

# Memory performance associates with serotonin transporter in midbrain and pons in healthy subjects

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#### Abstract

**Objective:** We aimed to evaluate the association between the availability of serotonin transporter (SERT) measured by ioflupane-DaTSCAN (<sup>123</sup>I-FP-CIT) and imaged by single photon emission tomography (SPET) and memory function in healthy subjects. **Subjects and Methods:** Specific binding of <sup>123</sup>I-FP-CIT indicating SERT was achieved using a region of interest analysis. Spherical volumes of interest for midbrain and pons were defined. The cerebellum was chosen as a reference region. Specific binding ratios (SBR) in midbrain and pons representing SERT availability were measured as follows: SBR=(target-cerebellum)/cerebellum. A hundred and eighty-one healthy subjects (117 male, 64 female) were included in this study. **Results:** Specific binding ratios of both midbrain (P=0.025) and pons (P=0.006) of males was higher than that of females. None of the SBR showed a correlation with age both in males: (midbrain; P=0.736, pons; P=0.875) and in females (midbrain; P=0.294, pons; P=0.170). In all our cases, SERT availability of midbrain correlated positively with total recall score (rho=0.159, P=0.033), and delayed recall score (rho=0.149, P=0.046). In females, the correlation between SERT availability in midbrain and delayed recall score was significant (rho=0.320, P=0.010), however, not in males (rho=0.112, P=0.229). **Conclusion:** In conclusion, we demonstrated that SERT availability was associated with memory function in healthy females from the PPMI database. Further studies are needed to clarify underlying mechanisms of this phenomenon.

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## Introduction

Serotonergic neurons are localized in the brainstem, especially in midline raphe nuclei and project to almost the entire brain [1, 2]. The action of serotonergic neurons is modulated by pre- and postsynaptic receptors, which are consisted of 7 different families, via serotonin [2]. The wide projection of serotonergic neurons modulates various functions including memory [3-5]. Serotonin transporter (SERT) on terminals of serotonergic neurons regulate reuptake of serotonin in the synaptic cleft and is thought to be an index of integrity of the axon terminal of brain serotonergic neurons [6].

Single photon emission tomography (SPET) and positron emission tomography (PET) studies have implicated alterations of both dopamine transporter (DAT) and SERT in neurodegenerative diseases. Ioflupane-DaTSCAN (<sup>123</sup>I-FP-CIT) is one of the most widely used radiotracers for DAT imaging [7, 8], which enables the in vivo demonstration of striatal dopamine activity [9]. In addition, <sup>123</sup>I-FP-CIT has an advantage that allows the combined evaluation of both DAT and SERT in a single scan [7], as DAT and SERT display a nonoverlapping distribution in subcortical structures [10]. Therefore, previous studies investigated the role of <sup>123</sup>I-FP-CIT in evaluating DAT of striatum [11] and SERT of midbrain [10] and pons [7].

Previously, SERT knockout rats showed impaired memory compared to controls [12]. In addition, rats injected with a serotonin neurotoxin, showed impaired memories of both short-and long-term [13]. In patients with mild cognitive impairment (MCI), low SERT availabilities were observed in cortical, striatal, thalamic, and limbic regions, and was associated with memory impairment [14]. However, the association between SERT availability and memory function has not been proved in healthy subjects. Therefore, we hypothesized that memory function might be associated with SERT in healthy subjects using the data from the Parkinson's Progression Markers Initiative (PPMI). This paper was reviewed and approved by PPMI in August 13, 2019 and before submitted to Hell J Nucl Med.

