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Altered Dopamine Responses to Monetary Rewards in Female Fibromyalgia Patients with and without Depression: A [^{11}C]Raclopride Bolus-plus-Infusion PET Study

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Dear Editor,

We herein report results of our pilot study using bolus-plus-infusion [^{11}C]raclopride positron emission tomography (PET) scanning to assess endogenous dopamine (DA) release associated with unpredictable monetary rewards in patients with fibromyalgia syndrome (FMS) and healthy controls. The aim of this project was to investigate whether FMS was associated with a dysfunction of the central reward system.

Twenty-four women with FMS, based on the American College of Rheumatology classification criteria for FMS, and 17 age-matched healthy women were included in the study. Eleven of the patients with FMS met the DSM-V criteria for major depressive disorder (MDD) [1] (current and past depressive episode). A slot machine task validated by Martin-Soelch et al. [2], which has been shown to reliably induce equilibrium and task-related changes in raclopride binding, was used to measure endogenous DA release in response to unpredictable rewards. PET examinations were performed on a full ring PET/computerized tomography (CT) scanner with a 15.3-cm axial field of view in 3-dimensional mode (Discovery DSTX, GE Healthcare, Waukesha, WI, USA), at the Department of Nuclear Medicine, University Hospital Zurich, Switzerland. The emission data were corrected for attenuation, scatter, random, and dead time using the corresponding CT (120 kV/80 mA), and reconstructed using filtered back projection. [^{11}C]Raclopride (415 ± 30 MBq) was administered as an initial bolus over 60 s, according to the protocol described by Watabe et al. [3], followed by a maintenance infusion over the remainder of the scanning session (a total of 90 min), using a computer-operated pump (Arcomed, Syramed SP600, Regensdorf, Switzerland). Dynamic emission scanning (41 frames of 0–6,000 s; 100-min scan; framed as 4 × 15, 8 × 30, 9 × 60, 2 × 180, 4 × 300, 6 × 200, and 8 × 300 s) was initiated with injection of the [^{11}C]raclopride bolus. The regional DA D2/3 nondisplaceable binding potential (BP_{ND}) was measured in the resting state, in all participants, 1 week before the reward study.

Each participant underwent MRI on a 3-T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands), in order to acquire a high-resolution T1-weighted magnetic resonance scan (3-D fast-field echo, 160 slices, 1 mm isotropic resolution, repetition time: 18 ms, echo time: 10 ms, flip angle: 30°) for comparison with PET images. All images were checked for structural abnormalities and lesions by a clinical neuroradiologist. PMOD software version 3.2 (PMOD Technologies Ltd., Zurich, Switzerland) was used for PET data analyses. The realigned frames acquired during the first 8 min of scanning were summed to generate an image that corresponded to the relevant MR image, using PMOD software. The transformation matrix was applied to the composite images consisting of (i) the baseline (frames acquired at 40–50 min) and (ii) reward condition (frames acquired at 60–80 min). These images were acquired under equilibrium conditions as participants performed the sensorimotor control and monetary reward task, similarly to the protocol used by Martin-Soelch et al. [2]. Mean tissue radioactivity concentrations from the baseline and reward images were extracted using MRI-based regions of interest (ROIs) in the anteroventral striatum, ventral putamen, dorsal putamen, middle caudate, dorsal caudate, nucleus accumbens, and cerebellum, similarly to previous research by Drevets et al. [4]. The mean radioactivity in a reference region (cerebellum: c') was used to control for the effects of free and nonspecifically bound [^{11}C]raclopride. The [^{11}C]raclopride binding potential (BP), which is inversely correlated with endogenous DA release, was selected as our measurement of D2 receptor binding in each brain region. The percentage in [^{11}C]raclopride binding was computed as the difference in BP_{ND} between baseline and reward images, similarly to the protocol described by Watabe et al. [3]. Negative values of [^{11}C]raclopride ΔBP indicated the percentage of [^{11}C]raclopride displacement by endogenously released DA. Greater negative values indicate greater [^{11}C]raclopride displacement. One-sample *t* tests were used to test the significance of ΔBP in each region and each group. The findings were corrected for multiple comparisons using Bonferroni correction (significance threshold set at $\alpha = 0.005$) for 2-tailed *p* values. The a priori hypothesis was tested using 1-way ANOVA with group as a factor for the ΔBP obtained in the striatal ROIs. Since age is known to influence D2/D3 receptor BP, this factor was included as covariate in the analysis. Significant group effects indicated by the ANOVA were further tested using the Gabriel post hoc test.

In additional analyses with the covariates severity of depressive symptoms, FMS duration, and antidepressant medication, no correlations were found with BP_{ND} in any striatal regions.

