Journal Club:

PK NeuroImaging to study the dose-related brain kinetics and target engagement of buprenorphine in vivo Auvity et al., NPP 2021

Background - Rationale

- Buprenorphine is key compound for addiction maintenance therapy

- Discrepancies on neuropharmacology of BUP
  - ‘Inverted U’ analgesic dose-response in animals
  - Full agonist analgesic dose-response in humans

- Receptor occupancy of acute BUP (0.3-0.6 mg) is lacking

- Goal: Assess range receptor occupancy of BUP @ wide range of doses, including analgesic doses.

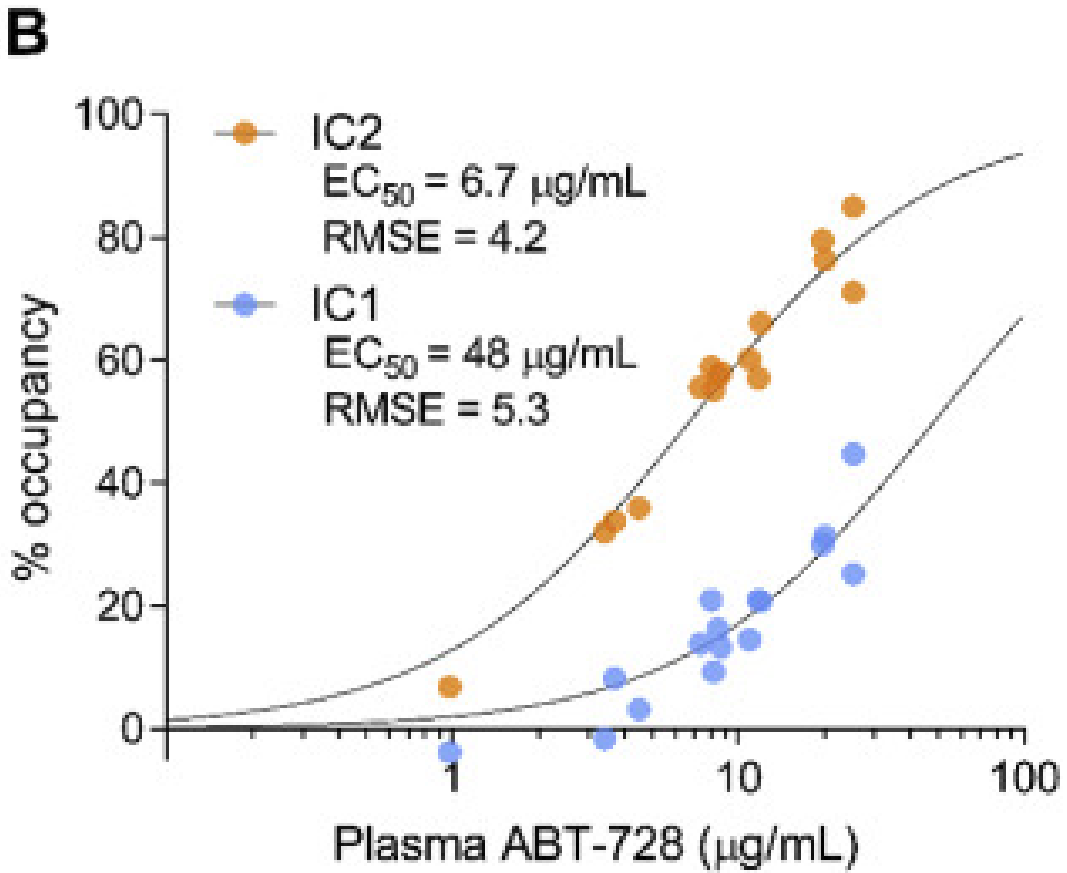
Background: Selectivity

- In vitro, Buprenorphine is high affinity partial agonist for μOR (K_i=0.08 nM), antagonist for κOR (K_i=0.44 nM), antagonist for δOR (K_i=0.82 nM) and agonist for ORL-1 (K_i=285 nM in rats)

