 ventral striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS- compared
326 to healthy subjects. Furthermore, the correlational analyses showed different associations between
327 striatal D2 receptor availability and thermal pain thresholds that differentiated between FMS patients
328 with and without depression and healthy controls. We found negative associations of D2/D3 receptor
329 availability in the left caudate nucleus in FMS- and right caudate nucleus in FMS+. In healthy
330 subjects, the thermal pain threshold correlated positively with D2/D3 receptor availability in the left
331 putamen and right caudate nucleus. Further, for the response criterion, we found a positive association
332 with D2/D3 receptor availability in the right nucleus accumbens in FMS- patients and a negative
333 correlation of the response criterion with D2/D3 receptor availability in the left caudate nucleus in
334 healthy controls. Finally, no correlations between D2/D3 receptor availability and discriminative
335 capacity in any of the groups or regions could be determined. Taken together, these findings provide
336 further support for a disruption of dopaminergic neurotransmission in FMS and implicate DA as
337 important neurochemical moderator of differences in pain perception in FMS patients with and
338 without co-morbid depression. Our findings are similar to previous studies which have demonstrated
339 reductions in 6-¹⁸F fluoro-L-DOPA uptake in dopaminergic centers of the midbrain (i.e. ventral
340 tegmental area and substantia nigra) in FMS (Wood, Patterson, et al., 2007), and lower raclopride BP
341 in FMS patients than healthy controls in all functional sub-regions of the striatum during non-painful
342 saline infusion (Wood, Schweinhardt, et al., 2007). However, it is not entirely clear if this result
343 reflects decreased DA receptor density or a greater release of DA in response to non-painful saline
344 infusion and is therefore not directly comparable to our experimental paradigm. No study so far has
345 investigated the baseline DA changes at the post-synaptic level in Fibromyalgia (i.e. in the absence of

346 noxious stimuli). Furthermore, several Positron Emission Tomography (PET) studies evidenced an
347 increased D2 receptor availability in chronic neuropathic pain conditions such as burning mouth
348 syndrome (Hagelberg, Forssell, Rinne, et al., 2003) or atypical facial pain (Hagelberg, Forssell, Aalto,
349 et al., 2003) suggesting a contribution of reduced dopaminergic inhibition to the chronic pain
350 condition. Our results indicating the opposite changes suggest that FMS patients differ from
351 neuropathic pain patients at a neurochemical level. Interestingly, we found significantly less BP_{ND}
352 raclopride binding in FMS patients with depression compared to those without depression in the left
353 ventral striatum, a region that has been shown to be associated with emotional processing of pain
354 (Scott et al., 2006). This suggests that FMS patients with and without depression can also be
355 distinguished on a neurochemical level which might also influence treatment options. FMS patients
356 with comorbid depression showed significantly less [^{11}C] raclopride binding in the left caudate nucleus
357 and nucleus accumbens compared to healthy controls, suggesting more free DA receptors or
358 dysfunctional receptors in these patients.

359 The Sensory Detection Theory analysis showed that Fibromyalgia patients with and without
360 depression did not set a higher criterion for reporting pain and did also not differ in terms of
361 discriminative capacity from our healthy controls. Consistent with previous studies, the thermal pain
362 tolerance and thresholds of the FMS patients in our study differed from healthy controls, further
363 confirming the findings of greater responsiveness to pain in FMS induced by a wide variety of
364 stimulus modalities (Klauenberg et al., 2008). However, we found no difference in terms of thermal
365 pain threshold and tolerance between FMS patients with and without comorbid MDD, which was also
366 described in another study comparing FMS patients with and without comorbid MDD (de Souza,
367 Goffaux, et al., 2009). The results from the correlation analysis between D2/D3 receptor availability
368 and psychophysical results in Fibromyalgia patients with and without depression support a disrupted
369 pain modulatory role of striatal D2 receptors in FMS. Our results suggest a potential link between
370 D2/D3 receptor availability and pain perception due to psychological factors in FMS which differ
371 however between patients with and without comorbid depression. In Fibromyalgia patients without
372 depression, D2/D3 receptor availability in the right nucleus accumbens was positively associated with
373 the criterion to report pain, but not in FMS patients without comorbid depression. Since the response

