

Figure S1. Injections of peripheral lipopolysaccharide (LPS) increases global [18F]FEPPA binding in the brain. (A) Acute and chronic LPS-dosing regimens were performed in two separate challenges separated by a 3-week washout. Two female monkeys received a PET scan using [18F]FEPPA after the washout period (baseline) and again 2 hrs post- acute or chronic LPS dosing. Acute animal (RUM7) received a single dose of 3E4 EU/kg LPS, while the chronically-treated monkey (RYJ10) received incremental doses (3E4, 4.5E4, 6E4 EU/kg) of LPS on Days 0, 3, and 6. Blood was collected at baseline (day 0) immediately prior to intravenous administration of LPS, 2 hrs post-LPS injection, and at end of the PET scan or approximately 4.5 hrs post-LPS injection. (B) Plasma levels of IL-6 and TNF increased after LPS injection(s) as measured with MesoScale multiplexed immunoassays. (C) PET images of [18F]FEPPA binding (SUV) at coronal and sagittal brain levels matched to representative MRI section in acute and chronic LPS animals at baseline and post-LPS. (D) Grouped baseline [18F]FEPPA SUV (mean \pm SEM) amongst cortical and subcortical ROIs demonstrate no difference in binding by region. Individual [18F]FEPPA binding % change of baseline demonstrate increased binding post-LPS in both LPS dosed animals.

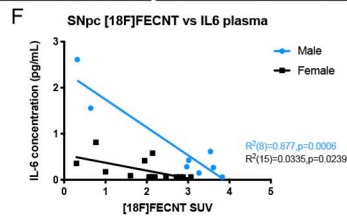
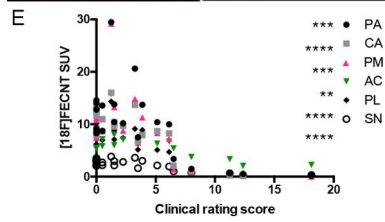
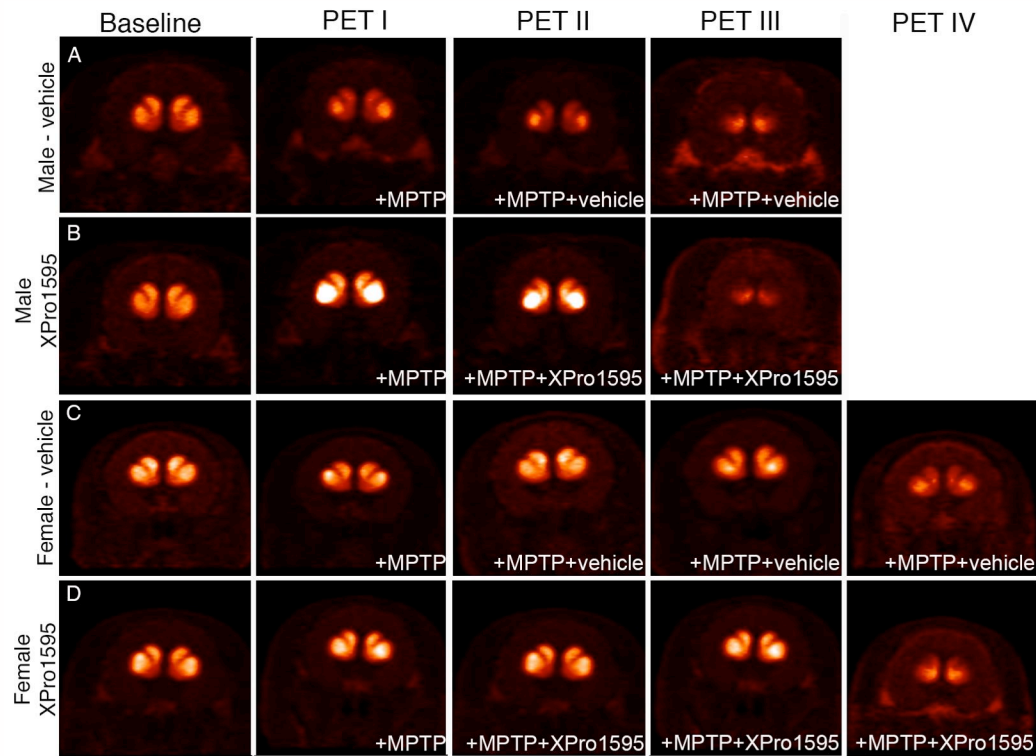


