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# Propofol Decreases In Vivo Binding of $^{11}\text{C}$ -PBR28 to Translocator Protein (18 kDa) in the Human Brain

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The PET radioligand  $^{11}\text{C}$ -PBR28 targets translocator protein (18 kDa) (TSPO) and is a potential marker of neuroimmune activation in vivo. Although several patient populations have been studied using  $^{11}\text{C}$ -PBR28, no investigators have studied cognitively impaired patients who would require anesthesia for the PET procedure, nor have any reports investigated the effects that anesthesia may have on radioligand uptake. The purpose of this study was to determine whether the anesthetic propofol alters brain uptake of  $^{11}\text{C}$ -PBR28 in healthy subjects. **Methods:** Ten healthy subjects (5 men; 5 women) each underwent 2 dynamic brain PET scans on the same day, first at baseline and then with intravenous propofol anesthesia. The subjects were injected with  $680 \pm 14$  MBq (mean  $\pm$  SD) of  $^{11}\text{C}$ -PBR28 for each PET scan. Brain uptake was measured as total distribution volume ( $V_T$ ) using the Logan plot and metabolite-corrected arterial input function. **Results:** Propofol decreased  $V_T$ , which corrects for any alteration of metabolism of the radioligand, by about 26% ( $P = 0.011$ ). In line with the decrease in  $V_T$ , brain time-activity curves showed decreases of about 20% despite a 13% increase in plasma area under the curve with propofol. Reduction of  $V_T$  with propofol was observed across all brain regions, with no significant region  $\times$  condition interaction ( $P = 0.40$ ). **Conclusion:** Propofol anesthesia reduces the  $V_T$  of  $^{11}\text{C}$ -PBR28 by about 26% in the brains of healthy human subjects. Given this finding, future studies will measure neuroimmune activation in the brains of autistic volunteers and their age and sex-matched healthy controls using propofol anesthesia. We recommend that future PET studies using  $^{11}\text{C}$ -PBR28 and concomitant propofol anesthesia, as would be required in impaired populations, include a control arm to account for the effects of propofol on brain measurements of TSPO.

**Key Words:** anesthesia; cognitive impairment; neuroinflammation

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Neuroimmune activation is measured in vivo using PET radioligands that target translocator protein (18 kDa) (TSPO) (1). Several groups have studied neuroimmune activation in this way in healthy subjects and in patients with various diseases, including epilepsy, multiple sclerosis, small strokes, and mild to moderate Alzheimer dementia (2–5). No published reports exist on patient populations with more profound cognitive or communicative impairments, as these patients are unable to tolerate the technical aspects of PET studies, which may include placement of an arterial line and intravenous lines, as well as remaining motionless in the scanner for about 2 h.

Deep sedation or anesthesia is necessary for patients who are unable to tolerate the requirements of clinical and research imaging studies, such as MRI or PET (6–8). The effects of anesthetic agents on the binding of various PET radioligands to their target receptors are highly variable (9). Binding of the PET radioligand may be decreased (10), increased (11), or unchanged (12) with the addition of anesthesia. For example, in healthy human volunteers, sevoflurane was found to increase  $\gamma$ -aminobutyric acid type A ( $\text{GABA}_A$ ) receptor binding of  $^{11}\text{C}$ -flumazenil (13). In contrast, ketamine does not affect  $\text{GABA}_A$  receptor binding (12), suggesting that different anesthetics will produce different outcomes that do not necessarily correlate with what is known about the preferential affinities for various anesthetics and receptors in the brain. Ouchi et al. demonstrated that in monkeys, the effects on receptor binding can vary among brain regions and with the concentration of anesthetic (14). The finding that there is a dose effect of anesthetic has also been shown for isoflurane in  $\text{GABA}_A$  receptor density measurements (15). In summary, the literature indicates that anesthetics can increase, decrease, or not affect radioligand binding to a target receptor, and these findings may vary across brain regions and with anesthetic dose.