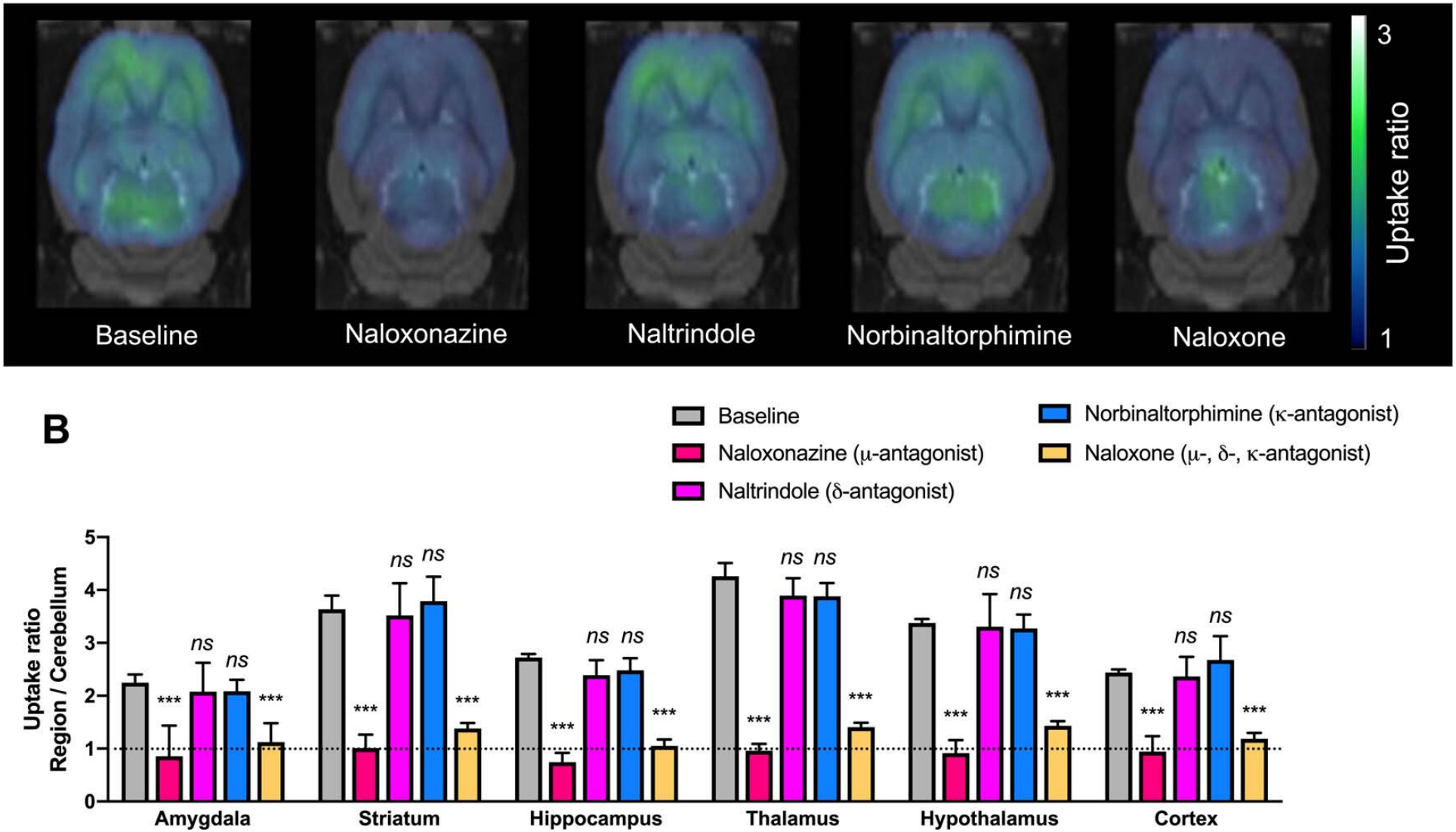
$$BP_{ND} = f_{ND}\left(\frac{B_{\max(\mu)}}{K_{D(\mu)}} + \frac{B_{\max(\kappa)}}{K_{D(\kappa)}} + \frac{B_{\max(\delta)}}{K_{D(\delta)}} + \frac{B_{\max(ORL)}}{K_{D(ORL)}}\right)$$