Katharina Ledermann and Josef Jenewein contributed equally to the paper.

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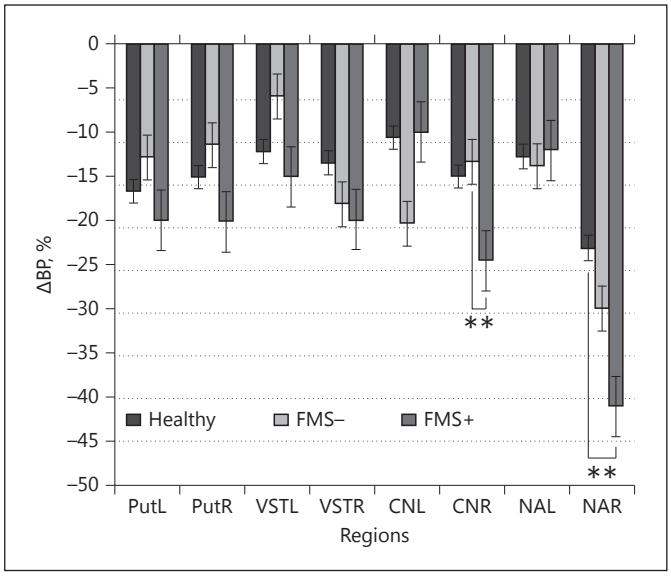

Fig. 1. Reward-related changes in regional binding potentials for [^{11}C]raclopride. Plot of mean percentage change in binding potential (ΔBP) in the ROI analyses. A significant group difference was evident in the right caudate nucleus and the right nucleus accumbens. Post hoc tests indicated a significant difference in ΔBP between FMS+ and FMS– patients in the right caudate nucleus and between healthy controls and FMS+ patients in the right nucleus accumbens. PutL, left putamen; PutR, right putamen; VSTL, left ventral striatum; VSTR, right ventral striatum; CNL, left caudate nucleus; CNR, right caudate nucleus; NAL, left nucleus accumbens; NAR, right nucleus accumbens. ** $p < 0.05$.

The study was approved by the Ethical Committee of the Canton Zurich and the Swiss Federal Department of Health, in accordance with the current version of the Declaration of Helsinki and the Swiss regulatory requirements.

We found unexpectedly significant reductions in D2/D3 receptor BPs in the reward versus the control condition in the right nucleus accumbens and caudate nucleus in both FMS groups compared to controls, which may indicate increased DA release (Fig. 1). The effects in the right nucleus accumbens were more prominent in patients with FMS and comorbid depression (41.1%) compared to healthy controls (23.3%; $p < 0.01$). Reductions in the right caudate nucleus of patients with FMS were also greater in patients with comorbid depression (24.6%) compared to patients without depression (13.4%; $p < 0.02$). The differences in percentage displacement observed between groups suggest differences in the neural processing of rewards as measured by the DA release associated with unpredictable rewards. Our findings in patients with FMS and MDD are not in line with previous attempts at elucidating the striatal response to reward in individuals with MDD [5, 6]. The finding that the DA response to rewarding stimuli increased in patients with FMS and comorbid depression is novel. One possible explanation for the accentuated DA reaction in our patients with FMS may be an upregulation of the mesolimbic DA system, which occurs due to underactivation of the striatal and prefrontal DA projections to the mesolimbic DA system. Another possibility is that chronic exposure to stress from persistent pain may have affected the DA response in our patients with FMS; recent animal studies have provided evidence that repeated exposure to stress can affect both tonic and phasic DA release in the nucleus accumbens and medial prefrontal cortex [7].

Our findings extend previous research on chronic pain-related impairments in reward processing [8, 9] and show that patients with FMS and depression can be distinguished from those without depression on a neurobiological level. Furthermore, the finding that FMS patients with and without MDD exhibited different DA release patterns has important implications for identifying distinct properties of the neural circuitry underlying FMS with and without comorbid MDD. Customized treatment strategies according to pathophysiological features defining FMS subgroups should be considered. Multidisciplinary pharmacologic and cognitive behavioral approaches are currently viewed as the most effective treatments. Drug selection should target the most prominent comorbid symptoms, e.g. amitriptyline or pregabalin for those with sleep disturbances, duloxetine for those with MDD [10]. Moreover, the present findings suggest that pharmacologic and psychotherapeutic interventions to restore DA regulation may be therapeutically beneficial in patients with FMS.

Disclosure Statement

Dr. K. Ledermann, Dr. J. Jenewein, Dr. G. Hasler, Dr. H. Sprott, Dr. U. Schnyder, Dr. G. Warnock, Dr. F. Buck, and Dr. C. Martin-Soelch report no financial relationships with commercial interests.

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