To our knowledge, no published reports exist on the effects of anesthesia on radioligands that target TSPO. In this first human study on the effects of anesthesia on TSPO binding in vivo, we selected the anesthetic propofol because of widespread use in clinical settings, a quick onset of

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action, and a favorable safety profile when used in a well-controlled setting (16). Of the radioligands that target TSPO, we selected  $^{11}\text{C}$ -PBR28 (17), because it has high sensitivity to specificity (18), because low-affinity binders of this radioligand (which occur in about 10% of the population) can be readily excluded using a peripheral blood assay, and because the 20-min half-life of  $^{11}\text{C}$  makes it feasible to perform PET on each subject twice in a day without concern for residual radioactivity. Although heterozygous and homozygous variants of a single nucleotide polymorphism confer mixed-affinity and high-affinity binding states (19), we planned an intrasubject comparison to look at the effects of propofol, thus making this polymorphic variant irrelevant for the main outcome measure of this study.

In sum, the specific purpose of this study was to determine whether intravenous propofol affects brain uptake of  $^{11}\text{C}$ -PBR28 in healthy subjects. The results of this study can be used to inform the design of future studies in patients who would require anesthesia, including those with more profound impairment of cognition, communication, and anxiety, as is seen in autism.

## MATERIALS AND METHODS

### Radiopharmaceutical Preparation

We synthesized  $^{11}\text{C}$ -PBR28 as described in our Investigational New Drug Application 76,441 (<http://pdsf.med.unc.edu/snidd/>) (20). In brief, we methylated the *O*-desmethyl analog of  $^{11}\text{C}$ -PBR28 using  $^{11}\text{C}$ -iodomethane. Using reverse-phase high-performance liquid chromatography, we then isolated  $^{11}\text{C}$ -PBR28. Radiochemical purity was greater than 97%. Specific activity at the time of injection was  $92.9 \pm 50.2$  GBq/ $\mu\text{mol}$  (mean  $\pm$  SD,  $n = 20$ ).

### Human Subjects

Approval for this study was obtained from the Combined Neurosciences Institutional Review Board of the National Institute of Mental Health and the Radiation Safety Committee of the National Institutes of Health. Verbal and written informed consent was obtained from all subjects in this study. We included subjects who were considered medically and psychiatrically healthy on the basis of history, Structured Clinical Interview for DSM Disorders–Nonpatient, Wechsler Abbreviated Scale of Intelligence (21,22), Social Responsiveness Scale, physical examination, electrocardiography, urine toxicology, urinalysis, and blood testing (complete metabolic profile; complete blood count with differential; thyroid stimulating hormone level; rapid plasma Reagin test for syphilis; HIV; hepatitis A, B, and C antibody testing; and vitamin B12 level). Before the PET scans, we confirmed that none of the participants were low-affinity binders via *in vitro* competitive binding assays using peripheral leukocytes (19). Full eligibility criteria are available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01322555). The participants in this study were 10 healthy subjects: 5 men and 5 women; age,  $29.8 \pm 7.2$  y; weight,  $83.0 \pm 19.2$  kg; and body mass index,  $26.5 \pm 4.2$ .

### MRI Procedures

Each subject underwent 1.5- or 3-T clinical brain MRI to exclude anatomic abnormalities before study enrollment. The scan series included T1-weighted, T2-weighted, and fluid attenuation inversion recovery sequences in the axial and coronal orientations. MRI data were also used for normalization of PET data into Montreal Neurologic Institute space.

### PET Scan Procedures

We followed the general procedure for PET image acquisition and reconstruction described previously by our group (23). An arterial catheter was placed in the radial artery after good collateral circulation had been confirmed. We monitored for safety by checking blood (complete blood count with differential, complete metabolic profile, and thyroid-stimulating hormone) and urine (urinalysis) within 24 h before and after the PET scans. For the baseline (awake) scan, blood pressure was obtained before tracer injection and at 15, 30, and 60 min after injection. The electrocardiogram was continuously monitored during the scan. Data were acquired on an Advance Nxi tomograph (GE Healthcare), which has a reconstructed resolution of 5.3 mm in full width at half maximum at the center of field of view in all directions in 3-dimensional mode. We acquired an 8-min transmission scan of the brain using rotating  $^{68}\text{Ge}$  rods for subsequent attenuation correction. We then administered  $680 \pm 15$  MBq (range, 662–714 MBq;  $n = 20$ ;  $688 \pm 13$  baseline scans;  $673 \pm 14$  scans with propofol; within-subject difference,  $2.6\% \pm 3.1\%$ ) of  $^{11}\text{C}$ -PBR28 intravenously over 60 s using a PHD 2000 syringe pump. We acquired 33 frames of dynamic emission scans, with acquisition cycles increasing in duration from 30 s to 5 min. In total, the emission scan was 120 min. PET images were reconstructed with ordered-subset expectation maximization in 33 subsets with 4 iterations and were corrected for attenuation.