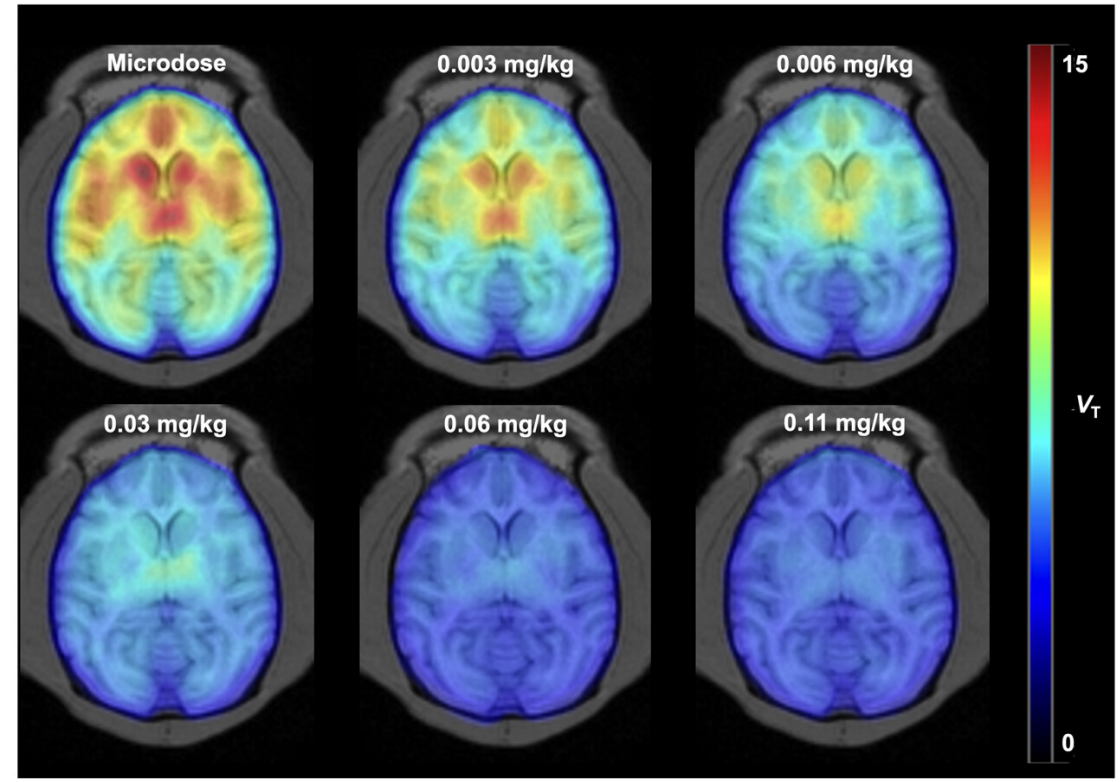
- Goal: Assess selectivity of [^{11}C]BUP to OR subtypes w/ blocking studies in rodent

Calculating Receptor Occupancy



$$r = \frac{1}{1 + \frac{EC_{50}}{[C]}}$$


A
Baseline
Naloxonazine
Naltrindole
Norbinaltorphimine
Naloxone
3
Uptake ratio
1
B
Baseline
Naloxonazine (μ-antagonist)
Naltrindole (δ-antagonist)
Norbinaltorphimine (κ-antagonist)
Naloxone (μ-, δ-, κ-antagonist)
Uptake ratio
Region / Cerebellum
0
1
2
3
4
5
***
ns
Amygdala
Striatum
Hippocampus
Thalamus
Hypothalamus
Cortex


Microdose
0.003 mg/kg
0.006 mg/kg
0.03 mg/kg
0.06 mg/kg
0.11 mg/kg
15
V_T
0

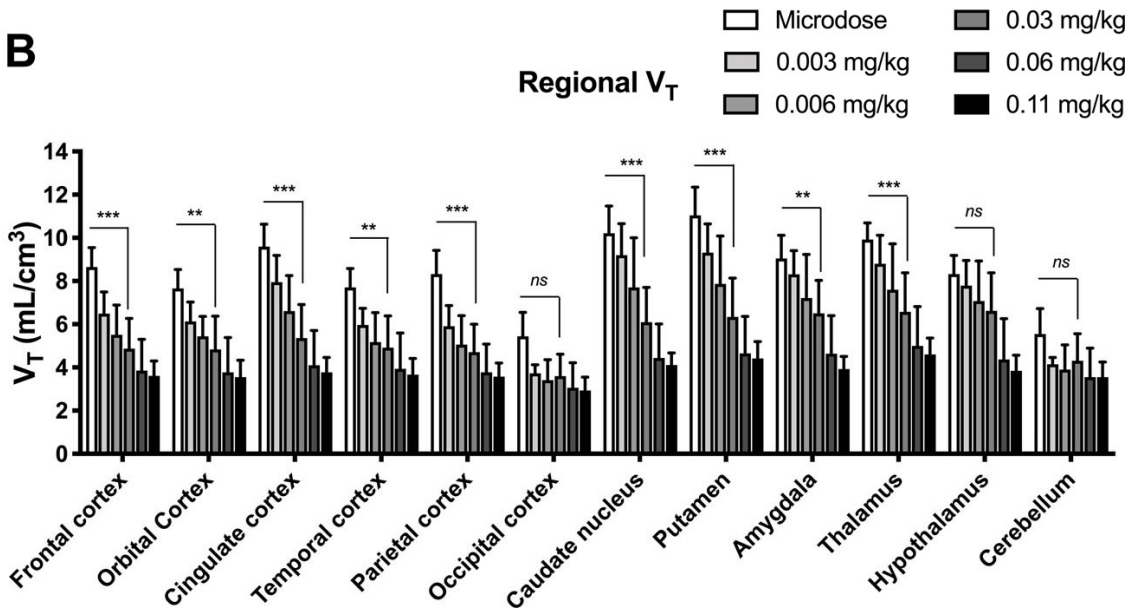

B
Regional V_T
Microdose
0.003 mg/kg
0.006 mg/kg
0.03 mg/kg
0.06 mg/kg
0.11 mg/kg
V_T (mL/cm^3)
14
12
10
8
6
4
2
0
***
**
***
**
***
ns
***
***
**
***
ns
ns
Frontal cortex
Orbital Cortex
Cingulate cortex
Temporal cortex
Parietal cortex
Occipital cortex
Caudate nucleus
Putamen
Amygdala
Thalamus
Hypothalamus
Cerebellum

