Neural effects of placebo analgesia in fibromyalgia patients and healthy individuals

Eleni Frangos*, Marta Ceko* , Binquan Wang, Emily A. Richards, John L. Gracely, Luana Colloca, Petra Schweinhardt, M. Catherine Bushnell

Supplementary Material

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1. Reported side effects of naloxone and saline.

Participants reported few to no side effects from either drug. Results are presented as mean (SD). The scale used to rate adverse effects of the drugs ranged from 0 (non-existent) to 6 (extremely strong).

Table 1. Reported side effects of naloxone and saline.

	FM (n=32)		HC (n=46)	
	saline	naloxone	saline	naloxone
Blurred vision	0	0	0	0.2(1.04)
Dizziness	0	0 (0.3)	0	0
Dry mouth	0.2(0.7)	0.7(1.5)	0.1(0.4)	0.3(0.9)
Dry skin	0.1(0.3)	0.1(0.2)	0	0
Headache	0.2(0.6)	0.4(1.4)	0.1(0.5)	0
Nausea	0	0	0	0(0.2)
Sedation	0	0.4(0.9)	0.1(0.4)	0.6(1.3)

2. Correlations between FM characteristics and pain ratings

Considering the evidence indicating that FM duration decreases placebo effects [22], we assessed the FM characteristics below to determine whether they related to FM placebo analgesic effects. We found no evidence of trends in the present FM cohort indicative of placebo response changing as a function of FM characteristics. As expected, the only significant positive correlation was found between placebo pain intensity and unpleasantness ratings.

Table 2. Pearson correlation matrix of FM characteristics and placebo response (pain ratings: control-placebo).

		M	SD	1	2	3	4	5
1	*Placebo response (intensity)	4.15	19.87	--				
2	◊Placebo response (unpleasantness)	24.01	18.67	0.77 (<0.001)	--			
3	Symptom duration	11.91	7.48	0.19 (0.30)	0.19 (0.30)	--		
4	FIQ	41.97	19.32	0.30 (0.13)	0.15 (0.48)	-0.13 (0.51)	--	
5	Daily pain	6.63	2.52	0.02 (0.89)	0.13 (0.52)	-0.20 (0.33)	0.41 (0.06)	--

Results are presented as r(*p*).

*Difference between control pain intensity rating and placebo.

◊Difference between control pain unpleasantness rating and placebo.

Symptom duration, N=32

FIQ, Fibromyalgia Impact Questionnaire, N=26

Daily pain, N=26

3. Results of heat pulse 2 of first placebo test scan

The neural results of the second anticipation period and heat pulse (black arrows in Fig. 1) of the first placebo test scan are summarized below in Table 3.

Heat stimulation period. As expected, the heat stimulation presented during the placebo and control cream conditions each produced significant activations in pain-related regions (e.g., insula, ACC, SII) when compared to baseline. However, as indicated by the control cream > placebo cream contrast, no placebo-related decreases were observed in any brain regions during heat pulse 2 of each trial. Placebo-related increases (i.e., placebo cream > control cream) were observed only in the frontal pole. No group or drug differences were found, and no group * cream interactions were observed. While we did observe a significant group * cream * drug interaction in the control cream > placebo cream contrast, we found that the interaction was produced when HCs with saline were grouped with FM patients with naloxone and then compared to HCs with naloxone grouped with FM patients with saline, i.e., $HC_{sal} + FM_{nal} > HC_{nal} + FM_{sal}$. For the purposes of the present study, we concluded that this was not scientifically meaningful.

Anticipation period. Similarly, the second anticipation period preceding heat pulse 2 produced activation within pain-related regions and also within frontal regions in the control cream and placebo cream conditions compared to baseline. However, only differences in within the occipital pole and intracalcarine cortex were observed in the control cream > placebo cream contrast. No expectation-related activations or any other activations were observed in the placebo cream > control cream contrast, and no interactions were observed.

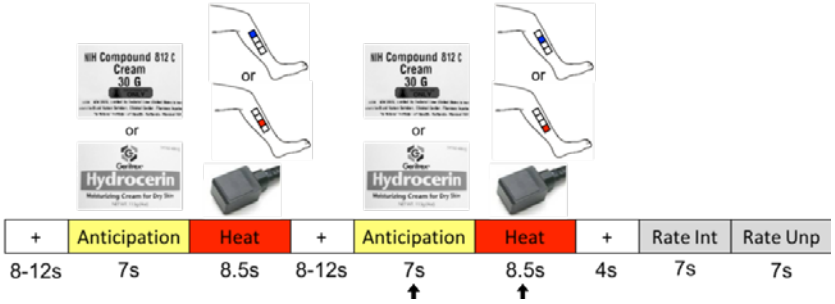

Figure 1. Trial paradigm for experimental scan. Black arrows indicate second heat pulse.