### Intravenous Propofol Sedation and Anesthesia

All subjects were evaluated by an anesthesiologist before enrolling in this study. Intravenous propofol sedation and anesthesia were performed as described by Bishu et al. (24). In brief, the subjects fasted for the 8 h preceding propofol administration. After completing the baseline PET scan while awake, they were provided the opportunity to empty their bladders. They then returned to the scanner and were reconnected to monitors including continuous electrocardiography, arterial blood pressure, capnography, oxygen saturation, and skin temperature. A continuous infusion of propofol was initiated intravenously about 15 min before radioligand injection. A nasopharyngeal airway was inserted after loss of the corneal blink reflex to ensure airway patency. Propofol was continuously administered over the subsequent 120-min emission scan to ensure motionlessness and lack of verbal response. On completion of the scan, all subjects were monitored for about 1 h in the postanesthesia care unit until the discharge criteria of that unit were met. The subjects were discharged from the hospital the following morning.

### Analysis of PET Images

PET images were analyzed as previously described (23), with minor modifications. Data were reconstructed on a  $128 \times 128$  matrix with a pixel size of  $2.0 \times 2.0 \times 4.25$  mm in the *x*-, *y*-, and *z*-axes, respectively. All data were corrected for attenuation and scatter. Frames were realigned relative to frame 18 and then were co-registered to each subject's MRI scan using Statistical Parametric Mapping 8 (Wellcome Department of Cognitive Neurology). PET and MRI data were normalized to Montreal Neurologic Institute space and then imported into pixelwise modeling software PMOD 3.2 (PMOD Technologies), where the anatomic automatic labeling template was applied to obtain radioactivity counts across the following 10 brain regions: frontal cortex, parietal cortex, occipital cortex, striatum, thalamus, cingulum, hippocampus–amygdala, insula, thalamus, and cerebellum. Data from bilateral regions were the mean of both the left and the right regions. Radiometabolite-corrected arterial input function and the Logan plot (25) were used for all subjects to

calculate total distribution volume ( $V_T$ ) because, in 1 subject, an unconstrained 2-compartment model applied in a previous report (23) gave unrealistic  $V_T$  values that were 5–10 times greater than the  $V_T$  of the other subjects because of unusually slow washout from the brain and poor identifiability of  $k_4$ .

### Statistical Analysis of Outcome Measures

Outcome measures ( $V_T$ , free fraction of radioligand [ $f_p$ ], and area under the curve [AUC] of parent radioligand in plasma) (26) in baseline versus propofol-sedated groups were analyzed using SPSS 15.0 software (release 19.0.0; SPSS Inc.). The Wilcoxon signed-rank test was applied for comparisons between  $f_p$  and AUC, because the Shapiro–Wilk test indicated significant deviations from a normal distribution.  $V_T$  values in the 10 regions were compared between awake and anesthetized conditions using within-subject, 2-way repeated-measures ANOVA. Statistically significant values were defined as those having a  $P$  value of less than 0.05.

## RESULTS

### Clinical Characteristics of Participants

The demographics of the study participants reflect a cohort balanced by sex and race and demonstrating average intelligence without evidence of impaired social reciprocity (Table 1). We selected younger adults for this study (mean age,  $26.5 \pm 7.3$ ;  $n = 10$ ) to assess a more homogeneous population unlikely to be influenced by any age-related changes in TSPO (4). The cohort was slightly overweight (body mass index,  $26.5 \pm 4.2$ ,  $n = 10$ ), reflecting the population of adults in the local area (27). Although we excluded low-affinity binders of  $^{11}\text{C}$ -PBR28, 7 of 10 subjects were heterozygous for the Ala147Thr polymorphism of TSPO, conferring mixed-affinity binding (19,28). Because this study had an intrasubject design, the affinity state of each individual did not affect statistical comparisons between baseline and propofol PET scans.

