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RESEARCH ARTICLE

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Limited power of dopamine transporter mRNA mapping for predicting dopamine transporter availability

Kyoungjune Pak[1] | Seongho Seo[2] | Myung Jun Lee[3] | Hyung-Jun Im[4] | Keunyoung Kim[1] | In Joo Kim[1]

[1] Department of Nuclear Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

[2] Department of Electronic Engineering, Pai Chai University, Daejeon, Republic of Korea

[3] Department of Neurology, Pusan National University Hospital, Busan, Republic of Korea

[4] Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Republic of Korea

Correspondence
Kyoungjune Pak, Department of Nuclear Medicine, Pusan National University Hospital 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea.
Email: ilikechopin@me.com

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Abstract

Dopamine transporters (DAT) are transmembrane proteins that translocate dopamine from the extracellular space into presynaptic neurons. We aimed to investigate the predictive power of DAT mRNA for DAT protein expression, measured using positron emission tomography (PET). We performed ^{18}F-FP-CIT PET scans in 35 healthy individuals. Binding potentials (BP_{ND}) from the ventral striatum, caudate nucleus, putamen, and middle frontal, orbitofrontal, cingulate, parietal, and temporal cortices were measured. DAT gene expression data were obtained from the freely available Allen Human Brain Atlas derived from six healthy donors. The auto-correlation of PET-derived BP_{ND}s for DAT was intermediate (mean ρ^2 = .66) with ρ^2 ranging from .0811 to 1. However, the auto-correlation of mRNA expression was weak across the probes with a mean ρ^2 of .09–.23. Cross-correlations between PET-derived BP_{ND}s and mRNA expression were weak with a mean ρ^2 ranging from 0 to .22 across the probes. In conclusion, we observed weak associations between DAT mRNA expression and DAT availability in human brains. Therefore, DAT mRNA mapping may have only limited predictive power for DAT availability in humans. However, the difference in distribution of DAT mRNA and DAT protein may influence this limitation.

KEYWORDS
dopamine plasma membrane transport proteins, messenger RNA, positron emission tomography

1 | INTRODUCTION

Dopamine is a neurotransmitter that plays a major role in reward-motivated behavior and motor control (Salamone & Correa, 2013). Dopamine neurotransmission is regulated by dopamine transporters (DATs), transmembrane proteins that actively translocate dopamine from the extracellular space into presynaptic neurons in the dopaminergic system (Vaughan & Foster, 2013). DAT dysfunction is linked to neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (Roessner et al., 2010), bipolar disorder (Mick et al., 2008), and alcohol use disorder (Du et al., 2011). In addition, DAT is a major target for various pharmacologically active drugs (Lee et al., 2021; Vaughan & Foster, 2013).

The Allen Human Brain Atlas is a freely available multi-modal atlas of gene expression and anatomy of all brain regions (Shen et al., 2012). Six post-mortem brains were analyzed for microarray-based expression, in situ hybridization gene expression, and magnetic resonance imaging-based brain mapping (Shen et al., 2012). Previous studies have determined the predictive power of brain mRNA mapping of the Allen Human Brain Atlas after comparison with positron emission tomography (PET)-derived protein expression data for serotonin receptors (Beliveau et al., 2017; Komorowski et al., 2017; Rizzo et al., 2014), serotonin transporters (Beliveau et al., 2017; Komorowski et al., 2017), opioid receptors (Rizzo et al., 2014), and

monoamine oxidase A (MAO-A) (Komorowski et al., 2017; Zanotti-Fregonara et al., 2014). Therefore, we measured striatal DAT availability using dynamic PET scans with ^{18}F-FP-CIT, a high-affinity radioligand for DAT (Pak et al., 2019) to measure DAT protein expression.

We hypothesized that DAT mRNA expression could predict DAT availability, as measured from PET scans. Therefore, we investigated the predictive power of DAT mRNA expression with (1) auto-correlation and (2) cross-correlation with PET-derived DAT availability.

