Title

No significant elevation of translocator protein binding in the brains of recently abstinent methamphetamine users.

Authors

London, Edythe D

Okita, Kyoji

Kinney, Kaitlin R

et al.

Publication Date

2020-08-01

Data Availability

The data associated with this publication are available upon request.

Peer reviewed

Drug and Alcohol Dependence 213 (2020) 108104

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

No significant elevation of translocator protein binding in the brains of recently abstinent methamphetamine users

Edythe D. London[a,b,c,d,*], Kyoji Okita[a,d,e,f], Kaitlin R. Kinney[a,d], Andrew C. Dean[a], Megan N. McClintick[a,d], Elizabeth J. Rizor[a,d], Maritza C. Johnson[a,d], Tarannom Mahmoudie[a,d], Arthur L. Brody[a,d,1], Erika L. Nurmi[a], Lauren C. Seaman[a], Judah Farahi[d], Nathaniel Ginder[a], Mark A. Mandelkern[d,g]

[a] Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, 90024, USA
[b] Department of Molecular and Medical Pharmacology, University of California Los Angeles (UCLA), Los Angeles, CA, 90024, USA
[c] Brain Research Institute, University of California Los Angeles (UCLA), Los Angeles, CA, 90024, USA
[d] Department of Research, Veterans Administration Greater Los Angeles Healthcare System (VAGLAHS), Los Angeles, CA, 90073, USA
[e] Department of Clinical Neuroimaging, Integrative Brain Imaging Center, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, 187-8551, Japan
[f] Department of Drug Dependence, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, 187-8551, Japan
[g] Department of Physics, University of California Irvine, Irvine, CA, 92697, USA

ARTICLE INFO

Keywords:
Neuroinflammation
Brain imaging
Methamphetamine
Stimulants
Translocator protein
Positron emission tomography

ABSTRACT

Background: Radioligands for the translocator protein (TSPO) 18 kDa have been used with positron emission tomography (PET) to assess neuroinflammation and microglial activation in psychiatric disorders. One study using this approach showed substantial TSPO elevation throughout the brain in chronic methamphetamine users following long-term abstinence (0.5–4 years), but clients typically present for treatment earlier in abstinence.
Methods: We used PET with [^{11}C]DAA1106 to compare standardized uptake values (SUVs) as an index of TSPO binding in the brains of methamphetamine-dependent participants who were abstinent for < 6 months (n = 11) and healthy controls (n = 12). We also assayed other typical correlates of Methamphetamine Dependence (e.g., striatal D2-type dopamine receptor deficits, depressed mood, anxiety and impaired emotion regulation).
Results: Methamphetamine users exhibited depression ($p < 0.0001$), anxiety ($p = 0.002$), difficulties in emotional regulation ($p = 0.01$), and lower striatal dopamine D2-type receptor availability vs. controls ($p = 0.02$). SUVs for [^{11}C]DAA1106 were larger in all brain regions of methamphetamine-dependent participants vs. controls, but the effect size was small to medium and not statistically significant.
Conclusions: The discrepancy between the lack of significant difference in TSPO binding in early-abstinent methamphetamine users vs. controls in this study and a previous report of elevated binding in longer-abstinent methamphetamine users may reflect methodological differences or limitations of TSPO binding as an index of neuroinflammation. It also seems possible that gliosis increases over time during the first 6 months of abstinence; longitudinal studies could clarify this possibility.

1. Introduction

While the age-adjusted rate of overdose deaths in the U.S. from prescription and illicit drugs declined from 2017 to 2018, deaths involving psychostimulants with abuse potential increased (Hedegaard et al., 2020). Effective medications are needed, and the immune system has been identified as a potential therapeutic target.

Methamphetamine alters immune function (Papageorgiou et al., 2019), producing reactive microgliosis (Pubill et al., 2002). Glial cell modulators reduce methamphetamine-induced behavioral abnormalities and neurotoxicity in rodents (Hashimoto et al., 2013). In clinical trials, ibudilast, which attenuates methamphetamine-induced increases

* Corresponding author at: Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, 760 Westwood Plaza, PO Box 175919, Los Angeles, CA, 90095, USA.
E-mail address: elondon@mednet.ucla.edu (E.D. London).
[1] Present address: Departments of Psychiatry and Research, VA San Diego Healthcare System, San Diego, CA; Department of Psychiatry, University of California, San Diego, CA 92161.

https://doi.org/10.1016/j.drugalcdep.2020.108104
Received 7 April 2020; Received in revised form 22 May 2020; Accepted 26 May 2020
Available online 11 June 2020
0376-8716/

in inflammatory markers (Kitazato et al., 2010; Lee et al., 2012), antagonized pro-inflammatory effects of methamphetamine (Li et al., 2000) but did not facilitate methamphetamine abstinence (Heinzerling et al., 2019).