### Adverse Events

There were no adverse events related to propofol in this study, consistent with other reports that propofol is safe when administered in a well-controlled setting by an anesthesiologist (16). The only adverse event in this study was a pre-syncope vasovagal episode during insertion of the first intravenous line in a subject hours before administration of propofol or radioligand. Each subject in this protocol demonstrated a clear sensorium before discharge from the hospital.

### Decreased Binding of TSPO

Propofol anesthesia decreased binding of TSPO by about 26% ( $F_{1,9} = 10.10$ ,  $P = 0.011$ ), as measured by the decreased  $V_T$  of  $^{11}\text{C}$ -PBR28 (Fig. 1). This reduction in  $V_T$  was observed globally across brain regions, with no significant region X condition interaction ( $P = 0.40$ ). Given that we had no a priori hypotheses regarding specific brain regions that might be affected more than others, data were analyzed using Logan plotting of large regions of interest. For our primary outcome measure, we applied the Logan plot rather than an unconstrained 2-compartment model (23) because the latter inaccurately measured  $V_T$  in 1 subject because of poor identifiability of  $k_4$ . By excluding the subject with poor  $k_4$

**TABLE 1**  
Clinical Demographics

Parameter	Value
Sex ( $n$ )	
Male	5
Female	5
Race ( $n$ )	
Caucasian	6
African-American	2
Asian	1
Hispanic	1
Age (y)	
Mean $\pm$ SD	$28.5 \pm 7.3$
Range	21–41
Body mass index	
Mean $\pm$ SD	$26.5 \pm 4.2$
Range	19.8–33.8
TSPO polymorphism ( $n$ )	
Mixed-affinity binders	7
High-affinity binders	3 (19)
Social Responsiveness Scale (39)*	
Mean $\pm$ SD	$19.0 \pm 10.0$
Range	11–35
Verbal IQ†	
Mean $\pm$ SD	$107.2 \pm 11.2$
Range	90–125
Performance IQ	
Mean $\pm$ SD	$114.0 \pm 9.1$
Range	103–133
Total IQ	
Mean $\pm$ SD	$111.7 \pm 9.3$
Range	97–125

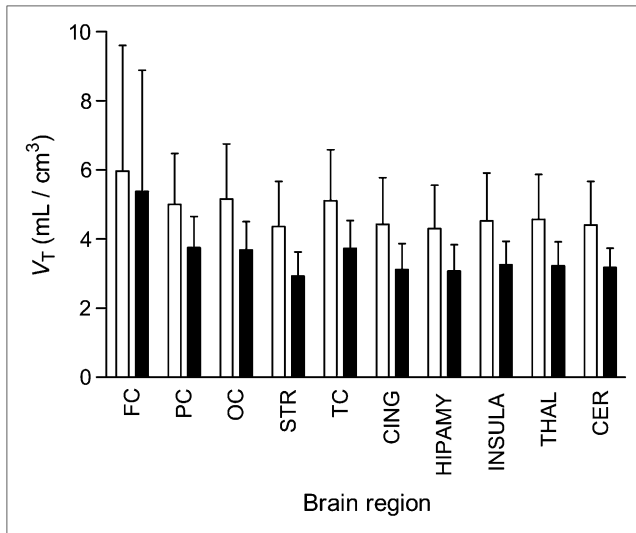
\*All scores were well below 59; approximate threshold is indicative of impaired social reciprocity (40).

†IQ measurements were based on Wechsler Abbreviated Scale of Intelligence (22).

identifiability, we obtained a similar reduction in  $V_T$  by both the unconstrained 2-compartment model and the Logan plot, which supported application of the Logan plot for all subjects in the current study. After exclusion of 1 subject, the Logan plot showed a decrease of 26% in  $V_T$  ( $F_{1,8} = 7.53$ ,  $P = 0.025$ ), and an unconstrained 2-compartment model obtained a similar decrease of 32% in  $V_T$  ( $F_{1,8} = 9.32$ ,  $P = 0.016$ ).