2 | MATERIALS AND METHODS

2.1 | PET data

Thirty-five healthy male participants without brain injury and neuropsychological disorders were included in this study. The majority of the participants in this study were included in a previous study on striatal DAT changes after glucose loading (Pak et al., 2019). The current study was approved by the institutional review board of Pusan National University Hospital. ^{18}F-FP-CIT was administered via intravenous bolus injection. The emission data were acquired over 90 min with 50 frames of progressively increasing durations (15 s × 8 frames, 30 s × 16 frames, 60 s × 10 frames, 240 s × 10 frames, and 300 s × 6 frames) using a Siemens Biograph 40 Truepoint PET/CT (Siemens Healthcare, Knoxville, TN, USA). The dynamic PET data were collected in the 3-dimensional mode, with 148 slices with image sizes of 256 × 256 and pixel sizes of 1.3364 × 1.3364 mm^2. The slices were reconstructed using an iterative method with a Gaussian filter. For a volume-of-interest (VOI)-based analysis, an averaged image (0—10 min after injection) was created from dynamic PET frames and spatially normalized to a ^{15}O-Water PET template in Statistical Parametric Mapping 5 (Wellcome Trust Centre for Neuroimaging, UK). To extract time-activity curves of VOIs from full dynamic PET scans, the Oxford-GSK-Imanova striatal atlas (https://fsl.fmrib.ox.ac.uk/fsl) for the ventral striatum, caudate nucleus, putamen, and an automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002) for the middle frontal, orbitofrontal, anterior/middle/posterior cingulate, parietal, and temporal cortices were applied. DAT availability, expressed in terms of binding potential (BP_{ND}), was measured by analyzing time-activity curves using the simplified reference tissue method (Lammertsma & Hume, 1996) with the cerebellum as a reference. Image analysis was performed using PMOD version 3.6 (PMOD Technologies LLC, Zurich, Switzerland).

2.2 | mRNA data

The gene expression information investigated in this study was obtained from the freely available Allen Human Brain Atlas (www.brain-map.org) (Hawrylycz et al., 2012). We downloaded the mRNA values of DAT to test for an association with the radiopharmaceutical tracer ^{18}F-FP-CIT. The data set of the Allen Human Brain Atlas was derived from six healthy donors. The Allen Human Brain Atlas contains the gene expression profiles of DAT throughout the brain obtained with six probes. We downloaded DAT mRNA expression data in log2-values for each sample. For VOI-based analysis, the mRNA data were averaged within the ventral striatum, caudate nucleus, putamen, and middle frontal, orbitofrontal, anterior/middle/posterior cingulate, parietal, and temporal cortices.

2.3 | Statistical analysis

Normality was assessed using the D'Agostino and Pearson normality tests. Spearman correlation analysis was performed for both (1) auto-correlation of BP_{ND}s of ^{18}F-FP-CIT PET and DAT mRNA expression and (2) cross-correlation between BP_{ND}s of ^{18}F-FP-CIT PET and DAT mRNA expression to ensure validity and consistency. In addition, with a mean BP_{ND}s of ^{18}F-FP-CIT PET and mean DAT mRNA expression, Spearman correlation analysis was performed for each VOI. All analyses were conducted using Prism (v7.0d, GraphPad Software Inc., La Jolla, CA, USA).

3 | RESULTS

PET-derived BP_{ND}s from 35 participants with a mean age of 24.4 years (range, 20—31 years) and DAT mRNA expression of six probes from six subjects were included in this study. PET-derived BP_{ND}s from the ventral striatum, caudate nucleus, and putamen were substantially higher than those from the middle frontal, orbitofrontal, anterior/middle/posterior cingulate, parietal, and temporal cortices. However, mRNA expression levels from probe 1 (A_24_P397435), 2 (CUST_942_PI417557136), 3 (CUST_941_PI417557136), 4 (CUST_588_PI416408490), and 5 (CUST_927_PI417557136) were systemically lower than those from probe 6 (CUST_15799_PI416261804), which could be due to a lack of sensitivity of these probes (Figure 1).

