Medial prefrontal neuroplasticity during extended-release naltrexone treatment of opioid use disorder – a longitudinal structural magnetic resonance imaging study

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SUPPLEMENTARY INFORMATION

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1. Cortical thickness change from pre-treatment to on-treatment – whole-brain results

The brain regions that showed significant difference in cortical thickness between the pre-treatment and on-treatment sessions in the OUD participants are summarized in **Table S1**.

2. Effect of the duration of abstinence and imaging data quality

Linear regression analyses showed no significant effect of duration of abstinence on mPFC/aCC cortical thickness of the OUD participants at pre-treatment ($F(1,45)=0.01$, $p=0.93$), on-treatment ($F(1,45)=0.22$, $p=0.64$), or its change from pre-treatment to on-treatment ($F(1,45)=1.15$, $p=0.29$). Similarly, there was no significant effect of duration of abstinence on opioid craving at pre-treatment ($F(1,45)=1.21$, $p=0.27$), on-treatment ($F(1,45)=0.09$, $p=0.77$), or its change from pre-treatment to on-treatment ($F(1,45)=0.39$, $p=0.54$).

We used MRIQC (1) to compute the following of imaging data quality metrics: contrast-to-noise ratio (CNR) that measures the separation of different brain tissues (2); signal-to-noise ratio (SNR) for foreground segmentation (3); median of intensity non-uniformity (INU) that reflects radiofrequency field inhomogeneity (4); coefficient of joint variation (CJV) that measures the impact of head motion and intensity non-uniformity (5); entropy focus criterion (EFC) for motion artifacts (6); residual partial volume effect (rPVE) of gray matter tissue; Mortamet's quality indices (QI1, QI2) of artifact effect on voxels and noise intensity distribution (7); foreground-background energy ratio (FBER) that measures the relative variance of brain voxels (8); white-matter to maximum intensity

ratio (WM2MAX) that reflects the effects of hyper-intensity blood vessels and fat tissues; fractional volume of gray matter (ICV) relative to total intracranial volume; and full width at half maximum (FWHM) that measures spatial smoothness (9). Visual inspection was additionally conducted on individual raw images and cortical thickness maps to ensure successful execution of the preprocessing pipeline. Of the 49 individuals who completed the pre-treatment and on-treatment MRI assessments, two were excluded due to poor data quality, leaving 47 participants in the final analyses. The pre-treatment images had lower rPVE (p=0.024), higher ICV (p=0.022), and marginally higher INU (p=0.089) values compared to the on-treatment images. Using the `lme4` and `lmerTest` packages in R, we fitted a linear mixed-effects (LME) model using restricted maximum likelihood estimation to compare mPFC/aCC thickness between pre-treatment and on-treatment while controlling for the above three quality metrics. Statistical significance was evaluated using the Satterthwaite approximation for degrees of freedom (10). We found that the reduction in mPFC/aCC thickness remained significant (2.91 vs. 2.77, difference=0.14, 95% CI=[0.09,0.20], F(1,51.94)=26.02, p<0.001). The pre-treatment and on-treatment images did not differ on other imaging data quality metrics (ps>0.11).

3. Cortical thickness at post-treatment

Following an average of 44.00 (SD=17.06) days after the third and last XR-NTX injection, a subsample of 25 OUD participants completed the post-treatment session (see **Figure S1**). Fisher's exact tests and independent t-tests showed that the demographic and clinical characteristics did not differ between the participants who completed the post-treatment session (N=25) and those who did not (N=22) (ps>0.11) (see **Table S2**).

We investigated whether the changes in cortical thickness observed from pre-treatment to on-treatment persisted during the post-treatment session in the OUD patients. We extracted the cortical thickness values from the mPFC/aCC ROI, which was defined based on the whole-brain paired t-test of pre-treatment vs. on-treatment. The values obtained from all available participants at the each timepoint were included in an LME model with random intercepts. Post-hoc analyses were performed with the `emmeans` package while correcting for multiple comparisons using the Holm method (11). Given that the pre-treatment vs. on-treatment contrast was already examined in the whole-brain analysis, here we only examined the pre-treatment vs. post-treatment and on-treatment vs. post-treatment contrasts to avoid circular inference. We found a main effect of session (F(2,71.07)=13.88, p<0.001) such that post-treatment mPFC/aCC cortical thickness was significantly lower than pre-treatment (2.79 vs. 2.92, difference=–0.13, 95% CI=[–0.23,–0.04], corrected p=0.005) and comparable to on-treatment (2.79 vs. 2.75, difference=0.04, 95% CI=[–0.06,0.13], corrected p=0.39) (see **Figure S2**).