Table 3. Whole-brain BOLD responses during heat pulse 2 of the first placebo experimental scan.

Region	voxels	MNI coordinates			Peak z-score	p-value
		x	y	z		
Anticipation period						
Control > baseline						
Occipital pole (L)	48025	52	12	37	11.80	<0.001
Hippocampus (L)		56	48	32	6.39	

Inferior frontal gyrus (L)		67	66	46	4.49	
post. Insula (R)		27	54	42	5.58	
Frontal medial ctx (L)		49	82	27	5.02	
Occipital pole (R)		36	19	32	11.50	
SII (L)		76	51	44	6.18	
SII (R)		18	52	45	5.67	
Thalamus (L)		50	53	38	3.79	
Thalamus (R)		38	51	37	3.91	
SI (R)	490	38	41	69	4.59	0.01
Placebo > baseline						
Occipital pole (L)	39683	59	18	30	9.95	<0.001
Hippocampus (L)		56	49	32	5.70	
mid Insula (L)		64	61	41	3.26	
Paracingulate gyrus (R)		39	86	47	3.01	
Occipital pole (R)		41	18	32	9.53	
SII (R)		20	50	44	5.88	
SII (L)		76	49	44	4.48	
Thalamus (L)		49	54	38	3.68	
Frontal pole (L)	439	51	94	47	3.73	0.029
Frontal pole (R)		41	93	43	3.28	
Control > Placebo						
Intracalcarine ctx (R)	616	37	19	40	3.96	0.002
Occipital pole (R)		36	16	46	3.64	
Placebo > Control						
-	-	-	-	-	-	-
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
-	-	-	-	-	-	-
Stimulation period						
Control > baseline						
Temporal pole (R)	66991	16	68	32	9.61	<0.001
ACC		45	67	57	7.91	
Central operc. ctx (R)		21	66	37	8.57	
post. Insula (L)		63	55	36	7.63	
ant. Insula (R)		28	72	37	9.53	
post. Insula (R)		28	53	40	8.84	
Precentral gyrus (R)		16	67	37	8.64	
Occipital ctx (L)		60	18	41	8.45	
Occipital ctx (R)		39	18	33	8.60	
SI (R)		36	44	70	7.08	
SII (L)		72	53	43	7.95	
SII (R)		15	53	44	8.08	

Thalamus (R)		39	57	36	6.51	
Placebo > baseline						
Occipital ctx (R)	77149	40	15	38	10.50	<0.001
ACC		46	67	57	9.51	
Central operc. ctx (R)		17	66	36	9.68	
ant. Insula (L)		64	66	37	8.22	
ant. Insula (R)		28	74	34	9.55	
Occipital ctx (L)		48	16	32	8.85	
SI (R)		36	44	69	7.50	
SII (L)		74	50	44	7.63	
SII (R)		15	51	46	8.75	
SMG (R)		13	50	47	9.93	
Control > Placebo						
-	-	-	-	-	-	-
Placebo > Control						
Frontal pole (R)	791	25	85	43	4.06	<0.001
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
Precuneous ctx	2912	45	34	56	4.34	<0.001
Lat. Occipital ctx (R)		20	29	48	4.04	
Lat. Occipital ctx (L)	1774	65	28	53	4.47	<0.001
Angular gyrus (L)		70	37	49	3.95	
Supramarginal gyrus (L)		70	40	59	3.96	
Middle frontal gyrus (L)	1067	65	67	52	4.06	<0.001
Superior frontal gyrus		54	78	58	3.78	

"-", no significant results; ACC, anterior cingulate cortex; ant., anterior; ctx., cortex; L, left; Lat., lateral; post., posterior; R, right; operc., operculum; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SMG; supramarginal gyrus.

4. Results of second placebo test scan

Behavioral results. For the second placebo experimental scan, the cream treated regions of the left leg (proximal vs. distal) were counterbalanced with the first placebo experimental scan. The participants received the same individualized heat temperatures as the first experimental scan. Although participants rated pain lower when the heat stimulus was presented to the placebo cream site than the control site, there was no significant main effect of cream (pain intensity: control 129.5±4.2, placebo 125.3±3.5, p=0.15). Furthermore, there was no difference between FM and HC participants (pain intensity: HC 128±4.5, FM 126.8±5.6, p=0.87), and no effect of naloxone (pain intensity: Sal 125.9±5.4, Nal 128.8±4.7, p=0.69). Finally, no significant interactions were found (pain intensity: cream*group, p=0.68; cream*drug, p=0.64; group*drug, p=0.8; cream*group*drug, p=0.1). Similarly, we found no significant effects on pain unpleasantness (cream: control -23.7±3.4, placebo -19.6±3.3, p=0.15; group: HC -26.7±4, FM -16.6±4.7, p=0.11; drug: Sal -19±4.7, Nal -24.3±4, p=0.4; cream*group, p=0.85; cream*drug, p=0.27 group*drug, p=0.83; cream*group*drug, p=0.14).