Figure S2. $[^{18}\text{F}]$ -FECNT PET demonstrates MPTP toxicity. Coronal images of $[^{18}\text{F}]$ FECNT PET in the pre-commissural striatum of chronic MPTP-treated rhesus monkeys that received systemic administration of vehicle (A,C) or XPro1595 (B,D) at baseline and 8 (PET I), 16 (PET II), 24/26 (PET III) and 38 weeks (PET IV) after the start of MPTP treatment. The severity of animal' clinical rating score is inversely correlated with $[^{18}\text{F}]$ FECNT standard uptake in various basal ganglia nuclei (I). Increased circulating IL-6 was associated with reduced $[^{18}\text{F}]$ FECNT in the substantia nigra of male monkeys (J, $R^2=0.529$, $p=0.041$). PA, putamen associative. CA, Caudate associative. PM, putamen motor. AC, accumbens. PL, putamen limbic. SN, substantia nigra. ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

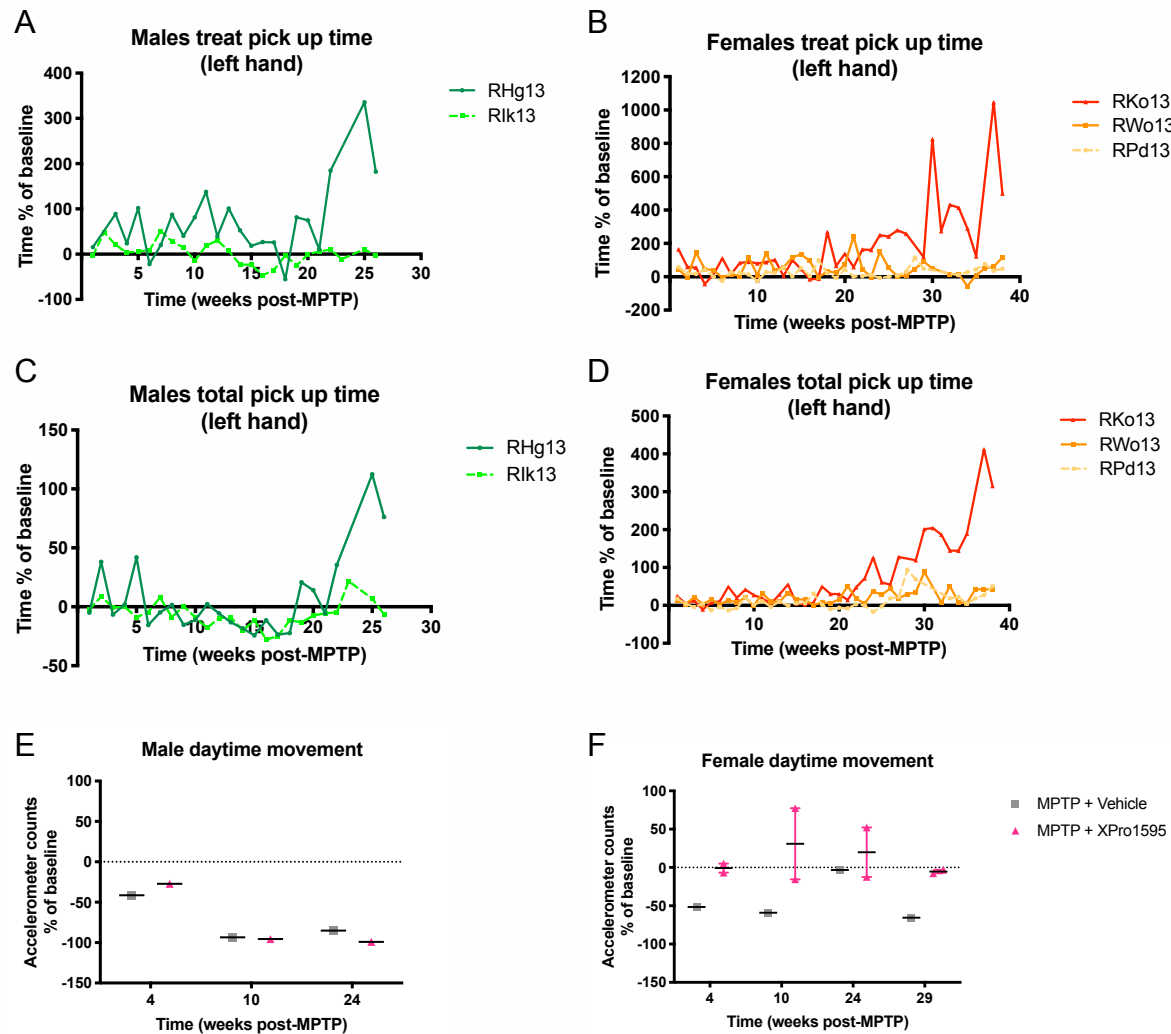


Figure S3. Chronic MPTP injections impair fine and gross motor movements. Fine-motor skill task demonstrates increased treat pick up and total pick up time for males (A,C) and females (B,D) with advanced time. Accelerometer collars recorded motion and revealed a deficit in gross motor movement in all males (E) and females (F) with escalating MPTP dosing. Solid line (vs dashed line) represent animals that received XPro1595.