Two additional LME analyses were performed to assess the impact of missing data on the above findings. First, we repeated the LME analysis while restricting the sample to the OUD individuals who completed all three MRI sessions (i.e., listwise deletion, N=25 for all timepoints). Similar to the unrestricted analysis above, there was a main effect of session (F(2,48)=3.93, p=0.026) such that post-treatment mPFC/aCC cortical thickness was marginally significantly lower than pre-treatment (2.77 vs. 2.88, difference=–0.11, 95% CI=[–0.22,0.00], corrected p=0.060) and comparable to on-treatment (2.77 vs. 2.75, difference=0.02, 95% CI=[–0.10,0.13], corrected p=0.73). Second, we performed inverse probability weighted LME analysis, where the probability (p) of missing post-treatment data was calculated using a logistic regression model that included all baseline characteristics as predictors. For each OUD participant, the weight was calculated as $A/p+(1–A)/(1–p)$, where A=1 if post-treatment data were missing and A=0 otherwise. The weights were subsequently truncated to the middle 95% of the distribution to minimize the impact of extreme weights (12). Similar to the unweighted analysis above, there was a main effect of session (F(2,70.80)=14.78, p<0.001) such that post-treatment mPFC/aCC cortical thickness was significantly lower than pre-treatment (2.75 vs. 2.96, difference=–0.20, 95% CI=[–0.29,–0.10], corrected p<0.001) and comparable to on-treatment (2.75 vs. 2.75, difference=–0.01, 95% CI=[–0.10,0.09], corrected p=0.88).

We also conducted a comparison between the non-OUD group and the OUD group at the post-treatment session. Two-sample t-test showed that the mPFC/aCC cortical thickness of the non-OUD group (mean±SD=2.96±0.34) was higher than the OUD group at post-treatment (t(40.1)=2.06, p=0.046) (see **Figure S2**). Linear regression that controlled for race and stimulant use disorder yielded similar results (coefficient=0.29, SE=0.10, t(74)=2.87, p=0.005).

4. Cortical thickness difference between OUD and non-OUD individuals – whole-brain results

The brain regions that showed significant difference in cortical thickness between the non-OUD group and the OUD group at pre-treatment are shown in **Figure S3a** and summarized in **Table S3**. The brain regions that showed significant difference in cortical thickness between the non-OUD group and the OUD group at on-treatment are shown in **Figure S3b** and summarized in **Table S4**.

5. Association between changes in cortical thickness and opioid craving – whole-brain results

The brain regions that showed a significant correlation between the change in cortical thickness and the change in opioid craving from pre-treatment and on-treatment are summarized in **Table S5**.

6. Confirmatory analysis with varying spatial smoothing parameters

Un-smoothed: There was a significant reduction in mPFC/aCC cortical thickness from pre-treatment to on-treatment among the OUD individuals (k=170, Z=4.71, x/y/z=5/48/–2). There was no increase in cortical thickness from pre-treatment to on-treatment. Cortical thickness of the mPFC/aCC ROI (defined using un-smoothed data) at post-treatment was lower than pre-treatment (main effect, $F(2,71.07)=17.10$, $p<0.001$; 3.48 vs. 3.73, difference=–0.25, 95% CI=[–0.41,–0.09], corrected p=0.002) and comparable to on-treatment (3.48 vs. 3.41, difference=0.07, 95% CI=[–0.10,0.23], corrected p=0.35). Compared to the non-OUD group (mean±SD=3.72±0.61), the OUD group had comparable mPFC/aCC cortical thickness at pre-treatment (3.73±0.75, $t(88.2)=–0.09$, p=0.93) but significantly lower thickness at on-treatment (3.41±0.67, $t(94.0)=2.39$, p=0.019). There was a positive correlation between the reduction in opioid craving and the reduction in mPFC/aCC thickness from pre-treatment to on-treatment in the OUD group (r=0.34, p=0.019). Whole-brain regression analysis showed that the change in opioid craving was positively associated with the change in cortical thickness of the mPFC (k=60, Z=4.71, x/y/z=11/14/–15; k=25, Z=4.60, x/y/z=14/49/3), right amygdala (k=55, Z=5.02, x/y/z=24/3/–14), left insula (k=91, Z=4.53, x/y/z=–38/–9/11; k=777, Z=4.43, x/y/z=–35/–15/20; k=174, Z=4.39, x/y/z=–42/–6/–6), right angular gyrus (k=121, Z=4.29, x/y/z=51/–56/17), and right middle temporal gyrus (k=47, Z=4.03, x/y/z=49/–57/7). There was no significant negative correlation.

