

**Table S7. Functional neuroimaging studies (conducted during 2000-2010) comparing neurotransmitter systems in individuals with addiction (S) and healthy controls (C).**

	Subjects	Abstinence length	Paradigm	Neurotransmitters	PFC results	Correlations with target or drug use
<b>Dopamine</b>						
Volkow, Chang et al. 2001	Meth 15 S 20 C	≥2 weeks	FDG + Raclopride	<b>S&lt;C</b> DA D2/3	NS	<b>DA D2/3 (+)</b> OFC
Volkow, Wang et al. 2005	Cocaine 21 S 15 C	14 days	FDG + Raclopride PL, iv MPH	<b>S&lt;C</b> DA D2/3 PL, MPH<PL	<b>S&lt;C PL&gt;MPH</b> ↑ R mOFC 25,11	<b>Drug desire &amp; mood (+)</b> R mOFC 25
Volkow, Wang et al. 2007	Alcohol 20 S 20 C	79 days	FDG + Raclopride PL, iv MPH	<b>S&lt;C</b> DA D2/3 PL, MPH<PL	NS	<b>DA D2/D3 change (+)</b> OFC 11, ACC 32, DLPFC 9 (C only)
Volkow, Wang et al. 2008	Obesity 10 S 12 C	NR	FDG + Raclopride	<b>S&lt;C</b> DA D2/3	NS	<b>DA D2/3 (+)</b> B DLPFC 9,45, ACC 32, L OFC 45, B PFC 10, vACC 25, mOFC 11
Fehr, Yakushev et al. 2008	Nicotine 17 S 21 C	As usual & 24 hours	Fallypride	<b>S&lt;C</b> DA D2/3	NA	<b>Desire to smoke (+)</b> L OFC <b>Desire to smoke (-)</b> B ACC, mACC
Narendran, Frankle et al. 2005	Ketamine 14 S 14 C	3 days	NNC 112	<b>S&gt;C</b> D1 (R DLPFC 9,46)	<b>S=C</b> DLPFC volume	<b>Drug use (+)</b> D1 (DLPFC)
<b>Opioid</b>						
Williams, Davies et al. 2009	Alcohol 11 S 13 C	14-30 days	Diprenorphine	<b>S&gt;C</b> 8% μ global receptor availability	NA	<b>Craving (+)</b> 17 of 21 a priori ROIs
Gorelick, Kim et al. 2005	Cocaine 17 S 16 C	1. ~24 hours 2. ~1 week 3. ~12 weeks	Carfentanil	<b>S&gt;C</b> μ receptor availability 1. B ACC/mFC, L aFC, B DLPFC, B PFC, R IFG 2. B ACC/mFC, L aFC, R PFC, R IFG 3. B ACC/mFC, L aFC (+progressive decrease)	NA	<b>Craving (+)</b> 1. L ACC, L FC, L PFC <b>Drug use (+)</b> 1. R ACC, R FC, B DLPFC (opposite for INS) <b>Craving (+)</b> 2. L FC, LPFC

	Subjects	Abstinence length	Paradigm	Neurotransmitters	PFC results	Correlations with target or drug use
Kling, Carson et al. 2000	Heroin 14 S 14 C	22 hours (after MMT)	Cyclofoxy	<b>S&lt;C</b> 19-32% $\mu<\kappa$ binding & $\uparrow$ B ACC, mPFC	NA	NS
Ghitza, Preston et al. 2010	Cocaine 25 S	NR (17 urine positive)	Carfentanil ( $\mu$ )	NA	NA	<b>Drug use (+)</b> R MidFG, L MedFG <b>Abstinence (-)</b> L medFG, L MidFG, L ACC
<b>Serotonin</b>						
Szabo, Owonikoko et al. 2004	Alcohol 15 S 17 C	17 years	(+)McN5652	<b>S&lt;C</b> DV global SERT & $\uparrow$ ACC, OFC	NA	<b>Abstinence (-)</b> DV (includes ACC, OFC, DLPFC)
Sekine, Ouchi et al. 2006	Meth 12 S 12 C	2 years	(+)McN5652	<b>S&lt;C</b> DV global SERT & $\uparrow$ B ACC, B DLPFC, B OFC	NA	<b>Drug use (-)</b> OFC
McCann, Szabo et al. 2008	MDMA 16 S 16 C	3 months	WIN 35,428 & DASB	<b>S&lt;C</b> DV global SERT & $\uparrow$ DLPFC, OFC, ACC	NA	NS

C controls, S subjects

Meth methamphetamine, MDMA 3,4-Methylenedioxymethamphetamine or Ecstasy, MMT methadone maintenance therapy, FDG positron emission tomography (PET) with [<sup>18</sup>F]fluorodeoxyglucose for glucose metabolism, PL placebo, MPH methylphenidate, iv intravenous administration, DA dopamine, D2/3 receptor availability (in striatum), DV distribution volume, SERT serotonin transporter