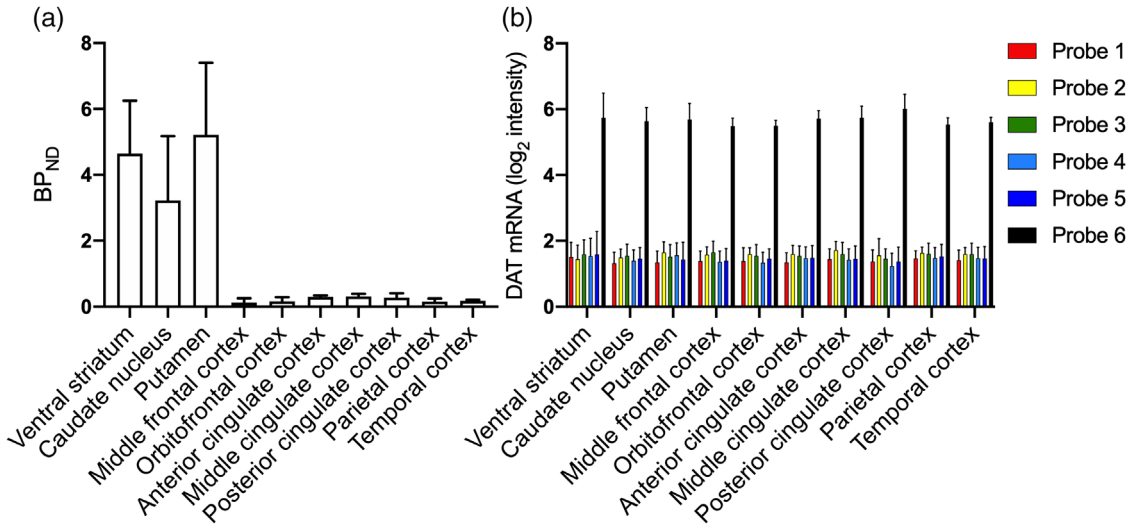

FIGURE 1 Mean and standard deviation of (a) positron emission tomography (PET)-derived binding potential (BP_{ND}) and (b) mRNA expression from the Allen Human Brain Atlas