### Insignificant Differences in Plasma Free Fraction Between Baseline and Propofol Scans

To control for any effects that propofol or its solvents might have had on concentrations of free radioligand, we calculated  $f_p$  for each subject before each scan (baseline and propofol). These data were collected because it is unknown whether propofol changes concentrations of free  $^{11}\text{C}$ -PBR28 (as may happen indirectly by displacing  $^{11}\text{C}$ -PBR28 from plasma proteins, for example) and only free  $^{11}\text{C}$ -PBR28 is available to enter the brain. Blood for measurement of  $f_p$  was obtained from each subject's arterial line about 5 min before radioligand injection. In parallel with obtaining plasma data from each subject at each scan, we measured  $f_p$  from a control blood sample obtained from a composite of healthy volun-



**FIGURE 1.** Decreased binding of TSPO as measured by  $V_T$  of  $^{11}\text{C}$ -PBR28 across brain regions. Relative to baseline scans (white bars),  $V_T$  is about 26% ( $P = 0.011$ ) lower in scans with propofol anesthesia (black bars). Error bars denote SD. FC = frontal cortex; PC = parietal cortex; OC = occipital cortex; STR = striatum; TC = temporal cortex; CING = cingulum; HIPAMY = hippocampus-amygdala; INSULA = insula; THAL = thalamus; CER = cerebellum.

teers from other studies. We then normalized  $f_p$  from all scans using measurements from the pooled control blood sample to account for fluctuations in day-to-day measurements of  $f_p$  (29). Using this approach, we found insignificant differences ( $P = 0.83$ ) in  $f_p$  between baseline and propofol scans ( $f_p$  was  $3.91\% \pm 0.96\%$  and  $3.82\% \pm 0.58\%$  in baseline and propofol scans, respectively).

Although only insignificant differences in  $f_p$  between the baseline and propofol studies were noted, the variability of measurements was moderate to high (30). For baseline studies,  $f_p$  was  $3.9 \pm 1.0$  (coefficient of variance, 25%), and for propofol studies,  $f_p$  was  $3.8 \pm 0.6$  (coefficient of variance, 15%). The source of the high variability in  $f_p$  measurements was unclear but could have resulted from technical differences in blood processing, such as time between obtaining and processing the sample and operator differences. Given that insignificant differences in  $f_p$  between the baseline and propofol scans were observed in conjunction with a moderate to high degree of variability in  $f_p$ , we decided to report  $V_T$  (as opposed to  $V_T/f_p$ ) as the outcome measure for this study.

#### Lower Brain Activity but Higher Plasma Concentrations of Parent Radioligand in Scans Obtained with Propofol

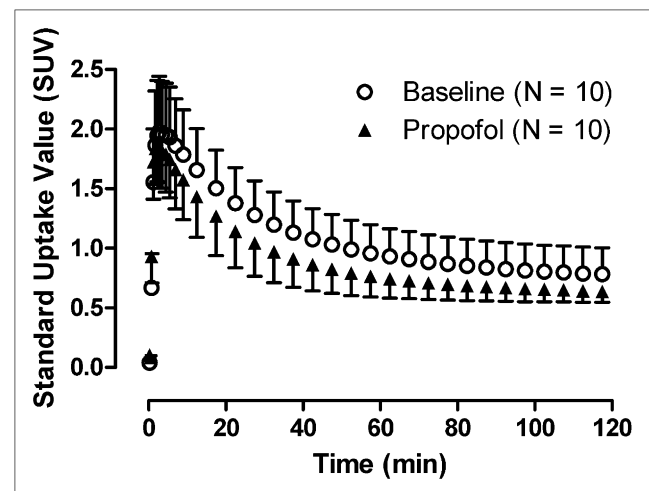
We compared both brain activity and plasma concentrations of parent radioligand in the baseline and propofol scans to determine whether the decreased  $V_T$  observed in the propofol scans might be an artifact resulting from decreased levels of available parent radioligand. Propofol significantly decreased brain activity calculated as AUC by 20% (baseline,  $126.8 \pm 15.4$  standardized uptake value [SUV]·min; with propofol,  $105.4 \pm 11.4$  SUV·min;  $P < 0.001$ ; Fig. 2).