Putative neuroinflammation and microglial activation in brain have been assessed using positron emission tomography (PET) with radiotracers targeting the translocator protein 18 kDa (TSPO). Using the TSPO radioligand, [^{11}C](R)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide) ([^{11}C](R)-PK11195), higher binding potential was observed in brains of long-term abstinent (0.5–4 years) methamphetamine users vs. controls (Sekine et al., 2008). Because most methamphetamine users approach treatment in earlier abstinence, we tested methamphetamine-dependent participants during the first 6 months of abstinence. The radiotracer used, [^{11}C]*N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2phenoxyphenyl) acetamide ([^{11}C]DAA1106), exhibits high specific binding in brain (Maeda et al., 2004) and [^{3}H]DAA1106 has higher affinity for TSPO than [^{3}H](R)-PK11195 (Venneti et al., 2008).

2. Methods

2.1. Participants

Written informed consent was obtained, as approved by the UCLA and VAGLAHS institutional review boards. Eligibility was determined using self-reports, physical examination, and the Structured Clinical Interview for DSM-IV (First et al., 1996) or the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Participants were classified into two groups: Methamphetamine-dependent, Control.

Exclusion criteria: CNS, cardiovascular, pulmonary, hepatic, or systemic disease; history of neurological disease or trauma with loss of consciousness > 30 min; structural brain abnormality; HIV seropositivity; pregnancy; lactation; English non-fluency; current psychotropic medication use; current psychiatric disorders other than Nicotine Dependence or Cannabis Abuse (allowed in both groups) or Methamphetamine Dependence (required for Methamphetamine group); any regular stimulant use (Control group); regular use (> once/week) of anti-inflammatory medications. Because smoking is prevalent among methamphetamine users and is associated with lower [^{11}C]DAA1106 binding in brain (Brody et al., 2017, 2018), daily smoking was required, verified by expired CO > 8 ppm and urinary cotinine (level > 2; Accutest NicAlert). Participants were genotyped for the single-nucleotide polymorphism (rs6971), which determines TSPO affinity and binding of second-generation TSPO radioligands (Owen et al., 2011, 2012); only high-affinity homozygotes were included.

Participants completed questionnaires about drug use, as well as the Fagerström Test for Nicotine Dependence (Fagerström, 1978; Heatherton et al., 1991), Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974), Spielberger State Trait Anxiety Index (STAI) (Spielberger and Gorsuch, 1983), and Difficulty in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004).

Methamphetamine-group participants were instructed to maintain abstinence from drugs of abuse ≥4 days before PET scans, demonstrating negative toxicology (methamphetamine, amphetamine, opiates, cocaine, benzodiazepines) and Breathalyzer tests (alcohol). Controls tested negative for abused substances except for cannabis and nicotine on screening and test days. All were instructed to abstain from smoking cigarettes for ≥12 h and cannabis for ≥48 h before PET scans. Because cannabinoids can be detected in urine for weeks, positive tests were allowed.

2.2. MRI scans and volumes of interest (VOIs)

MRI scans to guide anatomical sampling of PET data were acquired on a Siemens Trio (MPRAGE: repetition time = 1.9 s, echo time = 2.26 ms, voxel size = 1 mm^3, 176 slices), and processed using the FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/ index.html, Oxford University). Volumes of interest (VOIs) included the whole striatum for the D2-type receptor imaging, and an extended brain survey for TSPO binding (Table 2).

2.3. PET scans

TSPO binding (SUV) and D2-type dopamine receptor availability (BP_{ND}) were determined from PET scans acquired using a Philips Gemini TF PET-CT (transverse and axial resolution FWHM = 4.8 mm in the three-dimensional mode) (Brody et al., 2017; Crawshaw and Robertson, 2017). Participants lay on the scanning bed in the supine position. Images were obtained with a 2-mm voxel size (field of view = 128 × 128 × 90 mm^3). A low-dose CT scan, before each PET scan, provided data for attenuation correction.