Smoothed with 12-mm FWHM: There was a significant reduction in mPFC/aCC cortical thickness from pre-treatment to on-treatment among the OUD individuals (k=3521, Z=4.38, x/y/z=5/51/–2; k=568, Z=3.64, x/y/z=–2/32/–18; k=664, Z=3.58, x/y/z=–5/13/27). There was no increase in cortical thickness from pre-treatment to on-treatment. Cortical thickness of the mPFC/aCC ROI (defined using data smoothed with 12-mm FWHM) at post-treatment was lower than pre-treatment (main effect, $F(2,71.15)=8.35$, $p<0.001$; 2.14 vs. 2.23, difference=–0.09, 95% CI=[–0.16,–0.02], corrected p=0.012) and comparable to on-treatment (2.14 vs. 2.14, difference=–0.00, 95% CI=[–0.07,0.07], corrected p=0.89). Compared to the non-OUD group (2.30±0.27), the OUD group had comparable mPFC/aCC cortical thickness at pre-treatment (2.23±0.27, $t(98.22)=1.32$, p=0.19) but significantly lower thickness at on-treatment (2.14±0.26, $t(99.83)=3.09$, p=0.003). There was a significant positive correlation between the reduction in opioid craving and the reduction in mPFC/aCC thickness from pre-treatment to on-treatment in the OUD group (r=0.44, p=0.002). Whole-brain regression analysis showed that the change in opioid craving was positively associated with the change in cortical thickness of the mPFC (k=84962, Z=4.20, x/y/z=–4/36/31) extending to the left parietal cortex (Z=3.90, x/y/z=–46/–23/37), left temporal cortex (Z=3.88, x/y/z=–43/–6/–10), left prefrontal cortex (Z=3.84, x/y/z=–41/16/31), aCC (Z=3.72, x/y/z=–5/34/4), and left insula (Z=2.47, x/y/z=–38/15/–14), the right prefrontal cortex (k=34284, Z=4.19, x/y/z=46/7/15) extending to the right insula (Z=3.40, x/y/z=34/0/15), the right parietal cortex (k=2948, Z=3.91, x/y/z=41/–41/50), the left occipital cortex, (k=6538, Z=3.64, x/y/z=–15/–77/28), the precuneus/cuneus (k=1392, Z=3.40, x/y/z=20/–70/39), the right temporoparietal junction (k=9701, Z=3.39, x/y/z=47/–47/26), the supplementary motor area (k=1443, Z=2.99, x/y/z=12/–1/47), the right temporal cortex (k=809, Z=2.95, x/y/z=39/–33/13), and the right occipital cortex (k=562, Z=2.91, x/y/z=23/–94/6). There was no significant negative correlation.

7. Confirmatory analysis with voxel-based morphometry

We performed voxel-based morphometry (VBM) analysis using the CAT12 longitudinal pipeline (13). Gray matter volume images were spatially smoothed with 4-mm FWHM. Age, sex, and total intracranial volume (TIV) were treated as covariates and were controlled for.