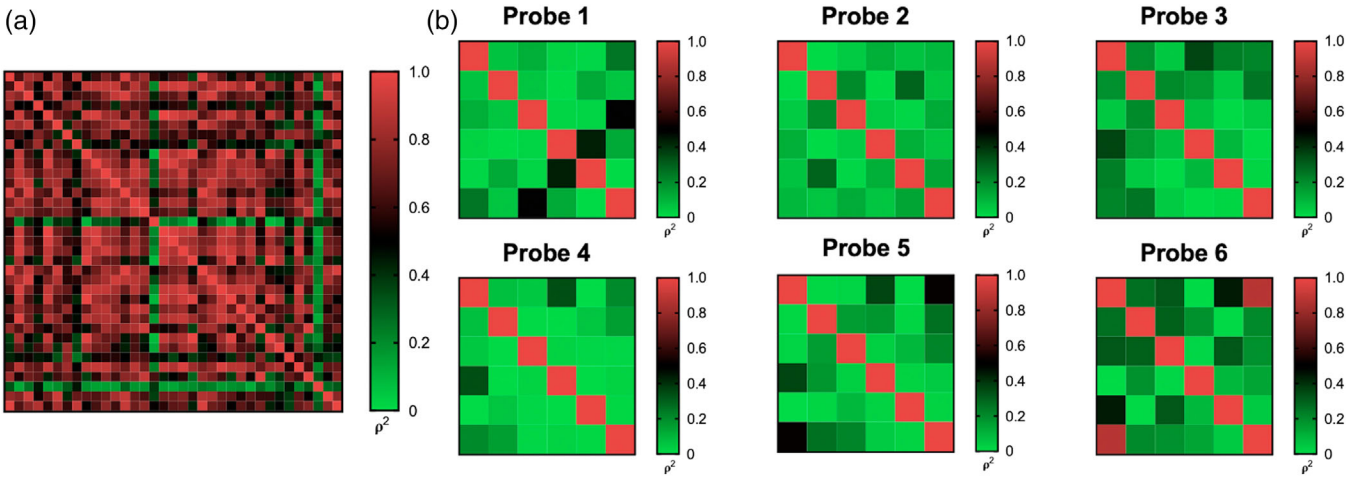

FIGURE 2 (a) Auto-correlation of positron emission tomography (PET)-derived BP_{ND}s for dopamine transporter (DAT) was intermediate (mean $\rho^2 = .66$) with ρ^2 ranging from .08 to 1. (b) The auto-correlation of mRNA expression from the Allen Human Brain Atlas was weak across the probes with a mean ρ^2 from .0889 to .23 (mean ρ^2 probe 1, .12; probe 2, .09; probe 3, .13; probe 4, .06; probe 5, .13; and probe 6, .23)

3.1 | Auto-correlation

The auto-correlation of PET-derived BP_{ND}s for DAT was intermediate (mean $\rho^2 = .66$) with ρ^2 ranging from .08 to 1 (Figure 2a). However, the auto-correlation of mRNA expression was weak across the probes with a mean ρ^2 from .09 to .23 (mean ρ^2 probe 1, .12; probe 2, .09; probe 3, .13; probe 4, .06; probe 5, .13; and probe 6, .23) (Figure 2b, Table 1).

3.2 | Cross-correlation

Between PET-derived BP_{ND}s, and mRNA expression, cross-correlations were weak with a mean ρ^2 ranging from 0 to .22 (mean ρ^2 probe 1, .14; probe 2, 0; probe 3, .08; probe 4, .13; probe 5, .14; and probe 6, .22) (Figure 3, Table 2). In addition, after averaging PET-derived BP_{ND}s, and DAT mRNA expression levels according to VOIs, cross-correlation was investigated for each probe. No significant association was observed except for probe 6 ($\rho = .65$, $p = .05$) (Figure 4).

TABLE 1 Auto-correlation of BP_{ND} of ^{18}F-FP-CIT positron emission tomography (PET) and dopamine transporter (DAT) mRNA expression

	Auto-correlation (ρ^2)		
Variables	Minimum	Maximum	Mean ± SD
^{18}F-FP-CIT PET			
BP_{ND}	.08	1	.66 ± .21
DAT mRNA expression			
Probe 1	0	.49	.12 ± .16
Probe 2	0	.29	.09 ± .08
Probe 3	0	.36	.13 ± .11
Probe 4	0	.34	.06 ± .10
Probe 5	0	.51	.13 ± .15
Probe 6	0	.87	.23 ± .22