Table 1. Outcome parameters obtained with PET pharmacokinetic modeling and in vivo binding experiments in macaques.

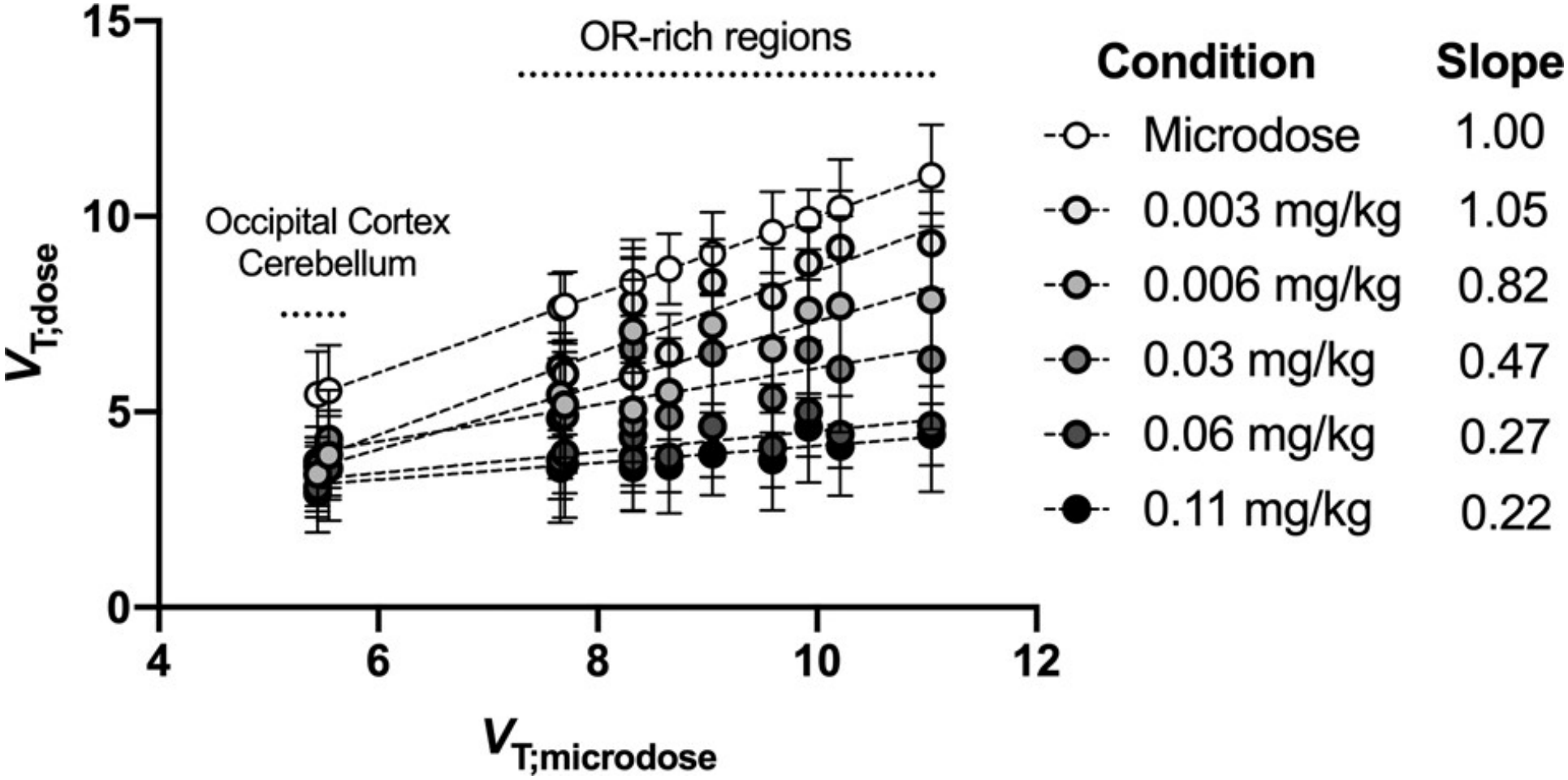
Brain region	$V_{ND,saturation}$ ($=V_{T,0.11\ mg/kg}$)	$V_{ND,graphical}$	$BP_{p,microdose}$	$DVR_{microdose}$	$DVR_{0.003\ mg/kg}$	Estimated receptor occupancy (%) associated with plasma levels of buprenorphine						EC_{50} (µg/L)
						0.3 µg/L	0.6 µg/L	1 µg/L	3 µg/L	6 µg/L	9 µg/L	
Frontal cortex	3.62 ± 0.68	3.44 ± 1.70	4.80 ± 0.75	1.40 ± 0.19	1.47 ± 0.11	33.2	49.7	62.1	82.7	90.2	93.1	0.60 (0.07–1.12)
Orbital cortex	3.56 ± 0.78	3.42 ± 1.33	4.01 ± 0.66	1.22 ± 0.15	1.39 ± 0.09	27.4	43.1	55.8	79.1	88.3	91.9	0.79 (0.30–1.30)
Cingulate cortex	3.77 ± 0.70	3.60 ± 1.78	5.48 ± 1.03	1.50 ± 0.28	1.67 ± 0.19	29.4	45.5	58.1	80.6	89.3	92.6	0.72 (0.33–1.11)
Temporal cortex	3.67 ± 0.75	3.46 ± 2.13	3.88 ± 0.83	1.26 ± 0.15	1.41 ± 0.05	31.0	47.4	60.0	81.8	90	93.1	0.67 (0.18–1.15)
Parietal cortex	3.57 ± 0.63	3.41 ± 1.80	4.48 ± 1.05	1.37 ± 0.13	1.40 ± 0.10	34.3	51.1	63.5	83.9	91.3	94	0.58 (0.20–0.95)
Occipital cortex	2.93 ± 0.62	2.84 ± 2.29	2.42 ± 1.05	NA	NA	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Caudate	4.11 ± 0.56	3.91 ± 1.80	5.82 ± 1.39	1.57 ± 0.31	1.8 ± 0.25	23.6	38.3	50.8	75.6	86.1	90.3	0.99 (0.43–1.50)
Putamen	4.42 ± 0.79	4.21 ± 1.83	6.41 ± 1.44	1.71 ± 0.31	1.9 ± 0.21	28.0	43.8	56.5	79.6	88.6	92.1	0.77 (0.34–1.20)
Amygdala	3.92 ± 0.59	[a]	4.90 ± 1.05	1.39 ± 0.24	1.62 ± 0.19	14.5	25.3	36.1	62.9	77.2	83.6	1.77 (0.60–2.94)
Thalamus	4.61 ± 0.76	4.33 ± 1.99	5.17 ± 0.93	1.54 ± 0.27	1.77 ± 0.19	23.4	37.9	50.4	75.3	85.9	90.1	0.98 (0.33–1.64)
Hypothalamus	3.85 ± 0.70	[a]	4.38 ± 0.79	1.27 ± 0.17	1.55 ± 0.08	23.4	37.9	50.4	75.3	85.9	90.1	0.98 (0.22–1.74)
Cerebellum	3.55 ± 0.70	3.43 ± 2.13	2.21 ± 0.93	1.06 ± 0.12	1.11 ± 0.05	[a]	[a]	[a]	[a]	[a]	[a]	[a]