NR not reported, NA not applicable, NS not significant

ACC anterior cingulate cortex, dACC dorsal ACC, pgACC perigenual ACC, rACC rostral ACC, scACC subcallosal ACC, vACC ventral ACC, FC frontal cortex, aFC anterior FC, mFC middle FC, IFC inferior FC, PFC prefrontal cortex, mPFC medial PFC, dmPFC dorsomedial PFC, vmPFC ventromedial PFC, DLPFC dorsolateral PFC, vlPFC ventrolateral PFC, IFG inferior frontal gyrus, OFC orbitofrontal cortex, mOFC medial OFC, MedFG medial frontal gyrus, MidFG middle frontal gyrus, SFG superior frontal gyrus, INS insula, SMA supplementary motor area

(+) positive correlation, (-) negative correlation

R right, L left, B bilateral, CL central

If available:  $\uparrow$  increase/activation/hyperactivation,  $\downarrow$  decrease/deactivation/hypoactivation, Brodmann Areas are noted by numbers

Subject column is in italics if groups are matched on 2 of the following: age, sex, race, education

**References**

- Fehr, C., I. Yakushev, N. Hohmann, H. G. Buchholz, C. Landvogt, H. Deckers, A. Eberhardt, M. Klager, M. N. Smolka, A. Scheurich, T. Dielentheis, L. G. Schmidt, F. Rosch, P. Bartenstein, G. Grunder and M. Schreckenberger (2008). "Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse." *Am J Psychiatry* **165**(4): 507-14.
- Ghitza, U. E., K. L. Preston, D. H. Epstein, H. Kuwabara, C. J. Endres, B. Bencherif, S. J. Boyd, M. L. Copersino, J. J. Frost and D. A. Gorelick (2010). "Brain mu-opioid receptor binding predicts treatment outcome in cocaine-abusing outpatients." *Biol Psychiatry* **68**(8): 697-703.
- Gorelick, D. A., Y. K. Kim, B. Bencherif, S. J. Boyd, R. Nelson, M. Copersino, C. J. Endres, R. F. Dannals and J. J. Frost (2005). "Imaging brain mu-opioid receptors in abstinent cocaine users: time course and relation to cocaine craving." *Biol Psychiatry* **57**(12): 1573-82.
- Kling, M. A., R. E. Carson, L. Borg, A. Zametkin, J. A. Matochik, J. Schluger, P. Herscovitch, K. C. Rice, A. Ho, W. C. Eckelman and M. J. Kreek (2000). "Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts." *J Pharmacol Exp Ther* **295**(3): 1070-6.
- McCann, U. D., Z. Szabo, M. Vranesic, M. Palermo, W. B. Mathews, H. T. Ravert, R. F. Dannals and G. A. Ricaurte (2008). "Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/-)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance." *Psychopharmacology (Berl)* **200**(3): 439-50.
- Narendran, R., W. G. Frankle, R. Keefe, R. Gil, D. Martinez, M. Slifstein, L. S. Kegeles, P. S. Talbot, Y. Huang, D. R. Hwang, L. Khenissi, T. B. Cooper, M. Laruelle and A. Abi-Dargham (2005). "Altered prefrontal dopaminergic function in chronic recreational ketamine users." *Am J Psychiatry* **162**(12): 2352-9.
- Sekine, Y., Y. Ouchi, N. Takei, E. Yoshikawa, K. Nakamura, M. Futatsubashi, H. Okada, Y. Minabe, K. Suzuki, Y. Iwata, K. J. Tsuchiya, H. Tsukada, M. Iyo and N. Mori (2006). "Brain serotonin transporter density and aggression in abstinent methamphetamine abusers." *Arch Gen Psychiatry* **63**(1): 90-100.
- Szabo, Z., T. Owonikoko, M. Peyrot, J. Varga, W. B. Mathews, H. T. Ravert, R. F. Dannals and G. Wand (2004). "Positron emission tomography imaging of the serotonin transporter in subjects with a history of alcoholism." *Biol Psychiatry* **55**(7): 766-71.
- Volkow, N. D., L. Chang, G. J. Wang, J. S. Fowler, Y. S. Ding, M. Sedler, J. Logan, D. Franceschi, J. Gatley, R. Hitzemann, A. Gifford, C. Wong and N. Pappas (2001). "Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex." *Am J Psychiatry* **158**(12): 2015-21.
- Volkow, N. D., G. J. Wang, Y. Ma, J. S. Fowler, C. Wong, Y. S. Ding, R. Hitzemann, J. M. Swanson and P. Kalivas (2005). "Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction." *J Neurosci* **25**(15): 3932-9.
- Volkow, N. D., G. J. Wang, F. Telang, J. S. Fowler, J. Logan, M. Jayne, Y. Ma, K. Pradhan and C. Wong (2007). "Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement." *J Neurosci* **27**(46): 12700-6.

- Volkow, N. D., G. J. Wang, F. Telang, J. S. Fowler, P. K. Thanos, J. Logan, D. Alexoff, Y. S. Ding, C. Wong, Y. Ma and K. Pradhan (2008). "Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors." Neuroimage **42**(4): 1537-43.
- Williams, T. M., S. J. Davies, L. G. Taylor, M. R. Dalglis, A. Hammers, D. J. Brooks, D. J. Nutt and A. Lingford-Hughes (2009). "Brain opioid receptor binding in early abstinence from alcohol dependence and relationship to craving: an [11C]diprenorphine PET study." Eur Neuropsychopharmacol **19**(10): 740-8.