Neural response to heat pulse 1 of second test scan

Heat stimulation period. As summarized in Table 4, the heat stimuli presented during both the control cream and placebo cream conditions produced pain-related activations (e.g., insula and SII) compared to baseline. In the control cream > placebo cream contrast during stimulation, which would indicate placebo-related reductions, we did not observe differences in any of these pain-related regions. We did observe significantly greater activations within the lingual gyrus and occipital cortex, which might relate to differences in visualization. Whereas in the first scan we did not observe any regions with significantly greater activation during the placebo condition than during the control condition, during the second scan, we found significant differences in several brain regions, including S1, despite lower pain ratings during placebo. No differences for group or drug were found, and no interactions were observed.

Anticipation period. Differences in the placebo cream > control cream contrast were only observed within the occipital cortex during the anticipation condition. No differences for group or drug were found, and no interactions were observed.

Neural response to heat pulse 2 of second test scan

Heat stimulation period. Table 5 shows pain-related activations in response to the heat stimuli during the control and placebo cream condition, similar to the activation patterns observed during the other heat pulses. However, no placebo-related reductions were observed in any brain regions (control > placebo contrast), and placebo-related increases (placebo > control) were only observed in the lingual gyrus. No differences for group or drug were found, and no interactions were observed.

Anticipation period. Significant differences were observed only within the lateral occipital cortex in the placebo cream > control cream contrast. Similar to the first anticipation period and the anticipation periods of the first scan, we did not observe any differences in placebo expectation-related regions. No differences for group or drug were found, and no interactions were observed.

Habituation to the heat stimuli may account for the lack of differences observed during the second experimental run, as pain intensity ratings across all participants and conditions (group, drug, and cream) significantly decreased between the first and second placebo scans (pain intensity ratings across groups and conditions, placebo scan 1, 137.9±3, placebo scan 2, 127.4±3.6, p<0.001).

Table 4. Whole-brain BOLD responses of the first anticipation and heat pulse of the second placebo experimental scan.

Region	voxels	MNI coordinates			Peak z-score	p-value
		x	y	z		
Anticipation period						
Control > baseline						
Occipital ctx (L)	14716	47	18	29	12.2	<0.001
Occipital ctx (R)		38	15	35	11	
SII (R)	412	21	49	46	4.48	0.039
Placebo > baseline						
Frontal pole (L)	549	49	91	45	4.16	0.008
Frontal pole (R)		39	95	40	3.75	
Occipital ctx (L)	28953	52	17	28	12.8	<0.001
Occipital ctx (R)		40	14	42	10.24	
SII (R)	1290	23	48	45	5.22	<0.001
SI (R)	436	34	43	69	4.57	0.029
Subcallosal ctx	2385	42	71	31	4.38	<0.001
Frontal medial ctx		49	86	28	4.20	
STG (R)	1852	14	64	36	4.80	<0.001
MTG (R)		14	60	29	4.23	
Control > Placebo						
-	-	-	-	-	-	-
Placebo > Control						
Lateral occipital ctx (R)	2766	26	20	42	4.72	<0.001
Occipital fusiform ctx (L)	2890	65	27	30	5.17	<0.001
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
-	-	-	-	-	-	-
Stimulation period						
Control > baseline						
Occipital ctx (R)	9389	38	14	42	8.99	<0.001
Lingual gyrus (L)		48	20	28	8.79	
Occipital fusiform gyrus (L)		59	22	28	8.55	
Paracingulate (R)	4189	44	71	56	6.72	<0.001
ACC (R)		43	70	52	5.87	
SI (R)		35	44	70	6.03	
STG (R)	6574	15	63	35	8.20	<0.001
Insula (anterior) (R)		25	71	32	8.03	
Insula (posterior) (R)		28	55	42	7.60	
SII (R)		17	52	47	6.77	