There was a significant reduction in gray matter volume from pre-treatment to on-treatment among the OUD individuals in a number of brain regions including the cuneus/precuneus (k=10167, Z=4.63, x/y/z=7.5/–70.5/25.5) extending to the mPFC/aCC (Z=4.51, x/y/z=–3/48/31.5; Z=3.82, x/y/z=4.5/42/12), the right temporal cortex (k=10123, Z=4.81, x/y/z=69/–15/–10.5) extending to the frontal (Z=4.69, x/y/z=30/46.5/36), occipital (Z=4.40, x/y/z=55.5/–69/–1.5), parietal (Z=4.02, x/y/z=63/–22.5/22.5), insular cortices (Z=3.86, x/y/z=33/16.5/9) and cerebellum (Z=3.51, x/y/z=10.5/–90/–30), the left temporal (k=242, Z=4.49, x/y/z=–51/–7.5/–16.5; k=41, Z=2.92, x/y/z=–66/–33/–1.5) and occipital cortices (k=75, Z=4.09, x/y/z=–34.5/–79.5/–18; k=1166, Z=4.08, x/y/z=–54/–72/9), the right prefrontal (k=39, Z=3.01, x/y/z=39/12/34.5) and temporal cortices (k=57, Z=3.01, x/y/z=66/–42/–16.5), the cerebellum (k=1032, Z=4.07, x/y/z=–3/–67.5/–48; k=142, Z=3.92, x/y/z=37.5/–42/–37.5; k=22, Z=3.59, x/y/z=48/–67.5/–43.5), the left temporoparietal junction (k=515, Z=3.77, x/y/z=–51/–55.5/16.5), the right fusiform gyrus (k=89, Z=3.70, x/y/z=22.5/–30/–22.5), the precuneus (k=35, Z=2.74, x/y/z=3/–64.5/39), and the right postcentral gyrus (k=42, Z=2.74, x/y/z=55.5/–19.5/40.5). There was no significant increase in gray matter volume. Gray matter volume of the mPFC/aCC ROI (defined by the Neuromorphometrics atlas) at post-treatment was lower than pre-treatment at trend level (main effect, $F(2,70.26)=4.40$, $p=0.016$; 0.56 vs. 0.57, difference=–0.005, 95% CI=[–0.011,0.001], corrected $p=0.10$) and comparable to on-treatment (0.56 vs. 0.56, difference=0.001, 95% CI=[–0.005,0.006], corrected $p=0.85$). The OUD group had lower mPFC/aCC gray matter volume than the non-OUD group at pre-treatment ($F(1,98)=8.01$, $p=0.006$) and on-treatment ($F(1,98)=11.94$, $p<0.001$). There was a positive correlation between the reduction in opioid craving and the reduction in mPFC/aCC gray matter volume from pre-treatment to on-treatment in the OUD group (adjusted for age, sex, and TIV, $r=0.29$, $p=0.048$). Whole-brain regression analysis did not show any significant association between the change in opioid craving and the change in gray matter volume at FDR-corrected $p<0.05$. Using an exploratory threshold of uncorrected voxel-level $p<0.005$ and cluster extent>600 mm^3 (14), we found positive associations at the mPFC/ACC (k=339, Z=3.57, x/y/z=3/21/21), left insula (k=446, Z=3.86, x/y/z=–40.5/1.5/–6), right insula (k=305, Z=3.99, x/y/z=46.5/3/–13.5; k=179, Z=3.68, x/y/z=36/22.5/1.5), and right occipital cortex/precuneus (k=803, Z=4.02, x/y/z=9/–75/0), and negative associations at the right cerebellum (k=414, Z=4.06, x/y/z=33/–67.5/–40.5).

Taken together, the VBM analysis replicated the cortical thickness results and revealed mPFC/aCC gray matter volume reduction from pre-treatment to on-treatment that was associated with the reduction in opioid craving. The VBM analysis additionally revealed reduced gray matter volume in the bilateral prefrontal, parietal, and temporal cortices. Prior studies show that gray matter volume is determined by not only cortical thickness but also other morphological characteristics such as cortical folding/gyrification and cortical surface (15, 16). Therefore, it is possible that the gray matter volume reduction outside the mPFC/aCC was mainly driven by those other, non-thickness variables.

8. References

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TABLES

Table S1. Brain regions showing a significant difference in cortical thickness between the pre-treatment and on-treatment sessions in the OUD group (whole-brain corrected p<0.025).