For TSPO-binding scans, each participant received 352 ± 58.9 MBq of [^{11}C]DAA1106 (specific activity: 306.4 ± 118.3 MBq/μmol) as a venous bolus, and underwent dynamic PET brain scanning brain for 90 min. Radiotracer binding was quantified using standardized uptake values (SUVs) as follows: SUV = decay-corrected mean tissue activity (Bq/mL)/(injected dose (Bq)/body weight (g)). Mean tissue activity from 20 to 40 min post-injection, when brain radioactivity is stable, was used in this equation. For measurement of D2-type receptor BP_{ND}, participants received an intravenous bolus of 205.8 ± 12.8 MBq [^{18}F] fallypride (specific activity: 355.9 ± 240.8 MBq/μmol). Emission data were acquired in two 80-min blocks with a 20-min intermission.

Time-activity data within VOIs, extracted from PET images, were imported into PMOD Kinetic Modeling (PMOD Technologies Ltd). The simplified reference tissue model (Lammertsma and Hume, 1996) was used to calculate BP_{ND} fromVOI time–activity curves as follows: $C_T(t) = R_1C_R(t) + (k_2' - R_1k_2/(1 + BP_{ND}))C_R(t) * \exp(-k_2t/(1 + BP_{ND}))$ where $C_T(t)$ is the radioactivity in the striatum VOI measured by PET, $C_R(t)$ is the radioactivity in the reference region (cerebellum), $R_1 = K_1/K_1` = k_2/k_2`$ (K_1, influx rate parameter for the striatum; K_1' for the cerebellum, k_2, efflux rate parameter to plasma for the striatum, $k_2`$ for the cerebellum), and * denotes the convolution integral. The parameters R_1, k_2, and BP_{ND} were estimated by nonlinear regression.

2.4. Statistical analyses

Group differences in demographics, measures of mood and emotion regulation, and striatal D2-type BP_{ND} were evaluated using t-tests or Chi-square tests, as appropriate. Our primary analysis (analysis of variance) tested for a group difference in whole-brain [^{11}C]DAA1106) SUV, with age and sex tested as covariates to determine if they explained a significant portion of variance. For descriptive purposes, independent-samples t-tests were used to evaluate group differences in SUV in 17 volumes of interest (VOIs). Because SUVs among regions were highly correlated (r > 0.90), we used the single whole-brain SUV in linear regressions to test associations with BDI, STAI trait anxiety, total DERS scores in each group, and past-month methamphetamine use (Methamphetamine group). Age, which was consistently significant, was included as a covariate in these regressions

3. Results

The groups did not differ in age, sex distribution, education level, cannabis or alcohol use in the month before screening, daily cigarette consumption, or nicotine dependence (Table 1). Methamphetamine participants reported heavy methamphetamine use (24.18 ± 8.13 days, past month). Two met criteria for Cannabis Dependence, and three for Cannabis Abuse; no Control participants met these criteria although one endorsed using cannabis daily. Methamphetamine participants were typical of those tested before in our lab, differing significantly from controls ($p < 0.05$) by having lower striatal D2-type BP_{ND} (−18.8 %), higher depressive symptoms and anxiety, and greater difficulty in

Table 1
Participant Characteristics.

	Control (n = 12)	Methamphetamine (n = 11)	Group Comparison p-value
Sex (*# of women / # of men)*	5 / 7	2 / 9	0.240
Age (years) [a]	33.8 ± 7.48	38.3 ± 9.31	0.219
Education (years) [a]	13.5 ± 2.10	13.4 ± 3.01	0.499
Race (% of participants)			
Caucasian	2	7	
African American	8	3	
Mixed	1	1	
Other	1	0	
Ethnicity (# of participants)			
Hispanic/Latino	2	5	
Not Hispanic/Latino	10	v6	
Other	0	0	
Striatal dopamine D2-type receptor binding (BP_{ND}) [a,b]	28.8 ± 2.16	23.4 ± 6.6	0.0135*
Self-Reports of Mood and Emotional States [a]			
Depressive symptoms [c]	1.17 ± 1.53	13.73 ± 9.19	0.0001****
Trait Anxiety [d]	28.58 ± 8.80	42.64 ± 10.14	0.002**
Difficulty in Emotion R egulation [e]	54.25 ± 15.96	74.91 ± 19.83	0.012*
Substance Use[a]			
Methamphetamine (days in past 30)	0 ± 0	24.18 ± 8.13	N/A
Average grams per day	0 ± 0	0.62 ± 0.31	N/A
Days abstinent at [^{11}C]DAA scan		35.18 ± 57.57	N/A
Cannabis (days in past 30)	8.09 ± 12.25	4.25 ± 8.70	0.393
Alcohol (days in past 30)	3.92 ± 5.07	5.6 ± 6.88	0.619
Tobacco (all participants daily smokers)			
Cigarettes per day [a]	9.00 ± 7.37	7.36 ± 6.52	0.580
Nicotine Dependence [f]	3.33 ± 2.77	2.27 ± 2.65	0.180