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374 criterion is a measure for psychological aspects of pain, the pain sensitivity in Fibromyalgia patients
375 without depression appears to be determined mainly by a dopaminergic influence on psychological
376 factors that in turn influence the subject's tendency to report pain rather than by physiological factors.
377 In line with this finding psychological factors have been shown to have an important role in variability
378 of pain ratings between subjects (Clark & Mehl, 1971). On the other hand cognitive and affective
379 variables frequently occurring in FMS such as depression, anxiety or pain-related anxiety (Lachaine,
380 Beauchemin, & Landry, 2010; Rutledge, Mouttapa, & Wood, 2009) were related to increased pain
381 report and responses. Also personality traits associated with FMS (Malin & Littlejohn, 2012) such as
382 detachment, anxiety, and novelty seeking, were related to D2/D3 receptor availability (Breier et al.,
383 1998; Farde, Gustavsson, & Jonsson, 1997; Suhara et al., 2001) and increased pain report (Farde et al.,
384 1997). This matches the assumption that emotional and psychological processes may play a
385 particularly important role in promoting pain in these patients and that affect may contribute to pain in
386 FMS (Staud, Price, Robinson, & Vierck, 2004). In addition, D2 receptor-mediated neurotransmission
387 in the ventral system involving the nucleus accumbens, has been shown to be associated with
388 emotional processing of pain (Scott et al., 2006). Consistent with the possibility that psychological
389 factors contribute to pain in FMS via DA transmission, it has recently been proposed that DA could
390 play a role in modulating the salience of a pain stimulus (Becker et al., 2013), fostering coping
391 responses, rather than having direct anti-nociceptive effects. This mediating role of DA might
392 eventually explain why we found associations between striatal D2/D3 receptor availability in regions
393 associated with emotional modulation of pain and psychophysical measures of emotional/attitudinal
394 aspects of pain in our FMS patients. In Fibromyalgia patients with depression, D2/D3 receptor
395 availability in the right caudate was negatively associated with thermal pain threshold, but not with the
396 response criterion or discriminative capacity. Evidence showing that D2 receptor-mediated
397 neurotransmission in the dorsal caudate and putamen is associated with subjective ratings of sensory
398 and affective qualities of pain (Scott et al., 2006), suggests that D2/D3 receptor availability in the right
399 caudate of Fibromyalgia patients with depression influences non-sensory mechanisms underlying the
400 pain response rather than actual pain sensitivity. These results are in line with a previous fMRI study
401 which suggested that the presence of depression had no effect on the sensory-discriminative

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402 processing of pain stimulation but had a selective effect on brain regions that process the affective-
403 motivational dimension of pain (Giesecke et al., 2005). Furthermore, this result and the fact that FMS
404 patients with depression conveyed a lower pain threshold than the other subject groups, support the
405 idea of a more pronounced deficit in pain inhibition in FMS with comorbid depressive symptoms (de
406 Souza, Potvin, Goffaux, Charest, & Marchand, 2009), suggesting that depression could influence pain
407 perception in FMS via DA. Our findings in Fibromyalgia patients with and without depression are not
408 consistent with previous reports in healthy subjects where the pain threshold and the response criterion
409 were inversely correlated with the D2/D3 BP in the human striatum (right putamen) (Pertovaara et al.,
410 2004). The same study showed that the discriminative capacity is not a critical factor responsible for
411 the association of pain responses with D2/D3 BP in healthy subjects (Pertovaara et al., 2004). This
412 result is in line with our findings both in healthy subjects and Fibromyalgia patients. In accordance
413 with our hypothesis, we found significant positive correlations between the thermal pain threshold and
414 D2/D3 receptor availability in striatal regions including the left putamen, and the right caudate nucleus
415 in healthy subjects. This result however, contradicts previous findings that reported direct correlations
416 between striatal D2/D3 receptors and pain thresholds in the right putamen (Hagelberg et al., 2002;
417 Pertovaara et al., 2004). Lateralization differences in the DA system are well documented and an
418 influence of gender on lateralization of the function of the DA system has previously been shown
419 (Martin-Soelch et al., 2011). The deviation from the previous finding could therefore be explained by
420 the inclusion of women in our study while the other studies included only men (Pertovaara et al.,
421 2004). Furthermore, some pain-related phenomena such as pain threshold have been shown to occur
422 with a laterality bias (Lugo, Isturiz, Lara, Garcia, & Eblen-Zaijuri, 2002). Moreover, associations
423 between the D2 binding capacity and conditioned pain modulation, which reflects the capacity of the
424 brain to inhibit and to modulate incoming pain signals, have been reported in the left putamen
425 (Hagelberg et al., 2002).