Region	Cluster extent (mm^3)	Z	MNI coordinates
OUD pre-treatment > OUD on-treatment			
Left middle frontal gyrus	88915	6.22	–47, 18, 43
Left postcentral gyrus		5.99	–53, –22, 55
Left inferior frontal gyrus		5.93	–53, 27, 20
Left superior temporal gyrus		5.61	–62, –2, –1
Right postcentral gyrus	94343	6.03	41, –30, 64
Right middle frontal gyrus		5.85	37, 27, 42
Right superior frontal gyrus		5.72	21, 13, 65
Right precentral gyrus		5.58	37, –15, 66
Right inferior frontal gyrus		5.31	58, 10, 27
Ventromedial prefrontal cortex	3129	5.44	–4, 12, –7
Anterior cingulate cortex		3.86	–1, 25, –7
Mid-cingulate cortex		3.85	–1, 11, 32
Left postcentral gyrus	3890	5.24	–18, –44, 71
Precuneus		4.42	–6, –42, 74
Left superior parietal lobule		4.03	–15, –76, 49
Cuneus	503	4.42	–7, –83, 39
Right orbitofrontal cortex	556	4.02	21, 27, –13
Mid-cingulate cortex	623	3.42	3, –3, 30
Right anterior insula	499	3.23	29, 23, 6
Left superior temporal gyrus	95	3.01	–52, –39, 6
Right parahippocampal gyrus	55	2.92	23, –20, –24
Left orbitofrontal cortex	57	2.85	–18, 6, –18
Left middle temporal gyrus	22	2.77	–46, –35, –4
Left postcentral gyrus	20	2.77	–49, –22, 23
Left anterior insula	51	2.51	–32, 5, 6
Dorsomedial prefrontal gyrus	23	2.45	–1, 48, 21
Left anterior insula	23	2.44	–30, 26, 11
Supplementary motor area	23	2.44	–1, –4, 47
OUD pre-treatment < OUD on-treatment			
(none)			

Abbreviation: MNI, Montreal Neurological Institute.

Table S2. Comparison of baseline characteristics between the OUD participants who completed the post-treatment session (i.e., completers) and those who did not (i.e., non-completers).

Variable	Completer	Non-completer	p-value[1]
N	25	22	–
Sex	15 male, 10 female	11 male, 11 female	0.56
Age (years)	30.92±9.28	26.91±7.69	0.11
Years of education	14.12±2.09	13.36±2.13	0.23
Race	23 White, 2 AA	21 White, 1 Asian	0.35
Ethnicity	3 Hispanic	0 Hispanic	0.24
Years of opioid use	5.72±4.58	5.95±7.31	0.90
Alcohol use disorder	3	6	0.27
Stimulant use disorder	6	7	0.75
Cannabis use disorder	8	7	>0.99
Prescription opioid use	16	16	0.55
Heroin use	18	15	>0.99
Number of days since last opioid use	17.52±14.46	19.05±20.97	0.77
Number of cigarettes per day	12.47±10.37	14.10±6.02	0.51
UDS positive for stimulant	2	3	0.65
UDS positive for cannabis	8	9	0.56
Opioid craving (0–9)	3.12±2.70	4.18±3.06	0.22

Abbreviation: OUD, opioid use disorder. AA, African American; UDS, urine drug screen.
[1] P-values were obtained from independent t-tests for numeric variables and Fisher's exact tests for categorical variables.

Table S3. Brain regions showing a significant difference in cortical thickness between the non-OUD group and the OUD group at pre-treatment (whole-brain corrected p<0.025).