[a] Mean ± standard deviation.
[b] Determined using [^{18}F]fallypride and positron emission tomography (see methods).
[c] Beck Depression Inventory (Beck and Beamesderfer, 1974).
[d] Y-2 form of the State-Trait Anxiety Inventory (Spielberger and Gorsuch, 1983).
[e] Difficulties in Emotional Regulation Scale, total score (Gratz and Roemer, 2004).
[f] Fagerström Test for Nicotine Dependence (Fagerström, 1978; Heatherton et al., 1991).

emotion regulation (London et al., 2004; Okita et al., 2016). At the time of [^{11}C]DAA1106 scan, they were abstinent for 35.2 ± 57.6 days (range = 4 days to 24 weeks, median = 6 days).

Whole brain SUV for [^{11}C]DAA1106 did not differ significantly between groups ($p = 0.363$); age and sex, which did not account for significant variance in this analysis, were not retained ($ps > 0.05$). The group difference in whole-brain SUV had a small-to-medium effect size (Cohen's D = 0.356, upper limit of 90 % CI = 0.89), indicating a requirement for n = 94 to detect a significant difference with 80 % power at $p < 0.05$. Means in every VOI were non-significantly higher in the Methamphetamine group (5.3–19.8 %, Table 2). Whole-brain SUV was not significantly associated with measures of mood and emotion regulation, except for a positive relationship between SUV and DERS score in Control participants ($p = 0.008$, nonsignificant after multiple-comparisons correction).

4. Discussion

TSPO binding was not significantly elevated in the brains of 12 abstinent methamphetamine-dependent participants vs. 11 controls, whereas substantially higher TSPO binding in methamphetamine users vs. controls was observed in a prior study of similar size (Sekine et al., 2008). Methodological differences possibly affecting this discrepancy were differences between the radiotracers, [^{11}C]PK11195 having lower affinity than [^{11}C]DAA1106 and low specific signal-to-background ratio (Banati et al., 2000; Venneti et al., 2008). Moreover, we quantified [^{11}C]DAA1106 binding using SUV, a measure that is limited by not being validated against the full model to test for bias and systematic errors (Acton et al., 2004). Sekine et al. (2008) determined [^{11}C]PK11195 binding potential using a normalized [^{11}C]PK11195 time-activity curve from the cortex of healthy controls as a reference-tissue input function to model regions of interest in methamphetamine users.

The samples differed. Our participants all endorsed daily cigarette smoking, which is associated with lower TSPO binding in brain (Brody et al., 2017, 2018); Sekine et al. (2008) studied participants who did not meet DSM-IV smoking-related criteria. Duration of methamphetamine abstinence also differed. Our participants were abstinent from methamphetamine ≤5.5 months, most for only 4–7 days; Sekine et al. (2008) studied participants in sustained abstinence (0.5–4 years). Although Sekine et al. (2008) showed inverse correlation of binding in some brain regions with duration of abstinence > 6 months, microglial activation may increase in brain during earlier abstinence, consistent with the increase in cerebral glucose metabolism over the first month of abstinence (Berman et al., 2008). Increasing glial cell number is thought to increase cerebral metabolism (Roh et al., 1998).