V_{ND} is the non-displaceable volume of distribution. $V_{ND,saturation}$ has been estimated using the Logan plot method and the maximum co-injected dose of unlabeled buprenorphine ($V_{T,\ 0.11\ mg/kg}$). $V_{ND,graphical}$ has been graphically estimated (see Supplementary material and Supplementary Fig. S3). BP_p is the binding potential relative to the plasma kinetic of ^{11}C-buprenorphine. DVR is the distribution volume ratio estimated with the Logan reference method using the occipital cortex as the pseudo-reference region. EC_{50} is the estimated plasma concentration of buprenorphine associated with 50% of buprenorphine brain receptor occupancy.

Data are expressed as mean (receptor occupancy) or mean ± SD. Estimated EC_{50} are reported as mean (90% confidence interval).

NA non-applicable.

[a]Poorly estimated.


15
10
5
0
4
6
8
10
12
$V_{T;dose}$
$V_{T;microdose}$
OR-rich regions
Occipital Cortex
Cerebellum
Condition
Slope
Microdose 1.00
0.003 mg/kg 1.05
0.006 mg/kg 0.82
0.03 mg/kg 0.47
0.06 mg/kg 0.27
0.11 mg/kg 0.22

E. Estimation of buprenorphine receptor occupancy in brain regions

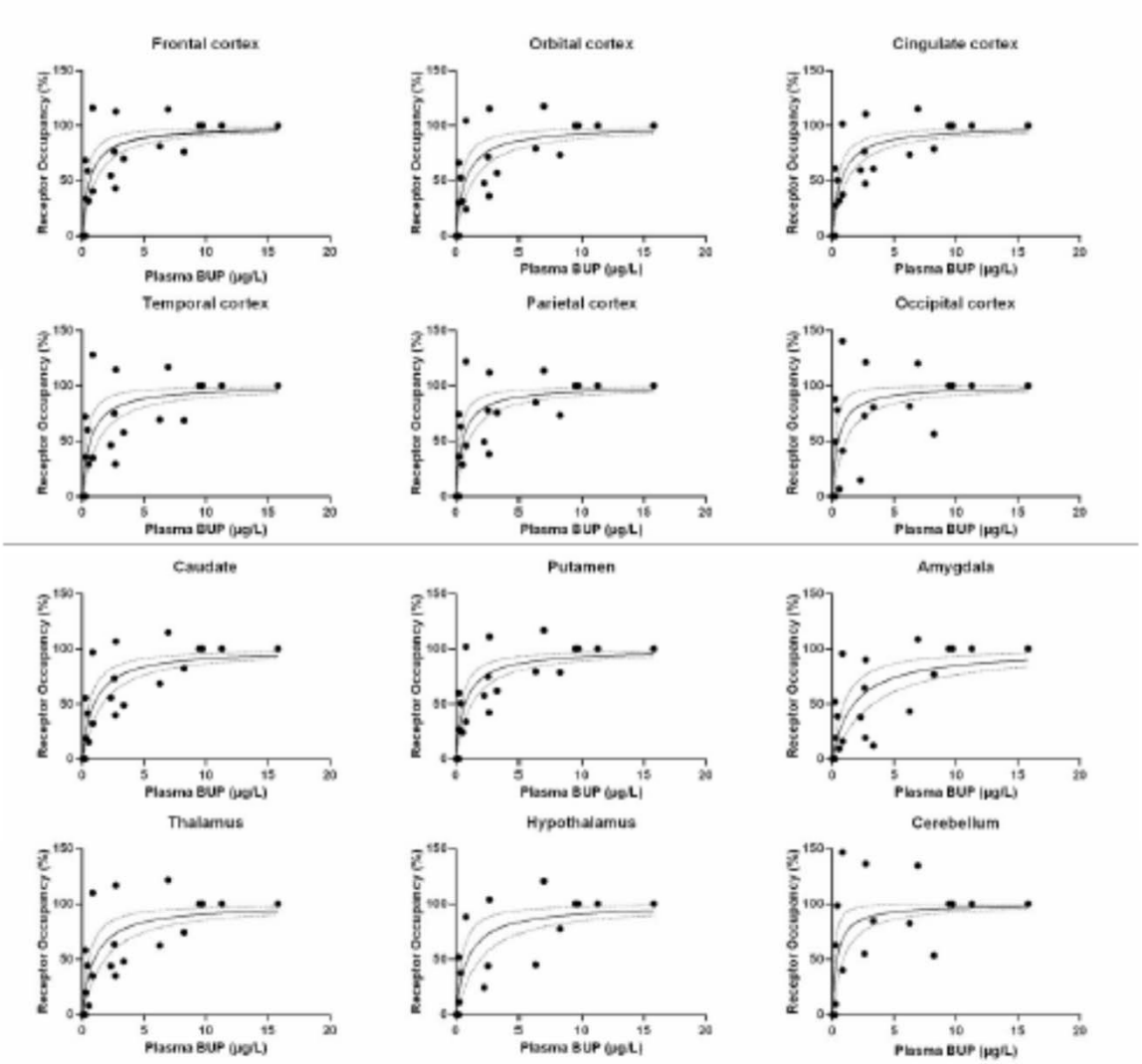
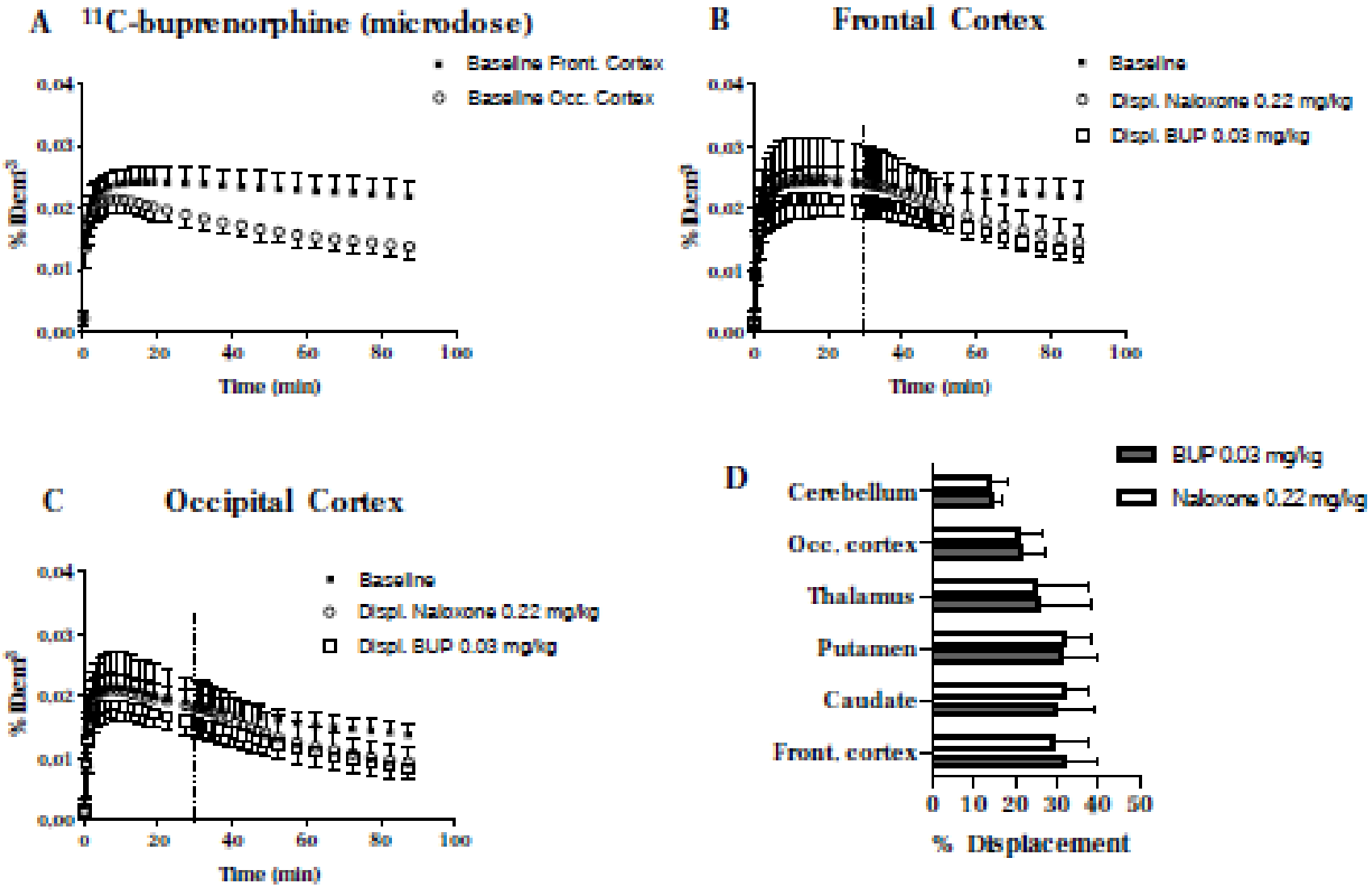
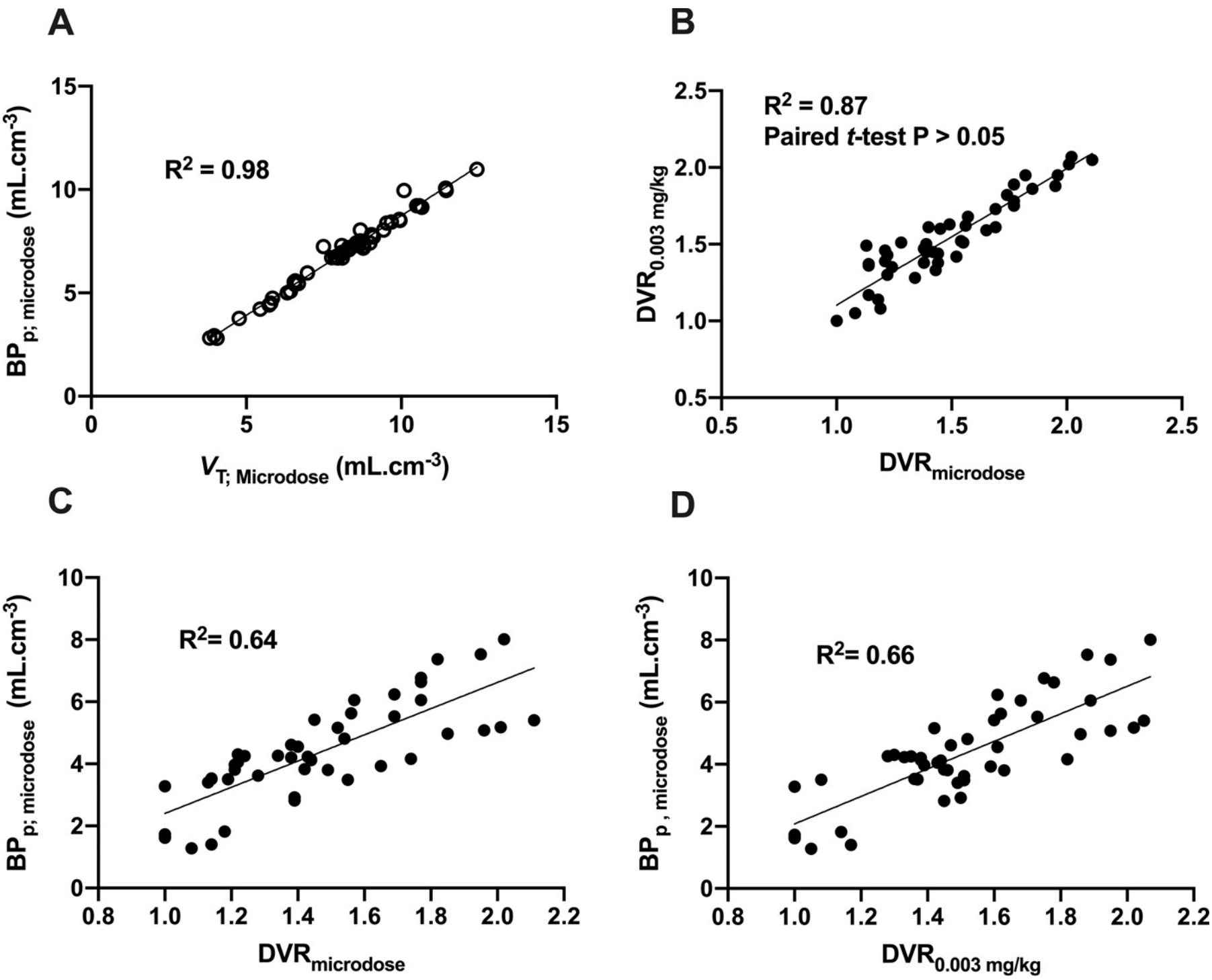