STG (L)	5449	75	62	35	7.48	<0.001
SII (L)		74	49	44	7.39	
Planum polar (L)		72	63	35	7.16	
Insula (ant) (L)		61	72	37	7.13	
Thalamus (R)	1015	40	57	39	5.01	<0.001
Thalamus (L)		48	58	35	3.86	
Placebo > baseline						
Insula (L)	5523	61	74	37	6.34	<0.001
Occipital ctx (L)	16245	55	23	28	9.30	<0.001
Occipital ctx (R)		34	14	44	8.42	
Planum Polar (R)	13921	16	62	36	8.41	<0.001
Central opercular ctx (R)		19	63	38	7.76	
Insula (anterior) (R)		26	67	40	7.43	
Insula (posterior) (R)		27	54	38	7.11	
Paracingulate/ACC		43	72	55	7.20	
SI (R)		35	43	70	6.19	
SII (R)		21	48	47	6.60	
Thalamus (R)		39	57	35	4.69	
Control > Placebo						
Lingual gyrus (L)	467	51	20	30	4.57	0.018
Occipital ctx (R)	434	35	14	40	4.87	0.027
Placebo > Control						
Cerebellum (R)	566	43	23	23	3.42	0.006
Lateral occipital ctx (R)	637	14	32	33	3.45	0.003
MTG (R)		13	48	31	3.40	
SPL (R)	1148	30	36	65	4.23	<0.001
SI (R)		24	48	57	3.94	
SMG (R)		24	42	59	3.53	
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
-	-	-	-	-	-	-

"-", no significant results; (L), left; (R), right; ACC, anterior cingulate cortex; ctx, cortex; MTG; middle temporal gyrus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; n., nucleus; SMG; supramarginal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus.

Table 5. Whole-brain BOLD responses during heat pulse 2 of the second placebo experimental scan.

Region	voxels	MNI coordinates			Peak z-score	p-value
		x	y	z		
Anticipation period						
Control > baseline						
Occipital fusiform gyrus (R)	27121	36	18	27	11.16	<0.001
Frontal medial ctx		48	80	25	4.52	
Occipital pole (L)		55	14	35	10.40	
Occipital pole (R)		37	13	37	9.54	
SI (L)	481	77	46	46	3.91	0.019
Heschl's gyrus		73	55	40	3.15	
STG (L)		75	63	35	3.43	
Temporal pole (L)		74	66	34	3.87	
Precentral gyrus (L)	459	75	64	52	4.92	0.025
Placebo > baseline						
Occipital pole (R)	43957	40	16	34	13.45	<0.001
Frontal medial ctx		49	82	27	3.89	
Lingual gyrus (L)		47	19	28	11.31	
Precentral gyrus		71	65	56	4.66	
SI (R)		39	41	70	3.66	
SII (L)		72	49	43	4.24	
SII (R)		22	48	47	5.30	
ACC	462	45	59	59	3.75	0.013
Control > Placebo						
-	-	-	-	-	-	-
Placebo > Control						
Lat. occipital ctx (L)	444	59	18	27	3.40	0.013
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
-	-	-	-	-	-	-
Stimulation period						
Control > baseline						
ant. Insula (R)	38407	26	68	39	8.01	<0.001
post. Insula (L)		64	54	38	7.56	
Central operc. ctx (R)		19	66	38	7.89	
Frontal pole (R)		25	84	49	4.82	
Occipital pole (R)		34	17	36	7.98	

Planum polar (L)		70	62	36	7.94	
SII (L)		75	50	45	6.65	
SII (R)		20	48	46	6.96	
Thalamus (L)		51	55	39	4.69	
Thalamus (R)		39	58	38	5.88	
Paracingulate gyrus	5416	42	70	58	8.72	<0.001
ACC		43	72	52	6.03	
SI (R)		35	44	70	6.16	
Placebo > baseline						
Lingual gyrus (L)	71439	47	18	32	10.59	<0.001
ACC		43	69	53	6.42	
Frontal pole (R)		22	81	47	6.54	
ant. Insula (R)		27	70	39	8.96	
ant. Insula (L)		62	70	38	7.67	
Occipital pole		45	17	32	10.08	
Paracingulate gyrus		44	70	58	8.06	
SI (R)		37	45	71	6.09	
SII (L)		75	49	46	7.01	
SII (R)		21	48	47	7.34	
Temporal pole (R)		16	68	32	9.12	
Thalamus (L)		49	55	34	5.65	
Thalamus (R)		40	54	34	6.01	
SI (L)	487	55	40	69	4.66	0.031
Control > Placebo						
-	-	-	-	-	-	-
Placebo > Control						
Lingual gyrus (R)	743	42	28	30	4.10	<0.001
Group x cream (F-test)						
-	-	-	-	-	-	-
Group x cream x drug (F-test)						
-	-	-	-	-	-	-

"-", no significant results; ACC, anterior cingulate cortex; ant., anterior; ctx., cortex; L, left; Lat., lateral; post., posterior; R, right; operc., operculum; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; STG, superior temporal gyrus.