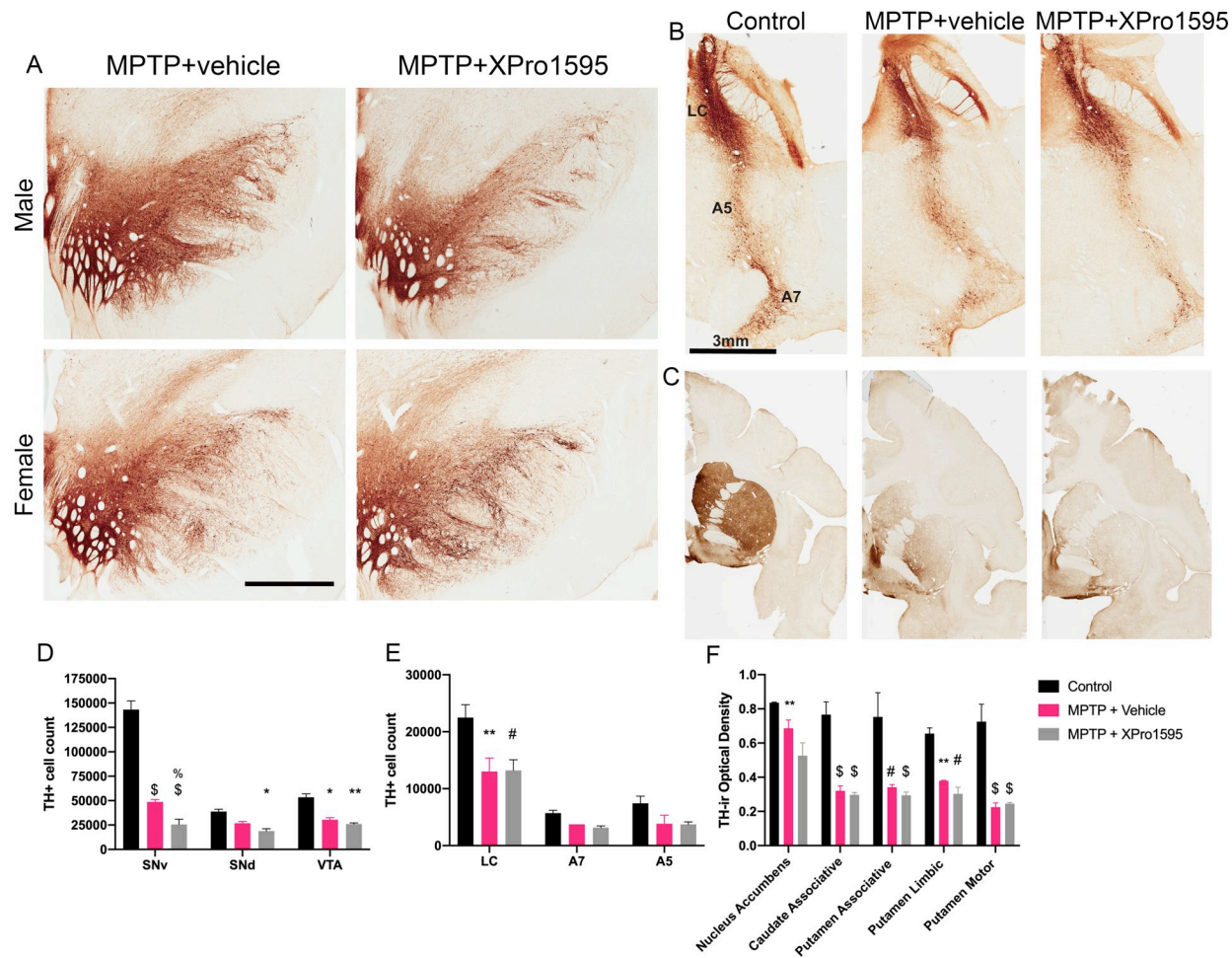


Figure S4. Chronic MPTP injections induce significant loss of TH+ cells in nigra and noradrenergic lower brainstem nuclei and TH-ir in the striatum. Representative microphotographs of TH+ immunohistochemical staining in the substantia nigra (A), lower-brainstem noradrenergic cell groups including the locus coeruleus (LC), A7 and A5 (B), and the striatum at the level of the anterior commissure (C). Unbiased stereological estimate of TH+ cells in the ventral and dorsal substantia nigra (SNv and SNd, respectively) and ventral tegmental area (VTA) reveals significantly decreased cell numbers in MPTP + vehicle and MPTP + XPro1595 animals compared to historical controls (D; $F(2,15)=133.6$, $p<0.0001$). Stereological estimate of TH+ cell count in the LC show significant differences between MPTP groups and historical controls (E; $F(2,15)=13.7$, $p=0.0004$). Optical density of TH-immunoreactivity in the striatum demonstrated significant reduction in multiple functional regions between MPTP groups and controls (F; $F(2,20)=87.2$, $p<0.0001$). * $p<0.05$, ** $p<0.01$, # $p<0.001$, \$ $p<0.0001$ when compared to controls. % $p<0.05$ when compared to MPTP + vehicle group.

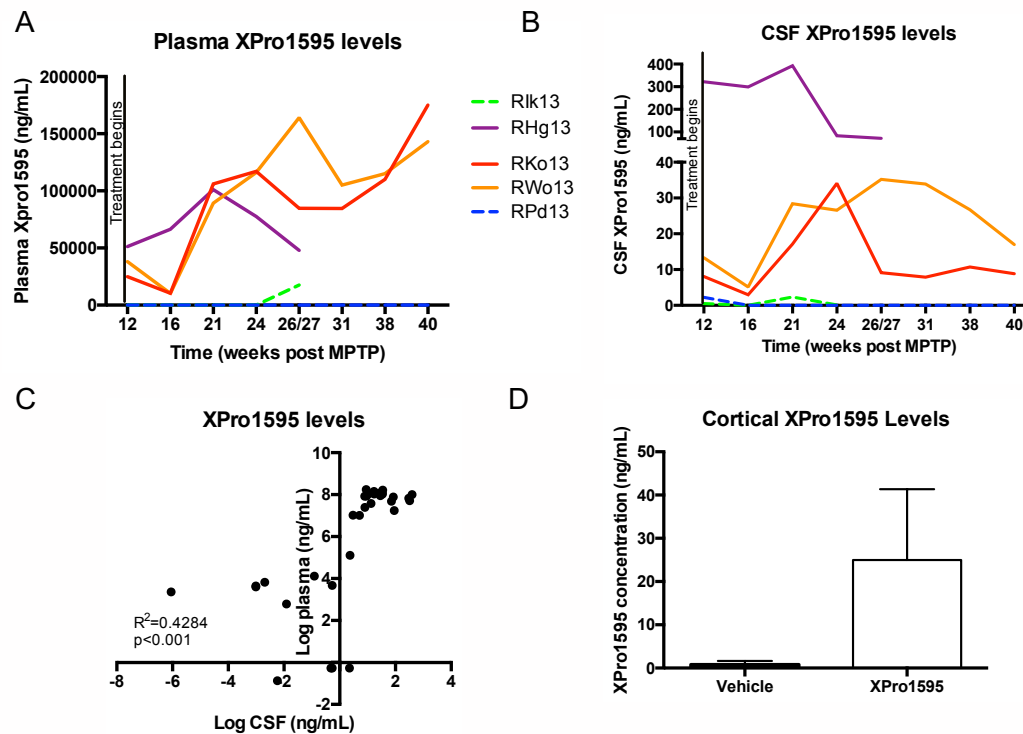


Figure S5. XPro1595 levels. Plasma (A) and CSF (B) were both collected monthly and a cortical biopsy was collected at necropsy for measurements of XPro1595 levels using a human TNF-specific immunoassay (MSD). Normalized plasma and CSF levels of XPro1595 positively correlate (C, $R^2=0.4284$, $p<0.001$). Cortical levels of XPro1595 measured from fresh tissue collected directly prior to perfusion (D). Solid lines (vs dashed lines) represent animals that received XPro1595.