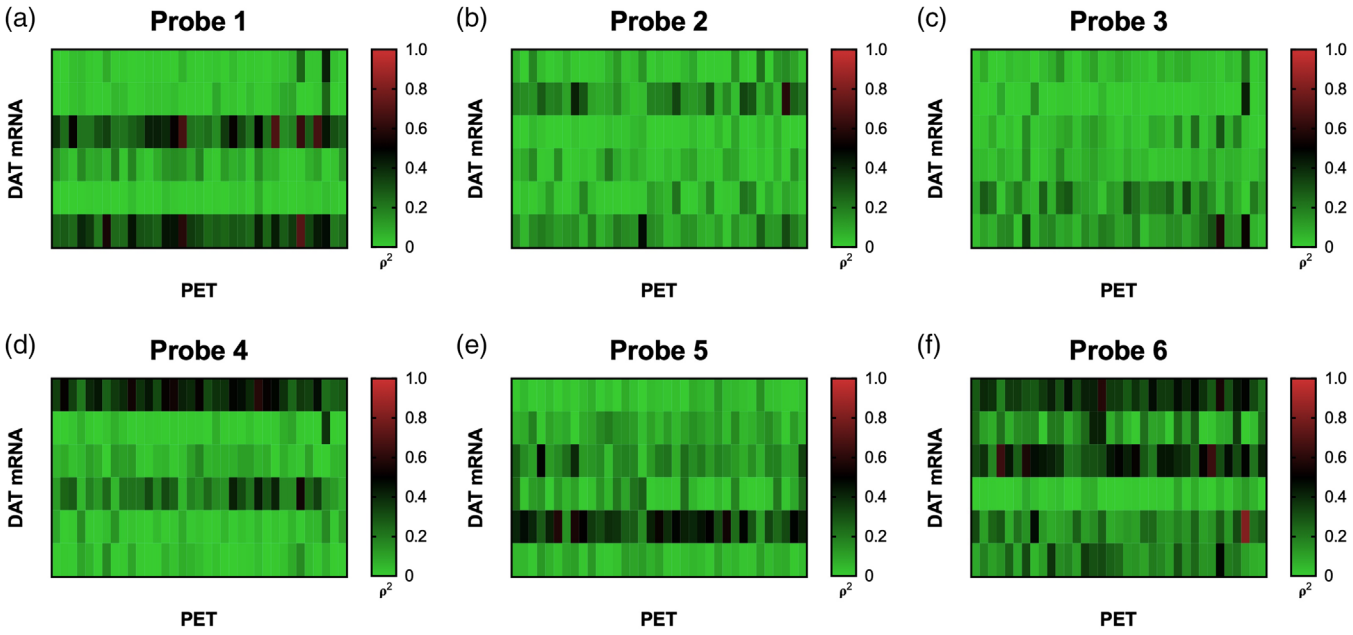

FIGURE 3 Cross-correlation between positron emission tomography (PET)-derived BP_{ND}s and mRNA expression from the Allen Human Brain Atlas was weak with a mean ρ^2 ranging from .0011 to .22 (mean ρ^2; (a) probe 1, .14; (b) probe 2, 0; (c) probe 3, .08; (d) probe 4, .13; (e) probe 5, .14; (f) probe 6, .22)

4 | DISCUSSION

In this study, we examined the association between in vivo DAT availability from PET and DAT mRNA expression from the Allen Human Brain Atlas. Among the six probes for DAT mRNA from the Allen Human Brain Atlas database, five probes showed much lower expression levels of DAT mRNA than probe 6, probably due to a lack of sensitivity. Although mRNA expression of probe 6 showed the highest expression levels in each VOI, the auto-correlation between subjects (inter-subject correlation) was weak with a mean $\rho^2 = .2263$. The cross-correlation with PET-derived BP_{ND}s was also weak with a mean $\rho^2 = .2220$. However, the mean mRNA expression of probe 6 showed a significant correlation with the mean PET-derived BP_{ND}.

The predictive power of brain mRNA mappings of the Allen Human Brain Atlas after comparison with PET-derived protein expression has been investigated for several proteins, including serotonin receptors (Beliveau et al., 2017; Komorowski et al., 2017; Rizzo et al., 2014), serotonin transporters (Beliveau et al., 2017; Komorowski et al., 2017), opioid receptors (Rizzo et al., 2014), and MAO-A (Komorowski et al., 2017; Zanotti-Fregonara et al., 2014). The association between mRNA expression and PET-derived protein expression was strong for serotonin receptors (Beliveau et al., 2017; Komorowski et al., 2017; Rizzo et al., 2014) and weak for opioid receptors (Rizzo et al., 2014). However, studies of MAO-A mRNA expression reported inconsistent results as it was weakly correlated with ^{11}C-harmine (Komorowski et al., 2017) and strongly correlated with ^{11}C-befloxatone (Zanotti-Fregonara et al., 2014).