426 Several previous PET studies also using [¹¹C] raclopride showed increased D2 receptor availability in
427 chronic neuropathic pain conditions such as burning mouth syndrome (Hagelberg, Forssell, Rinne, et
428 al., 2003) or atypical facial pain (Hagelberg, Forssell, Aalto, et al., 2003). An overlapping
429 pathophysiology between FMS and neuropathic pain has been suggested due to shared clinical

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430 features such as paresthesias, hyperalgesia and allodynia (Maletic & Raison, 2009), but our results
431 indicate that striatal D2/D3 receptor availability in FMS patients with and without depressive
432 symptoms are not impaired in the same way as in chronic neuropathic pain conditions.
433 Abnormal sensory thresholds were also evidenced in neuropathic pain such as burning mouth
434 syndrome or trigeminal non-idiopathic neuropathic pain (de Siqueira, Teixeira, & de Siqueira, 2013).
435 Abnormal sensory findings are considered important features in the classification of neuropathic pain
436 according to the International Association for the study of pain (IASP). Therefore, the observation of
437 abnormal sensory thresholds and the disrupted modulatory role of striatal D2/D3 receptors in pain
438 processing in FMS could be added to other neuronal changes observed in these patients (for instance
439 impaired small fiber function in FMS) (Uceyler et al., 2013), contradicting the opinion that FMS is a
440 pure somatization disorder without demonstrable abnormality.

441
442 Some limitations merit attention. This study did not allow for differentiation between D2/D3 receptor
443 density or intrasynaptic dopamine concentration and the interpretation of underlying neuronal factors
444 should be treated with caution. Prior work indicates that [¹¹C] raclopride values from the bolus method
445 are almost identical to binding values generated by a bolus-infusion method (Carson, 2000), in which
446 DA release can be indirectly measured for the same subjects. Although SPM analysis of PET ligand
447 studies is a viable alternative to ROI analysis, especially for the exploration of changes without a
448 priori region definitions, requirements of the analysis include transformation of the PET data to
449 standard anatomical space, smoothing of the data and quantitative normalization to account for global
450 effects. In a small cohort as in our study, these processes may reduce the sensitivity to subtle changes
451 in raclopride binding. Standardization of the basal ganglia anatomy for SPM analysis is a known
452 challenge (in comparison to cortical anatomy). Therefore, our individual anatomy MR-based VOI
453 analysis may be considered to better account for individual basal ganglia anatomy and improve the
454 sensitivity of our PET measurements. Further, we did not correct for multiple comparisons, and
455 therefore it remains possible that our results would not survive methods for the correction of multiple
456 testing. Another limitation is that we did not include chronic neuropathic pain patients to control for
457 similarities or differences between FMS and neuropathic pain. A further limitation is that the painful

458 stimuli were not adapted to the different pain thresholds of FMS patients and controls thus making the
459 comparison of the evoked processes difficult. Further, we did not control for phases of menstrual cycle
460 in our participants. However, the majority of the participants were postmenopausal (N=19, see Table
461 1). Finally, DA receptor binding results as well as the individual responses to pain may have been
462 biased by the patients' medication, which possibly influenced the testing procedures, including slower
463 reaction times and anti-nociceptive effects of antidepressants (N=12). Nevertheless, we found
464 significant differences between FMS patients and healthy subjects with regard to the estimation of
465 pain thresholds, and a previous study (Klauenberg et al., 2008) found no significant group difference
466 concerning SSRI medication regarding all pain thresholds. It is however possible that the lack of
467 differences in D2/D3 receptor availability may be related to the medication.

468

469 **Conclusion**

470 To our knowledge, this is the first report on the association between D2/D3 receptor availability and
471 pain perception in FMS, distinguishing between FMS patients with and without comorbid depression.
472 Additionally, in comparison to previous studies in this field, our study included a relatively large
473 sample of patients. In conclusion, our data suggest that there are differences in D2/D3 receptor
474 availability at rest between FMS patients with depression and without depression compared to healthy
475 subjects. This study presents novel results suggesting that the association between D2/D3 receptor
476 availability and pain perception differs between healthy subjects and patients with Fibromyalgia.
477 Furthermore, this association also differed between FMS patients with and without depression,
478 suggesting that depression could influence pain perception in FMS. Our results suggest that alterations
479 in the dopaminergic system appear to be linked to pain sensitivity in FMS patients. Striatal D2/D3
480 receptor availability in FMS patients with and without depression is associated with psychological
481 aspects of pain rather than the discriminative capacity of the sensory system mediating pain. However,
482 the exact mechanisms have yet to be elucidated and similarities with chronic neuropathic pain patients
483 with regard to the modulatory function of DA in pain should be further explored. These findings
484 contribute to the understanding of the function of the dopaminergic system in central pain processing
485 in healthy individuals and in patients with FMS.

486

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492 **Declaration of conflicts of interest:**

493 The authors report no conflicts of interest. The authors alone are responsible for the content and
494 writing of the article.

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DOPAMIN RECEPTOR 2 BINDING IN FMS PATIENTS WITH AND WITHOUT DEPRESSION – RELATION TO PAIN PERCEPTION

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