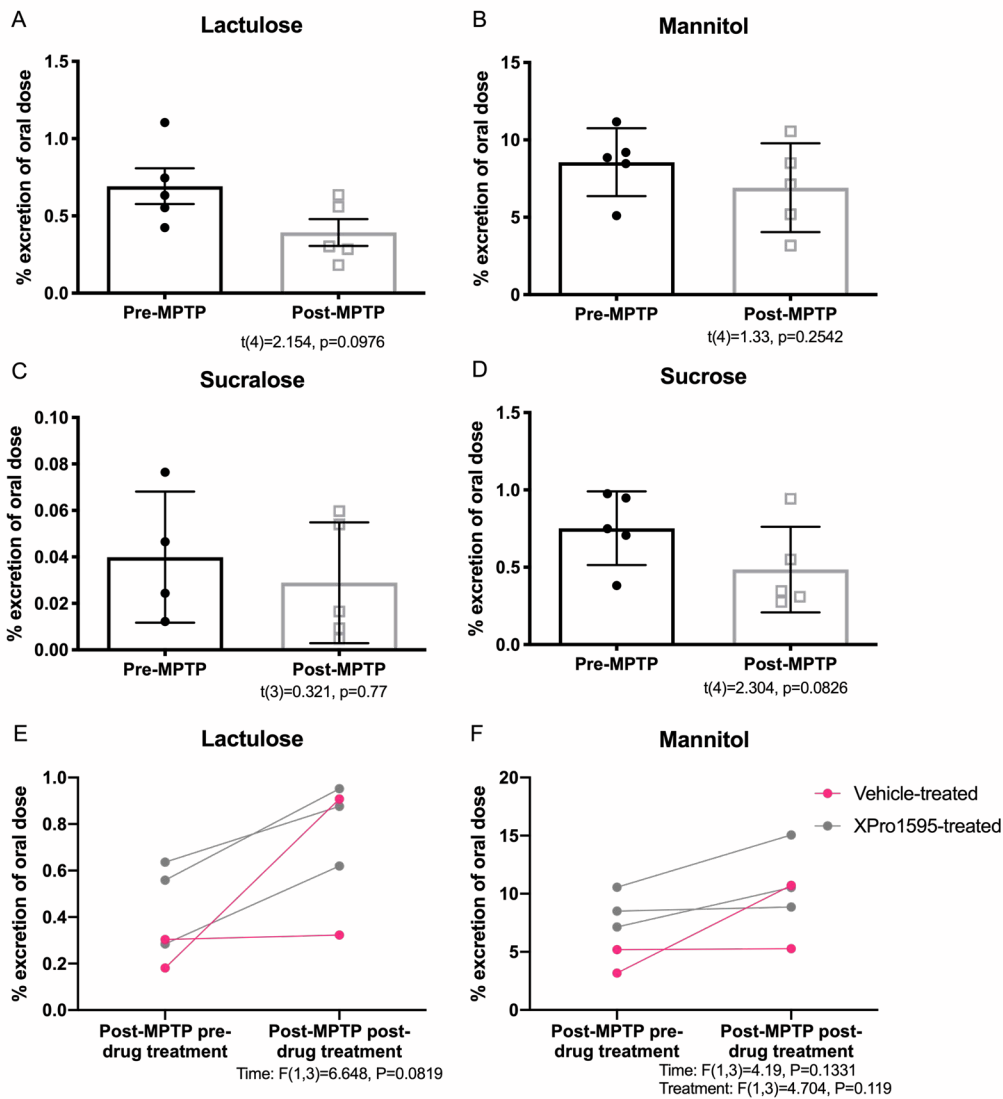


Figure S6. Gastrointestinal permeability assay. No significant changes in sugar absorption were observed in the early period of MPTP dosing (A-D). The % of lactulose (E) and mannitol (F) output post-MPTP/pre-drug treatment and post-MPTP/post-drug treatment timepoints suggest no influence of drug treatment on permeability, yet continued MPTP trended to enhance excretion or alter gut leakiness to lactulose.