TABLE 2 Cross-correlation of BP_{ND} of ^{18}F-FP-CIT positron emission tomography (PET) and dopamine transporter (DAT) mRNA expression

Variables	Auto-correlation (ρ^2)		
	Minimum	Maximum	Mean ± SD
Probe 1	0	.70	.14 ± .17
Probe 2	0	.59	0 ± .20
Probe 3	0	.57	.08 ± .09
Probe 4	0	.59	.13 ± .16
Probe 5	0	.57	.14 ± .14
Probe 6	0	.82	.22 ± .16

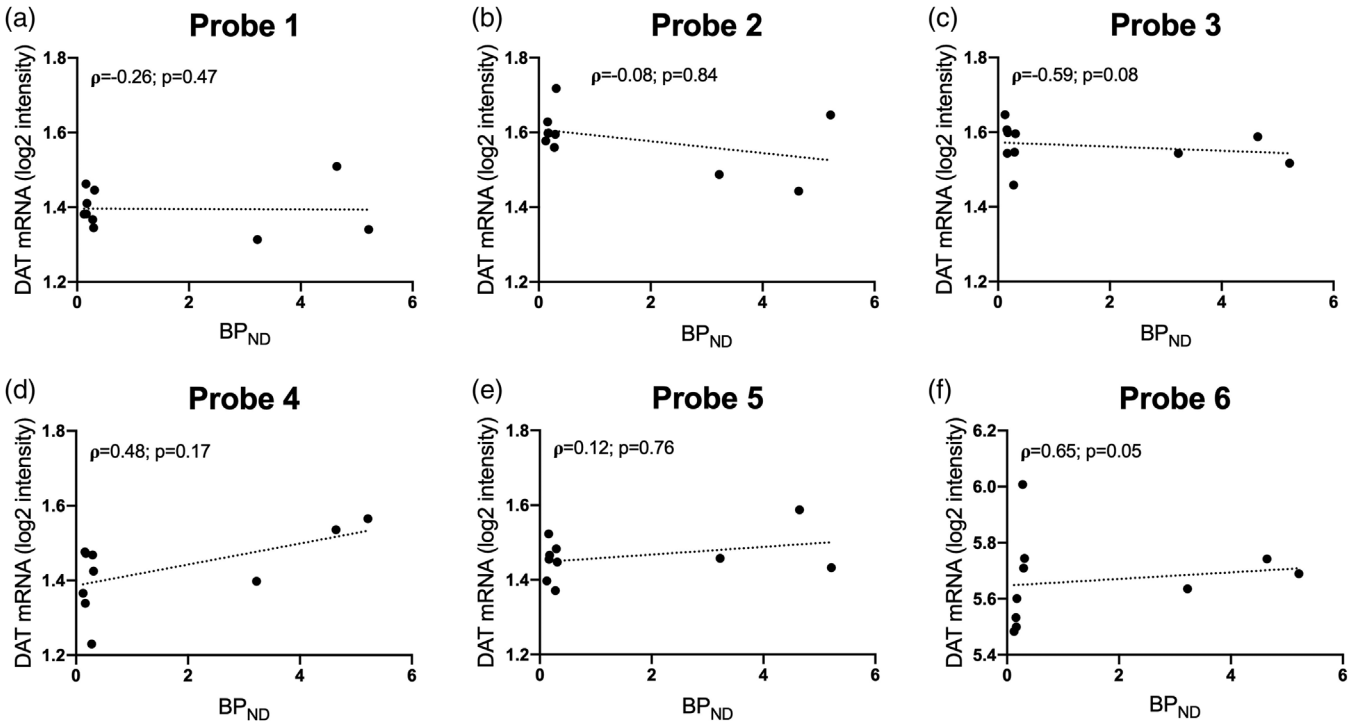

FIGURE 4 Cross-correlation between mean positron emission tomography (PET)-derived BP_{ND}s and mean dopamine transporter (DAT) mRNA expression from the Allen Human Brain Atlas showed no significant association except for probe 6 ($\rho = .65$, $p = .05$)

