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

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### 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.

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#### 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.

Declaration of Competing Interest

No conflict declared.

**Methods:** We used PET with [<sup>11</sup>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 [<sup>11</sup>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.

## Keywords

Neuroinflammation; Brain imaging; Methamphetamine; Stimulants; Translocator protein; Positron emission tomography

## 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 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, [<sup>11</sup>C](R)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide) ([<sup>11</sup>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, [<sup>11</sup>C]N-(2,5-dimethoxybenzyl)-N-(5-fluoro-2phenoxyphenyl) acetamide ([<sup>11</sup>C]DAA1106), exhibits high specific binding in brain

(Maeda et al., 2004) and [<sup>3</sup>H]DAA1106 has higher affinity for TSPO than [<sup>3</sup>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 [<sup>11</sup>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<sup>3</sup>, 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<sub>ND</sub>) 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<sup>3</sup>). 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 [<sup>11</sup>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<sub>ND</sub>, participants received an intravenous bolus of 205.8 ± 12.8 MBq [<sup>18</sup>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<sub>ND</sub> from VOI time-activity curves as follows:  $C_T(t) = R_1 C_R(t) + (k_2' - R_1 k_2 / (1 + BP_{ND})) C_R(t) * \exp(-k_2 t / (1 + BP_{ND}))$  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<sub>ND</sub> were estimated by nonlinear regression.

### 2.4. Statistical analyses

Group differences in demographics, measures of mood and emotion regulation, and striatal D2-type BP<sub>ND</sub> 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 [<sup>11</sup>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<sub>ND</sub> (-18.8%), higher depressive symptoms and anxiety, and greater difficulty in emotion regulation (London et al., 2004; Okita et al., 2016). At the time of [<sup>11</sup>C]DAA1106 scan, they were abstinent for  $35.2 \pm 57.6$  days (range = 4 days to 24 weeks, median = 6 days).

Whole brain SUV for [<sup>11</sup>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, [<sup>11</sup>C]PK11195 having lower affinity than [<sup>11</sup>C]DAA1106 and low specific signal-to-background ratio (Banati et al., 2000; Venneti et al., 2008). Moreover, we quantified [<sup>11</sup>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 [<sup>11</sup>C]PK11195 binding potential using a normalized [<sup>11</sup>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 [<sup>18</sup>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).

#### 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.

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**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) <sup>a</sup>	33.8 ± 7.48	38.3 ± 9.31	0.219
Education (years) <sup>a</sup>	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 (BPND) <sup>a,b</sup>	28.8 ± 2.16	23.4 ± 6.6	0.0135*
Self-Reports of Mood and Emotional States <sup>a</sup>			
Depressive symptoms <sup>c</sup>	1.17 ± 1.53	13.73 ± 9.19	0.0001****
Trait Anxiety <sup>d</sup>	28.58 ± 8.80	42.64 ± 10.14	0.002**
Difficulty in Emotion R regulation <sup>e</sup>	54.25 ± 15.96	74.91 ± 19.83	0.012*
Substance Use <sup>a</sup>			
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 [ <sup>11</sup> 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 <sup>a</sup>	9.00 ± 7.37	7.36 ± 6.52	0.580

	Control ( <i>n</i> = 12)	Methamphetamine ( <i>n</i> = 11)	Group Comparison <i>p</i> -value
Nicotine Dependence <sup><i>f</i></sup>	3.33 ± 2.77	2.27 ± 2.65	0.180

<sup>*a*</sup>Mean ± standard deviation.

<sup>*b*</sup>Determined using [<sup>18</sup>F]fallypride and positron emission tomography (see methods).

<sup>*c*</sup>Beck Depression Inventory (Beck and Beamesderfer, 1974).

<sup>*d*</sup>Y-2 form of the State-Trait Anxiety Inventory (Spielberger and Gorsuch, 1983).

<sup>*e*</sup>Difficulties in Emotional Regulation Scale, total score (Grazt and Roemer, 2004).

<sup>*f*</sup>Fagerström Test for Nicotine Dependence (Fagerström, 1978; Heatherlton et al., 1991).

**Table 2**

Brain Uptake of [<sup>11</sup>C]DAA1106 in Control and Methamphetamine-Dependent Participants<sup>a</sup>.

	Control (n = 12)	Methamphetamine (n = 11)	% vs. Control	Group Comparison p
Whole Brain	0.77 ± 0.15	0.85 ± 0.28	9.9	0.363
Brain Regions <sup>b</sup>				
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.

<sup>a</sup>All values are means ± standard deviations.

<sup>b</sup>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.