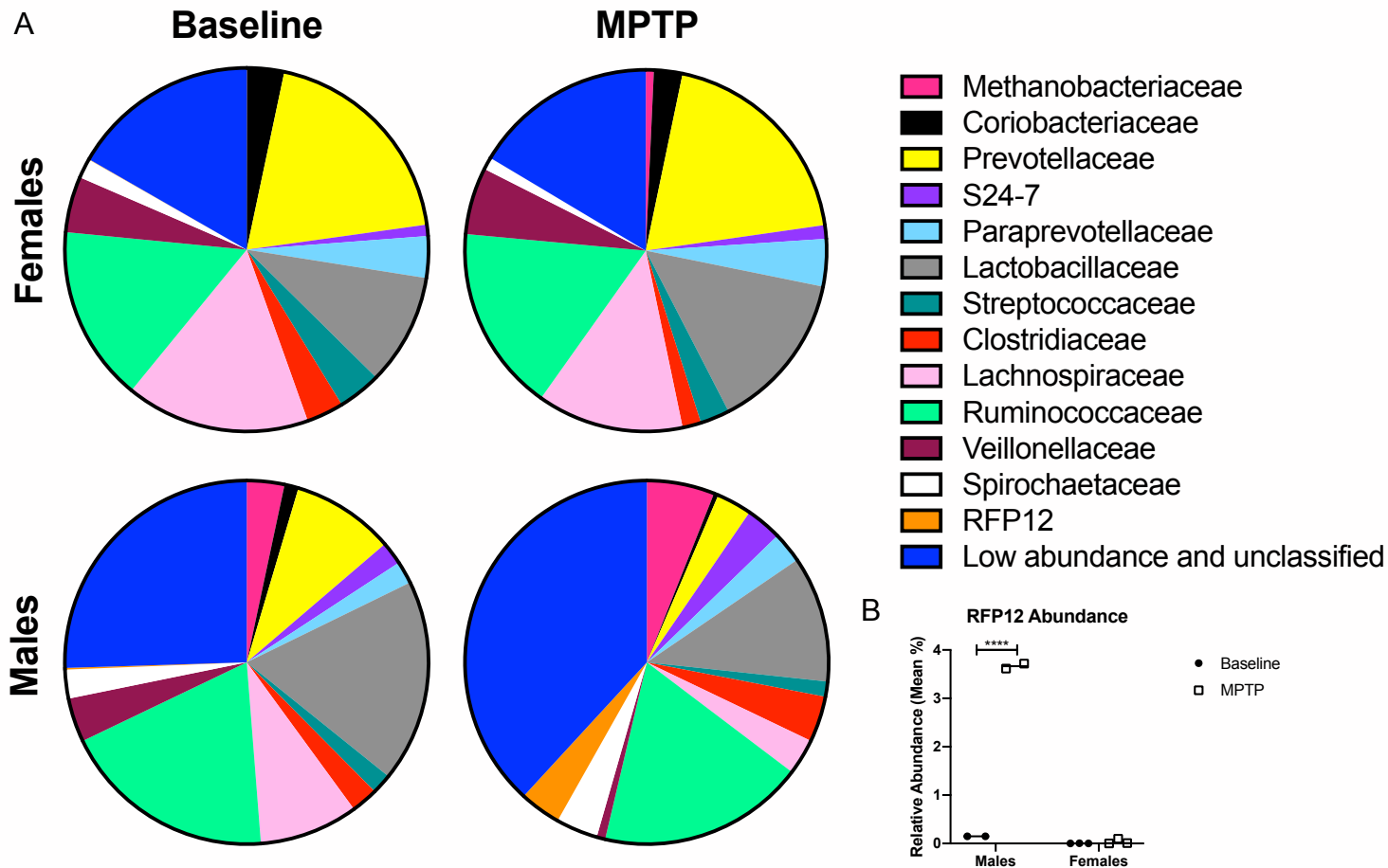


Figure S7. Gut microbiota relative abundance of family taxon differs between sexes. Pie charts display the average relative abundance of bacterial families in female (n=3) and male (n=2) monkeys at baseline and after 10 weeks of chronic MPTP (A). Males present with increased relative abundance of the bacterial family RFP12 following MPTP dosing (B). Post-hoc analysis was conducted using Sidak's multiple comparisons. ****p<0.0001