Region	Cluster extent (mm³)	Z	MNI coordinates
non-OUD > OUD pre-treatment			
Left postcentral gyrus	119305	6.42	–48, –23, 58
Left orbitofrontal gyrus		6.01	–32, 62, –10
Left inferior frontal gyrus		5.88	–54, 25, 18
Left middle frontal gyrus		5.85	–46, 18, 44
Left superior temporal gyrus		5.47	–62, –1, –1
Right middle frontal gyrus	104874	5.92	37, 27, 42
Right superior frontal gyrus		5.56	18, –6, 73
Right postcentral gyrus		5.21	56, –12, 49
Right precentral gyrus		5.19	37, –16, 67
Right inferior frontal gyrus		5.10	58, 10, 28
Right orbitofrontal gyrus	1113	4.17	21, 27, –13
Right orbitofrontal gyrus/anterior insula		3.08	19, 18, –24
Mid-cingulate cortex	610	3.41	3, –21, 46
Precuneus		2.95	7, –38, 52
Posterior cingulate cortex		2.23	1, –34, 45
Left inferior temporal gyrus	403	3.33	–48, –19, –29
Left inferior temporal gyrus	55	2.91	–47, –8, –31
Mid-cingulate cortex	29	2.69	–1, –28, 47
Mid-cingulate cortex	34	2.45	–5, –24, 30
non-OUD < OUD pre-treatment			
(none)			

Abbreviation: OUD, opioid use disorder. MNI, Montreal Neurological Institute.

Table S4. Brain regions showing a significant difference in cortical thickness between the non-OUD group and the OUD group at on-treatment (whole-brain corrected p<0.025).

Region	Cluster extent (mm³)	Z	MNI coordinates
non-OUD < OUD on-treatment			
Medial prefrontal cortex	2587	4.87	5, 48, –3
Anterior cingulate cortex		4.32	–3, 51, 2
Anterior/mid-cingulate cortex	377	3.86	2, 4, 35
Anterior/mid-cingulate cortex	107	3.60	–6, 3, 42
Anterior cingulate cortex	276	3.55	–2, 33, 17
Medial prefrontal cortex	44	3.47	–4, 42, 28
non-OUD < OUD on-treatment			
(none)			

Abbreviation: OUD, opioid use disorder. MNI, Montreal Neurological Institute.

Table S5. Brain regions showing a significant correlation between the change in cortical thickness and the change in opioid craving from pre-treatment and on-treatment in the OUD group (whole-brain corrected p<0.05).

Region	Cluster extent (mm^3)	Z	MNI coordinates
Positive correlation with the change in craving			
Right inferior frontal gyrus	952	5.07	42, 32, 2
Right anterior insula		3.72	38, 19, –13
Right orbitofrontal cortex	274	4.65	23, 5, –14
Medial prefrontal cortex	3751	4.54	–11, 53, –4
Anterior cingulate cortex		4.05	–2, 38, 19
Left posterior insula	6133	4.28	–41, –6, –7
Left superior temporal gyrus		4.13	–66, –30, 1
Left anterior insula		3.97	–44, 2, 4
Left inferior frontal gyrus		3.94	–39, 8, 9
Left postcentral gyrus	42	4.22	–43, –24, 38
Left supramarginal gyrus	453	4.14	–52, –29, 45
Medial orbitofrontal gyrus	89	4.09	13, 14, –17
Right posterior insula	1246	4.04	42, –8, –6
Medial orbitofrontal gyrus	797	4.04	–19, 10, –5
Left postcentral gyrus	310	4.04	–62, –19, 39
Right inferior frontal gyrus	370	4.02	36, 16, 32
Left precentral gyrus	92	3.92	–33, –17, 42
Right inferior frontal gyrus	345	3.72	52, 12, 12
Left supramarginal gyrus	397	3.68	–55, –35, 19
Medial prefrontal cortex	222	3.68	–9, 55, 17
Right anterior insula	291	3.64	31, 21, 12
Right anterior insula	41	3.55	46, 17, –2
Left middle frontal gyrus	146	3.47	–27, 10, 58
Left precentral gyrus	80	3.46	–40, –5, 45
Left supramarginal gyrus	26	3.46	–65, –41, 22
Left middle frontal gyrus	74	3.30	–38, 1, 51
Right inferior frontal gyrus	51	3.28	60, 13, 15
Left precentral gyrus	24	3.14	–43, 1, 37
Negative correlation with the change in craving			
(none)			

Abbreviation: OUD, opioid use disorder. MNI, Montreal Neurological Institute.