Dopamine is a neurotransmitter involved in reward-motivated behavior and motor control (Salamone & Correa, 2013). Dopamine neurotransmission is regulated by DAT, which drives the reuptake of extracellular dopamine into presynaptic neurons (Vaughan & Foster, 2013). DAT dysfunction is linked to neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (Roessner et al., 2010), bipolar disorder (Mick et al., 2008), and alcohol use disorder (Du et al., 2011). In addition, DAT is a major target of various pharmacologically active drugs (Vaughan & Foster, 2013). From genomic maps, such as the Allen Human Brain Atlas, gene expression can be visualized across whole brain regions, yielding insights into the relationship between structure and function of the human brain (Sandberg et al., 2000), facilitating neuroscientific studies and drug development (Rizzo et al., 2014). DAT mRNA is mainly translated in the soma of the midbrain neurons, and DAT protein is transported by axonal transport to the presynapse in the striatum. However, in a postmortem study (Little et al., 1998), DAT mRNA levels in the midbrain were not correlated with DAT binding measured by ^{3}H-WIN35428 in the striatal region. Additionally, in chronic cocaine users, DAT mRNA expression levels in the midbrain were decreased, but, paradoxically, striatal DAT binding was markedly increased, which could be due to compensatory mechanisms, either by conformational change or by increasing level of DAT protein. Recently, axonal translation has been shown to play an important role in neuronal development and normal regeneration (Spaulding & Burgess, 2017). The local expression and trafficking of tyrosine hydroxylase mRNA is involved in dopamine synthesis (Gervasi et al., 2016). However, the axonal translation of DAT mRNA is still unclear. Therefore, we investigated the association of DAT availability measured by PET with mRNA expression from the Allen Human Brain Atlas. However, in this study, we observed relatively weak associations between DAT availability and DAT mRNA expression, regardless of the probe. In addition, the correlation between the mean PET-derived BP_{ND}s and mean DAT mRNA expression levels was marginally significant in one of the six probes. Therefore, maps of the human mRNA

transcription architecture from DNA microarray analysis of DAT may have limited predictive value, after comparison with PET-derived DAT availability in this study. Possible reasons of the limited predictive role of mRNA mapping for protein expression have been reported previously (Rizzo et al., 2014). First, posttranscriptional mechanisms of splicing or translational modifications might influence protein expression for each cell type (Cheng et al., 2005; Rizzo et al., 2014). In addition, mRNA expression is analyzed in the cytoplasm, whereas DAT protein is predominantly expressed presynaptically (Komorowski et al., 2017), which might affect the limited role of DAT mRNA mapping.

This study has several limitations. First, the sample size of the Allen Human Brain Atlas database was small with six donors. In addition, as the participants included in the Allen Human Brain Atlas and those in PET scans were different, there might have been inter-study differences. Second, although mRNA data of six probes were included across the regions, mRNA expression from five probes was systemically low, probably due to a lack of sensitivity of the probes. In addition, the auto-correlation of mRNA expression between individuals was weak, probably due to inter-individual variations. Furthermore, the levels of both DAT mRNA expression and PET-derived BP_{ND}s might be affected by the functional status of the dopaminergic system and dopamine levels in the brain. Finally, the substantia nigra and ventral tegmental area might play a relevant role in the description of mRNA for DAT protein expression.

In conclusion, we observed weak associations between DAT mRNA expression and DAT availability in the human brain. Therefore, DAT mRNA mapping may have limited predictive power for DAT protein expression in humans.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ORCID

Kyoungjune Pak https://orcid.org/0000-0001-5051-1894
Seongho Seo https://orcid.org/0000-0001-7894-0535
Myung Jun Lee https://orcid.org/0000-0002-0101-6472

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