## Subjects and Methods

Data used in the preparation of this article were obtained from PPMI database ([www.ppmi-info.org/data](http://www.ppmi-info.org/data)). For up-to-date information on the study, visit [www.ppmi-info.org](http://www.ppmi-info.org) [15]. In PPMI database, 192 healthy controls were enrolled with screening  $^{123}\text{I}$ -FP-CIT SPET. According to PPMI criteria of healthy subjects, males or females aged 30 years or older at the time of screening were included, while subjects with a neurological disorder, a first degree relative with idiopathic Parkinson's disease, Montreal Cognitive Assessment score of 26 or less, medications that might interfere with DAT SPET scans, anti-coagulants that might preclude safe completion of the lumbar puncture, or investigational drugs, and a condition that precludes the safe performance of routine lumbar puncture were excluded. Subjects without the results of Hopkins verbal learning test-revised (HVLTR) were also excluded. Medical history and  $^{123}\text{I}$ -FP-CIT SPET scans were downloaded. The PPMI study was approved by the local Institutional Review Boards of all participating sites (Institute for Neurodegenerative Disorders, University of Pennsylvania, University of California, Los Angeles, Coriell Institute for Medical Research, Clinical Trials Coordination Center, Laboratory of Neurogenetics; National Institute on Aging NIH, Institute for Neurodegenerative Disorders, Clinical Trials Statistical and Data Management Center, University of Iowa). Written informed consent was obtained from each subject at the time of enrollment for imaging data and clinical questionnaires. All methods were performed in accordance with the relevant guidelines and regulations.

### Hopkins verbal learning test-revised (HVLTR)

Hopkins verbal learning test-revised consists of a word list-learning and recall task, containing 3 words from 1 of 4 semantic categories, for a total of 12 words. A list of words is read aloud, then the test taker attempts to recall the words in any order for each trial 1, 2, and 3. After approximately 20 minutes delay, delayed recall trial was assessed. After delayed recall trial, delayed recognition trial was done with a list of 24 words (12 from the list and 12 distractors) to identify those on the list. Total recall score was calculated after adding all correct responses of trial 1, 2, and 3. Learning score

was calculated by subtracting the score of trial 1 from higher score of trials 2 or 3. Delayed recall score was the number of correct responses on delayed recall trial. Retention score was calculated by dividing delayed recall score with higher score of trials 2 or 3 and multiplying by 100. Discrimination score was calculated as number of true positives minus number of false positives on delayed recognition trial. Higher values indicate better performance [16-19].

### $^{123}\text{I}$ -FP-CIT SPET

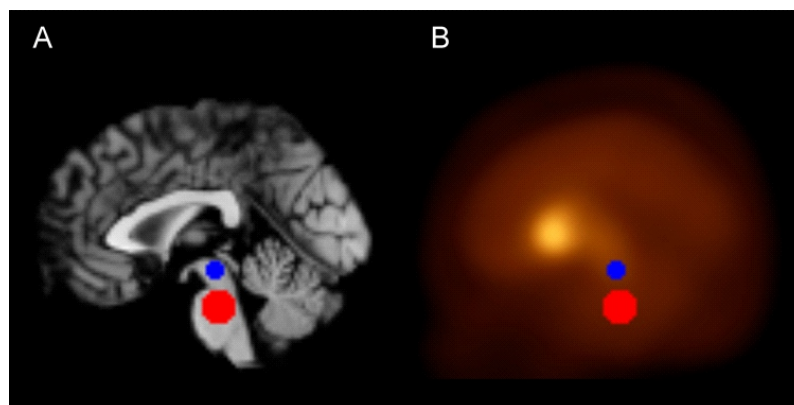
$^{123}\text{I}$ -FP-CIT SPET was performed during the screening visit for all subjects. Single photon emission tomography scans were acquired  $4\pm 0.5$ hrs after injection of 111-185MBq of  $^{123}\text{I}$ -FP-CIT. Subjects were pretreated with iodine solution or perchlorate prior to injection to block thyroid uptake. Raw data were acquired into a 128x128 matrix stepping each 3 or 4 degrees for the total projections. Raw projection data were reconstructed using iterative ordered subset expectation maximization with HERMES (Hermes Medical Solutions, Stockholm, Sweden). The reconstructed images were transferred to pmod (PMOD Technologies LLC, Zürich, Switzerland) for subsequent processing including attenuation correction.