If plasma discrepancies could explain this change in brain activity, we would expect to see lower plasma concentrations of parent radioligand in propofol studies. However, we observed the opposite—plasma concentrations of parent radioligand were higher in scans obtained with propofol (Fig. 3). For plasma curves, the peak was higher for propofol scans, consistent with a 13% higher calculated AUC for propofol scans ( $5,418 \pm 637$  SUV·min) versus baseline scans ( $4,803 \pm 727$  SUV·min) ( $P = 0.02$ ) (Fig. 3). Furthermore, the greater decrease in  $V_T$  (26%) than in brain activity (20%) is well explained by the 13% higher levels of plasma  $^{11}\text{C}$ -PBR28 with propofol because  $V_T$  is equivalent to the AUC of brain divided by that of plasma  $^{11}\text{C}$ -PBR28 from time zero to infinity. Therefore, our main outcome of decreased TSPO binding ( $V_T$ ) in the presence of propofol was unlikely to have been only an artifactual outcome secondary to changes in metabolism or blood profiles.

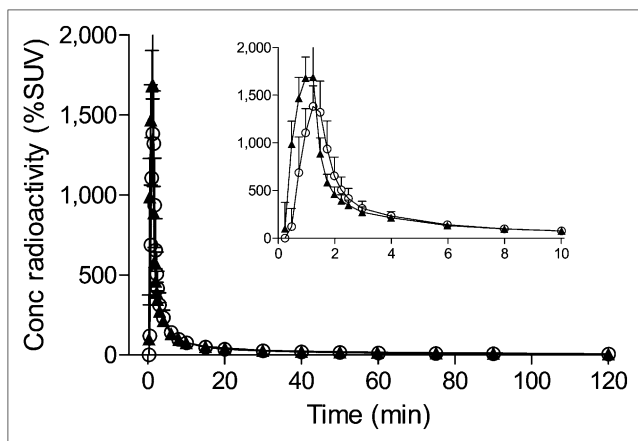
#### DISCUSSION

The main outcome of this study was that TSPO binding was decreased in the presence of propofol anesthesia by about 26% ( $P = 0.011$ ). Reduction of TSPO binding was observed globally across all brain regions. Furthermore, no clear confounders were noted when considering possible artifactual causes of this main outcome, including altered arterial input function (Fig. 3) and differences in technical procedures (Table 2). It should also be noted that  $V_T$  is in theory independent of cerebral blood flow (31), and we acquired both brain and blood data far beyond the peak time, ensuring no artifacts from cerebral blood flow (Figs. 2 and 3).

Thus, propofol altered  $^{11}\text{C}$ -PBR28 binding to the TSPO receptor and this finding cannot be attributed to an artifactual effect. We do not know how or why receptor binding



**FIGURE 2.** Mean brain time-activity curves for 10 subjects over entire brain show that, compared with baseline scans, scans acquired with propofol demonstrate SUV reduced by about 20% (baseline,  $126.8 \pm 15.4$  SUV·min; with propofol,  $105.4 \pm 11.4$  SUV·min). Time-activity curves for other 10 brain regions showed similar pattern of reduction in SUV with addition of propofol. Peak SUV in baseline and propofol scans was about 2.0.



**FIGURE 3.** Plasma concentrations of parent radioligand are higher in sedated scans. Time–activity curves show percentage SUV vs. time (min) for baseline (○) vs. propofol (▲) scans. Peak is higher for sedated scans, consistent with our higher calculation of AUC for propofol (5,418 SUV·min) vs. baseline (4,803 SUV·min) scans. Inset shows data from 0 to 10 min, and larger graph shows data from entire scan. Of note, there appears to be little variation in tails of blood curves.

may have changed. For some neurotransmitter receptors, decreased binding was hypothesized to be caused by release of the native neurotransmitter in the presence of anesthetic (13,15). Such a condition would not apply to TSPO, which has no endogenous neurotransmitter and which is protected intracellularly as protein in the outer membrane of mitochondria (32). We can only speculate.