FIGURES

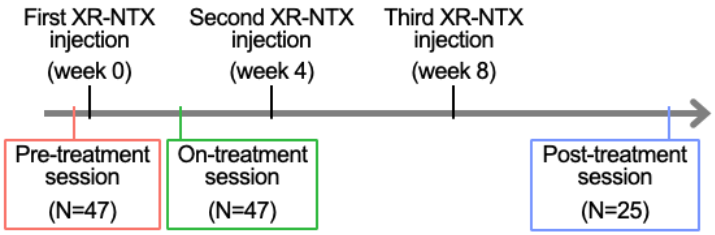

Figure S1. Study procedure and sample size of the OUD group at each study session. **Abbreviation:** OUD, opioid use disorder; XR-NTX, extended-release naltrexone.

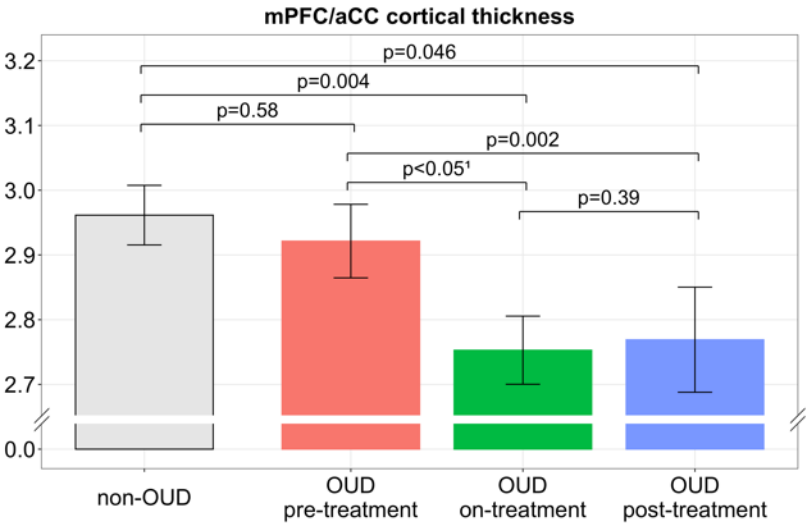

Figure S2. mPFC/aCC cortical thickness of the OUD individuals was higher at pre-treatment (N=47) than at on-treatment (N=47) and post-treatment (N=25), but the on-treatment and post-treatment sessions did not significantly differ. mPFC/aCC cortical thickness of the non-OUD individuals (N=56) was comparable to that of the OUD individuals at pre-treatment and was higher than that of the OUD individuals at on-treatment and post-treatment. **Abbreviation**: OUD, opioid use disorder; mPFC, medial prefrontal cortex; aCC, anterior cingulate cortex. Error bars represent standard errors of the means. ¹ The comparison between the pre-treatment and on-treatment sessions was performed in the whole-brain analysis at corrected p<0.05 using the threshold-free cluster enhancement algorithm.

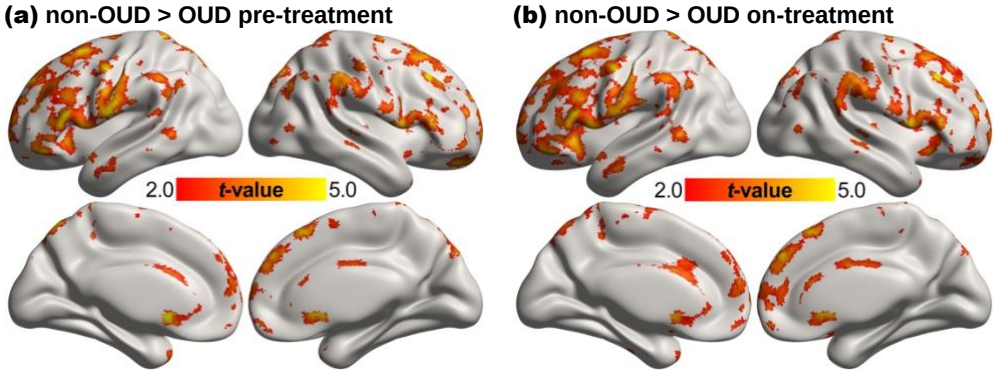

Figure S3. Significant higher cortical thickness in the non-OUD individuals than the OUD individuals at pre-treatment (a) and on-treatment (b) revealed by whole-brain two-sample t-test, thresholded at corrected p<0.025. **Abbreviation**: OUD, opioid use disorder.