Lack of a positive finding on TSPO binding here is consistent with a postmortem study in which levels of several protein markers of microgliosis and astrogliosis did not differ in samples of autopsied brain of chronic methamphetamine users vs. matched controls (Tong et al., 2014). Half of the methamphetamine samples in that study were from individuals who died of drug intoxication, and therefore not in long-term abstinence. A very recent *in vivo* study using PET and [^{18}F]FEPPA another second-generation TSPO radioligand, also showed no group difference as well (Rathitharan et al., 2020)

The ubiquity of TSPO in brain, especially at the blood-brain barrier (Turkheimer et al., 2007), and its interaction with numerous ligands, such as cholesterol (Kim et al., 2018), preclude assigning specificity of TSPO-imaging findings to microglial activation. Notably, a study using mouse models of schizophrenia showed changes in TSPO levels that involved astrocytes and vascular endothelial cells as well as microglia, and PET imaging revealed a trend towards reduced TSPO binding in the middle frontal gyrus of patients who had recent-onset schizophrenia and increased levels of inflammatory cytokines in peripheral and central tissues (Notter et al., 2018).

Table 2
Brain Uptake of [^{11}C]DAA1106 in Control and Methamphetamine-Dependent Participants[a].

	Control (n = 12)	Methamphetamine (n = 11)	Δ% vs. Control	Group Comparison p
Whole Brain	0.77 ± 0.15	0.85 ± 0.28	9.9	0.363
Brain Regions[b]				
Cerebral Cortex				
Orbitofrontal	0.84 ± 0.18	0.94 ± 0.28	11.2	0.292
Dorsolateral Prefrontal	0.85 ± 0.18	1.01 ± 0.32	17.2	0.141
Dorsomedial Prefrontal	0.84 ± 0.18	0.98 ± 0.33	15.4	0.215
Ventrolateral Prefrontal	0.84 ± 0.16	0.95 ± 0.29	12.3	0.297
Ventromedial Prefrontal	0.80 ± 0.19	0.90 ± 0.30	11.8	0.332
Anterior Cingulate	0.73 ± 0.17	0.89 ± 0.32	19.8	0.140
Insular	0.78 ± 0.16	0.87 ± 0.29	10.9	0.357
Temporal	0.76 ± 0.14	0.85 ± 0.27	11.2	0.337
Parietal	0.85 ± 0.17	0.96 ± 0.32	12.2	0.283
Occipital	0.92 ± 0.16	0.97 ± 0.30	5.3	0.569
Hippocampus	0.69 ± 0.13	0.76 ± 0.26	9.7	0.429
Caudate Nucleus	0.69 ± 0.17	0.74 ± 0.26	7.0	0.592
Putamen	0.83 ± 0.17	0.91 ± 0.30	9.2	0.400
Nucleus Accumbens	0.76 ± 0.17	0.85 ± 0.30	11.2	0.356
Globus Pallidus	0.64 ± 0.13	0.70 ± 0.23	9.0	0.431
Amygdala	0.63 ± 0.12	0.69 ± 0.23	9.1	0.450
Thalamus	0.82 ± 0.16	0.87 ± 0.29	5.9	0.566

The groups did not differ significantly in body mass [Control: 80.36 ± 16.9 kg; Methamphetamine: 80.8 ± 15.7 kg] or injected dose [Control: 1026 ± 201 MBq; Methamphetamine: 1091 ± 200 m Bq], which were used to determine SUV values.

[a] All values are means ± standard deviations.

[b] For descriptive purposes only, independent-samples t-tests were used to evaluate group differences in SUV in 17 VOIs, p values are not adjusted for multiple comparisons.

4.1. Conclusions

TSPO binding is not significantly elevated in brains of early-abstinent methamphetamine-dependent participants, questioning the role of inflammation in the behavioral problems they exhibit. Testing whether brain inflammation increases with duration of early abstinence from methamphetamine is warranted, and requires longitudinal studies using direct markers for microglial activation.

Role of funding source

Nothing declared.

Contributors

EDL conceived of and designed the study, directed the program, and wrote the first and final drafts of the manuscript. KO, ALB and MAM developed the PET acquisition and analysis procedures for TSPO binding; KO and MAM took part in all PET studies; MAM was responsible for nuclear medicine oversight and shared in responsibility for statistical analysis with ACD; MNM, KRK, EJR, TM, and MCJ took part in data acquisition; KRK conducted data analyses (with guidance from MNM, MAM, and ACD). ELN and LCS provided genetic analysis. JF prepared radiotracers. NG provided medical support. ALB, KO, ACD, MNM, and MAM critically reviewed the report and proposed revisions. All authors approved of the final manuscript.