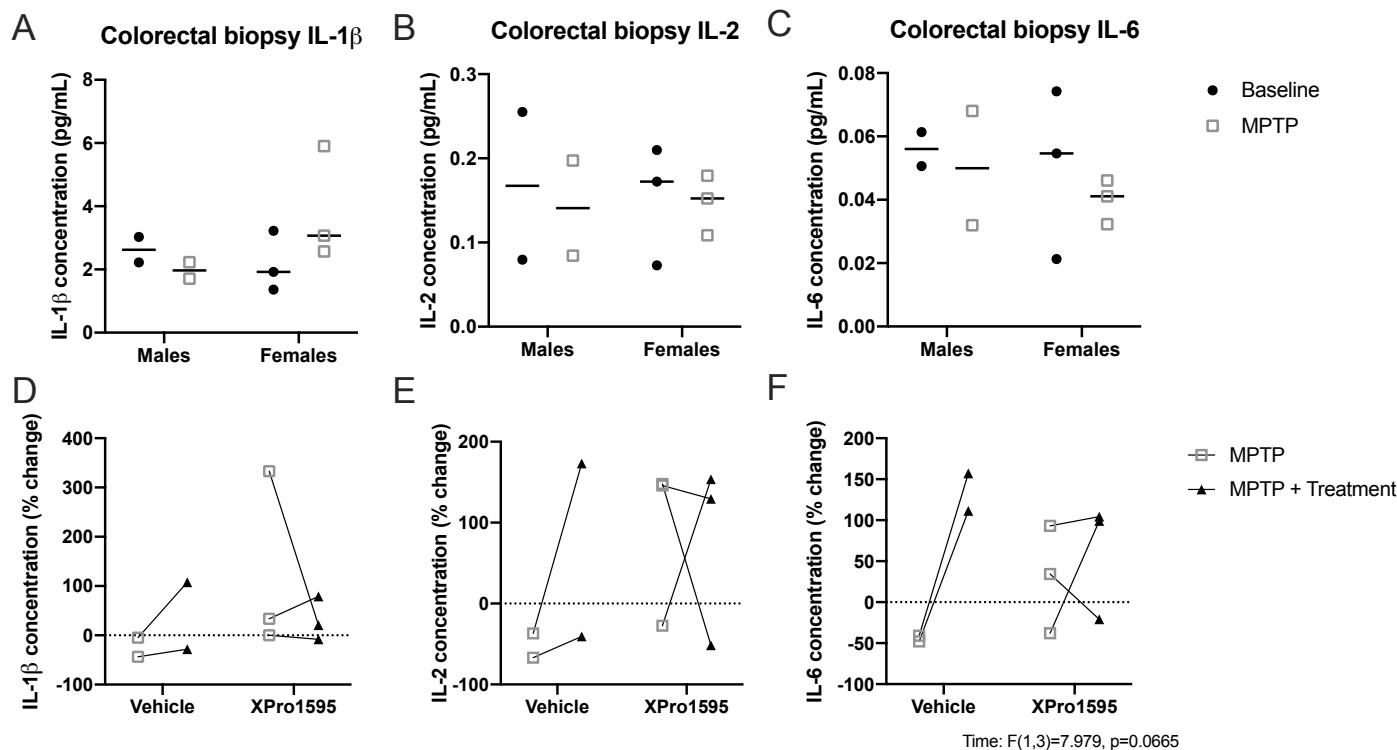


Figure S8. No significant changes in cytokine levels in gut biopsies after MPTP injections and drug treatment. Colorectal biopsies were collected at baseline, MPTP and at endpoint following MPTP + drug treatment. Biopsies showed no significant effect of sex or MPTP in IL-1 β IL-6 or IL-2 cytokine levels (A-C). Analysis of cytokine levels as a % change from baseline suggests no effect of treatment or time on IL1 β and IL-2 and a trend toward increased levels of IL-6 (p=0.0665) at endpoint (MPTP + treatment) compared to MPTP alone (D-F). MPTP = 10 weeks of MPTP dosing and pre-drug treatment; MPTP + treatment = endpoint measurement post-MPTP and post-drug treatment after 26 weeks of MPTP in males and 40 weeks of MPTP in females.