Propofol has several mechanisms of action that might affect TSPO binding of a radioligand. These include reduction of GABA in the cerebrospinal fluid of the spinal cord (33), retraction of neurites in glial cells (34), retrograde movement of synaptic vesicles in cortical neurons (35), reduced phosphorylation of mitogen-activated protein kinases involved in GABA<sub>A</sub> signal transduction (36), reduction in neurotransmitter release via SNAREs (soluble *N*-ethylmaleimide-sensitive factor receptor attachment proteins) (37), and blockage of sodium channels (38).

No reports exist implicating these mechanisms as directly involved in TSPO stability, processing, localization, or affinity state. A host of indirect interactions could also account for our

observation that TSPO binding of the radioligand is reduced with propofol. For example, it is possible that reducing GABA<sub>A</sub> signal transduction decreases a terminal signaling molecule that serves as a cofactor for TSPO stability. Without this cofactor, TSPO may not be in the appropriate conformation to bind radioligand. Lastly, the literature lacks negative results on any interactions between propofol and TSPO. Published molecular studies, whether positive or negative, are needed to address the mechanisms for reducing TSPO binding by <sup>11</sup>C-PBR28 in the presence of propofol.

Regardless of the precise mechanisms, our data have demonstrated that healthy human subjects anesthetized with propofol have a 26% decrease in TSPO binding in vivo. Further, although safety evaluation of the anesthesia regimen used is beyond the scope of this study, others have demonstrated the safety of propofol sedation and anesthesia in both clinical (16) and research (6,7) settings. In keeping with the findings of others, our use of propofol sedation and anesthesia in healthy volunteers was not associated with any untoward events. We are now measuring neuroimmune activation in the brains of individuals with autism using <sup>11</sup>C-PBR28 PET scans under propofol sedation and anesthesia. Future studies will compare data obtained from autistic individuals with data from healthy controls without autism, all of whom were scanned using propofol. We recommend that future PET studies assessing TSPO in the context of propofol deep sedation and anesthesia (as would be required in impaired populations) contain a control arm to account for the effects of propofol. Such a control arm may also prove useful for other study designs using anesthesia, which may affect radioligand uptake.

## CONCLUSION

Propofol anesthesia reduces the  $V_T$  of <sup>11</sup>C-PBR28 by about 26% in the brains of healthy human subjects. Given this finding, future studies will measure neuroimmune activation in the brains of autistic volunteers and their age- and sex-matched healthy controls using propofol anesthesia. We recommend that future PET studies using <sup>11</sup>C-PBR28 and concomitant propofol anesthesia, as would be required in impaired populations, include a control arm to account for the effects of propofol on brain measurements of TSPO.

**TABLE 2**  
Comparison of Parameters in Baseline ( $n = 10$ ) Versus Propofol ( $n = 10$ ) Scans

Parameter	Baseline	Propofol	% change	<i>P</i>
Injected mass associated with radioactive dose (nmol/kg)	0.092 ± 0.04	0.098 ± 0.03	+6.5%	0.35
Radiochemical purity (%)	97.6 ± 1.8	97.9 ± 0.7	+0.3%	0.33
Plasma <sub>50%</sub> (min)	9.66 ± 2.3	10.84 ± 2.7	+12.2%	0.09
$T_{max}$ (min)	1.36 ± 0.14	1.13 ± 0.12	-16.9%	0.00
Parent plasma AUC <sub>0→120</sub>	4,803.2 ± 726.8	5,418.2 ± 637.2	+12.8%	0.02

% change = (propofol – baseline)/baseline; plasma<sub>50%</sub> (min) = time from peak to 50% decrease from peak of <sup>11</sup>C-PBR28 concentration in arterial plasma; AUC<sub>0→120</sub> = area under curve of <sup>11</sup>C-PBR28 concentration in arterial plasma calculated from time 0 to 120 min.

## DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. PMOD Technologies (Zurich, Switzerland) provided its image analysis software. No potential conflict of interest relevant to this article was reported.

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