Support

The Katherine K. and Thomas P. Pike Chair in Addiction Studies (EDL) and the Marjorie Greene Family Trust (EDL). Also supported by the Tobacco-Related Disease Research Program (#28IR-0064; ALB) and the National Institute on Drug Abuse (R01DA044909; ALB). The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of Competing Interest

No conflict declared.

References

Acton, P.D., Zhuang, H., Alavi, A., 2004. Quantification in PET. Radiol. Clin. North Am. 42, 1055–1062.

Banati, R.B., Newcombe, J., Gunn, R.N., Cagnin, A., Turkheimer, F., Heppner, F., et al., 2000. The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. Brain 123, 2321–2337.

Beck, A.T., Beamesderfer, A., 1974. Assessment of depression: the depression inventory. In: In: Pichot, P., Olivier-Martin, R. (Eds.), Psychological Measurements in Psychopharmacology. Mod. Trends Pharmacopsychiatry Vol. 7. Karger, Basel, pp. 151–169.

Berman, S.M., Voytek, B., Mandelkern, M.A., Hassid, B.D., Isaacson, A., Monterosso, J., et al., 2008. Changes in cerebral glucose metabolism during early abstinence from chronic methamphetamine abuse. Mol. Psychiatry 13, 897–908.

Brody, A.L., Hubert, R., Enoki, R., Garcia, L.Y., Mamoun, M.S., et al., 2017. Effect of overnight smoking abstinence on a marker for microglial activation: a [(11)C] DAA1106 positron emission tomography study. Neuropsychopharmacology 42, 1630–1639.

Brody, A.L., Gehlbach, D., Garcia, L.Y., Enoki, R., Hoh, C., Vera, D., et al., 2018. Effect of cigarette smoking on a marker for neuroinflammation: a [(11)C]DAA1106 positron emission tomography study. Psychopharmacology 235, 3525–3534.

Crawshaw, Ania, Robertson, Neil, 2017. The role of TSPO PET in assessing neuroinflammation. J. Neurol. 265 (8), 1825–1827. https://doi.org/10.1007/s00415-017-8565-1.

Fagerström, K.O., 1978. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3 (34), 235–241.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1996. Structured clinical interview for the DSM-IV Axis I disorders. Am. Psychiatr. Press.

Gratz, K.L., Roemer, L., 2004. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J. Psychopathol. Behav. Assess. 26, 41–54.

Hashimoto, K., Ishima, T., Fujita, Y., Zhang, L., 2013. Antibiotic drug minocycline: a potential therapeutic drug for methamphetamine-related disorders. Nihon Arukoru Yakubutsu Igakkai Zasshi 48, 118–125.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerström, K.O., 1991. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. Br. J. Addict. 86, 1119–1127.

Hedegaard, H., Miniño, A.M., Warner, M., 2020. Drug Overdose Deaths in the United States, 1999–2018. NCHS Data Brief, No 356. National Center for Health Statistics, Hyattsville, MD.

Heinzerling, K.G., Briones, M., Thames, A.D., Hinkin, C.H., Zhu, T., Wu, Y.N., et al., 2019. Randomized, placebo-controlled trial of targeting neuroinflammation with ibudilast to treat methamphetamine use disorder. J. Neuroimmune Pharmacol. https://doi.