Fig. S4. Dose-related receptor occupancy (%) of ^{11}C-buprenorphine to selected brain regions. Non-linear regression analysis was performed to estimate the *in vivo* binding parameters of buprenorphine in brain regions.


A
^{11}C-buprenorphine (microdose)
Baseline Front. Cortex
Baseline Occ. Cortex
% Dcm³
Time (min)
B
Frontal Cortex
Baseline
Displ. Naloxone 0.22 mg/kg
Displ. BUP 0.03 mg/kg
% Dcm³
Time (min)
C
Occipital Cortex
Baseline
Displ. Naloxone 0.22 mg/kg
Displ. BUP 0.03 mg/kg
% Dcm³
Time (min)
D
BUP 0.03 mg/kg
Naloxone 0.22 mg/kg
Cerebellum
Occ. cortex
Thalamus
Putamen
Caudate
Front. cortex
% Displacement


A
R^2 = 0.98
$BP_{p;\ microdose}$ (mL.cm^{-3})
$V_{T;\ Microdose}$ (mL.cm^{-3})
0
5
10
15
B
R^2 = 0.87
Paired *t*-test P > 0.05
$DVR_{0.003\ mg/kg}$
$DVR_{microdose}$
0.5
1.0
1.5
2.0
2.5
C
R^2= 0.64
$BP_{p;\ microdose}$ (mL.cm^{-3})
$DVR_{microdose}$
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
D
R^2= 0.66
$BP_{p\ ,\ microdose}$ (mL.cm^{-3})
$DVR_{0.003\ mg/kg}$

Brain regions	Microdose ^{11}C-buprenorphine	^{11}C-buprenorphine + buprenorphine 0.003 mg/kg	^{11}C-carfentanil‡	^{11}C-diprenorphine‡
Frontal cortex	0.87	0.76	0.81	0.56
Orbital Cortex	0.77	0.75	*NA*	*NA*
Cingulate	0.97	0.91	0.98	0.72
Temporal cortex	0.78	0.72	0.79	0.56
Parietal cortex	0.84	0.69	0.69	0.48
Occipital cortex	0.55	0.45	0.31	0.27
Caudate nucleus	1.03	1.03	0.87	0.67
Putamen	1.11	1.05	*NA*	*NA*
Amygdala	0.91	0.94	0.85	0.81
Thalamus	1.00	1.00	1.00	1.00
Hypothalamus	0.84	0.92	NA	NA
Cerebellum	0.56	0.49	0.45	0.46

‡data reported from Frost et al. [6].