org/10.1007/s11481-019-09883-w. [published online ahead of print, Dec 9].
Kim, S.W., Wiers, C.E., Tyler, R., Shokri-Kojori, E., Jang, Y.J., et al., 2018. Influence of alcoholism and cholesterol on TSPO binding in brain: PET [^{11}C]PBR28 studies in humans and rodents. Neuropsychopharmacology 43, 1832–1839.
Kitazato, K.T., Tamura, T., Tada, Y., Yagi, K., Satomi, J., Nagahiro, S., 2010. Ibudilast inhibits cerebral aneurysms by down-regulating inflammation-related molecules in the vascular wall of rats. Neurosurgery 66, 551–559.
Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. Neuroimage 4, 153–158.
Lee, J.-Y., Cho, E., Ko, Y.E., Kim, I., Lee, K.J., Kwon, S.U., et al., 2012. Ibudilast, a phosphodiesterase inhibitor with anti-inflammatory activity, protects against ischemic brain injury in rats. Brain Res. 1431, 97–106.
Li, M.J., Briones, M.S., Heinzerling, K.G., Kalmin, M., Shoptaw, S.J., 2000. Ibudilast attenuates peripheral inflammatory effects of methamphetamine in patients with methamphetamine use disorder. Drug Alcohol Depend. 206, 107776.
London, E.D., Simon, S.L., Berman, S.M., Mandelkern, M.A., Lichtman, A.M., Bramen, J., et al., 2004. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. Arch. Gen. Psychiatry 61, 73–84.
Maeda, J., Suhara, T., Zhang, M.-R., Okauchi, T., Yasuno, F., Ikoma, Y., et al., 2004. Novel Peripheral Benzodiazepine Receptor Ligand [11C]DAA1106 for PET: An Imaging Tool for Glial Cells in the Brain. Synapse 52 (4), 283–291. https://doi.org/10.1002/syn.20027.
Notter, T., Coughlin, J.M., Gschwind, T., Weber-Stadlbauer, U., Wang, Y., Kassiou, M., et al., 2018. Translational evaluation of translocator protein as a marker of neuroinflammation in schizophrenia. Mol. Psychiatry 23, 323–334.
Okita, K., Ghahremani, D.G., Payer, D.E., Robertson, C.L., Dean, A.C., Mandelkern, M.A., et al., 2016. Emotion dysregulation and amygdala dopamine D2-type receptor availability in methamphetamine users. Drug Alcohol Depend. 161, 163–170.
Owen, D.R., Gunn, R.N., Rabiner, E.A., Bennacef, I., Fujita, M., Kreisl, W.C., et al., 2011. Mixed-affinity binding in humans with 18-kDa translocator protein ligands. J. Nucl. Med. 52, 24.
Owen, D.R., Yeo, A.J., Gunn, R.N., Song, K., Wadsworth, G., Lewis, A., et al., 2012. An 18-kDa Translocator Protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. J. Cereb. Blood Flow Metab. 32, 1–5.
Papageorgiou, M., Raza, A., Fraser, S., Nurgali, K., Apostolopoulos, V., 2019. Methamphetamine and its immune-modulating effects. Maturitas 221, 13–21.
Pubill, D., Verdaguer, E., Sureda, F.X., Camins, A., Pallàs, M., Camarasa, J., et al., 2002. Carnosine prevents methamphetamine-induced. Gliosis but not dopamine terminal loss in rats. Eur. J. Pharmacol. 448, 165–168.
Rathitharan, G., Truong, J., Tong, J., McCluskey, T., Meyer, J.H., Mizrahi, R., et al., 2020. Microglia imaging in methamphetamine use disorder: a positron emission tomography study with the 18 kDa translocator protein radioligand [F-18]FEPPA [published online ahead of print, 2020 Feb 4]. Addict. Biol. e12876. https://doi.org/10.1111/adb.12876.
Roh, J.K., Nam, H., Lee, M.C., 1998. A case of central pontine and extrapontine myelinolysis with early hypermetabolism on 18FDG-PET scan. J. Korean Med. Sci. 13, 99–102.
Sekine, Y., Ouchi, Y., Sugihara, G., Takei, N., Yoshikawa, E., Nakamura, K., et al., 2008. Methamphetamine causes microglial activation in the brains of human abusers. J. Neurosci. 28, 5756–5761.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., et al., 1998. The mini-international neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33 quiz 34-57.
Spielberger, C.D., Gorsuch, R.L., 1983. Manual for the State-Trait Anxiety Inventory (Form Y). Consulting Psychologists Press, Palo Alto, CA.
Tong, J., Fitzmaurice, P., Furukawa, Y., Schmunk, G.A., Wickham, D.J., Ang, L.-C., Sherwin, A., McCluskey, T., Boileau, I., Kish, S.J., 2014. Is brain gliosis a characteristic of chronic methamphetamine use in the human? Neurobiol. Dis. 67, 107–118.
Turkheimer, F.E., Edison, P., Pavese, N., Roncaroli, F., Anderson, A.N., Hammers, A., Gerhard, A., Hinz, R., Tai, Y.F., Brooks, D.J., 2007. Reference and target region modeling of [^{11}C]-(R)- PK11195 brain studies. J. Nucl. Med. 48, 158–167.
Venneti, S., Wang, G., Nguyen, J., Wiley, C.A., 2008. The positron emission tomography ligand DAA1106 binds with high affinity to activated microglia in human neurological disorders. J. Neuropathol. Exp. Neurol. 67, 1001–1010.