### Image analysis

Downloaded scans were loaded using pmod v3.6 (PMOD Technologies LLC, Zürich, Switzerland) with  $^{123}\text{I}$ -FP-CIT template [20]. Specific binding of  $^{123}\text{I}$ -FP-CIT regarding SERT was calculated using a region of interest analysis. Spherical volumes of interest for midbrain and pons were defined (Figure 1). The cerebellum was chosen as a reference region. Specific binding ratios (SBR) of midbrain and pons representing SERT availability were measured as follows;  $\text{SBR} = (\text{target-cerebellum}) / \text{cerebellum}$ .

### Statistical analysis

Normality was examined using D'Agostino-Pearson omnibus test. Spearman correlation was used to measure the relationship of SBR with age, and HVLTR scores. Mann-Whitney test was applied to compare SBR, and HVLTR scores according to sex. Statistical analyses were performed using GraphPad Prism 7 for Mac OS X (GraphPad Software Inc, San Diego, CA, USA).



**Figure 1.** Regions of interest of midbrain (blue) and pons (red) used for image analysis (A) and corresponding  $^{123}\text{I}$ -FP-CIT template (B)

## Results

### Subjects' characteristics

A hundred and eighty one healthy subjects (117 male, 64 female) were included in this study. Mean age was  $61.07 \pm 11.23$  years. Serotonin transporter availabilities of both midbrain ( $P=0.025$ ) and pons ( $P=0.006$ ) of males were higher than those of females (Figure 2A). However, in results of HVLTR, total recall score ( $P=0.008$ ), delayed recall score (0.013), and discrimination score ( $P=0.017$ ) of males were lower than those of females. Sex difference was not significant in learning ( $P=0.650$ ) and retention scores ( $P=0.260$ ) (Figure 2B). Subjects' characteristics are summarized in Table 1.

### Correlation of SERT availability with age, and HVLTR scores

None of SERT availabilities of midbrain and pons showed the correlation with age in males (midbrain;  $P=0.736$ , pons;  $P=0.875$ ), and females (midbrain;  $P=0.294$ , pons;  $P=0.170$ ). In 181 healthy subjects, SERT availability of midbrain correlated positively with total recall score ( $\rho=0.159$ ,  $P=0.033$ ) (Figure 3A), and delayed recall score ( $\rho=0.149$ ,  $P=0.046$ ) (Table 2, Figure 3B). In females, the association between SERT availability of midbrain and delayed recall score was significant ( $\rho=0.320$ ,  $P=0.010$ ), however, not in males ( $\rho=0.112$ ,  $P=0.229$ ) (Figure 4). Learning, retention, and discrimination scores were not significantly associated with SERT availability of midbrain and pons in males, and females (Table 3).

Table 1. Subjects' characteristics.

Variables	Male (n=117)	Female (n=64)	P
Age (years)	$61.60 \pm 10.92$	$60.09 \pm 11.81$	0.376
<b>Specific binding ratio</b>			
Midbrain	$0.41 \pm 0.21$	$0.33 \pm 0.22$	0.025
	$0.26 \pm 0.20$	$0.17 \pm 0.17$	0.006
<b>HVLTR</b>			
Total recall score	$25.25 \pm 4.55$	$27.08 \pm 4.48$	0.008
Delayed recall score	$8.92 \pm 2.46$	$9.84 \pm 1.99$	0.013
Learning score	$3.19 \pm 1.50$	$3.30 \pm 1.78$	0.650
Retention score	$89.58 \pm 19.58$	$92.61 \pm 14.87$	0.260
Discrimination score	$9.83 \pm 2.86$	$10.44 \pm 2.62$	0.017

\*HVLTR; The Hopkins Verbal Learning Test-Revised

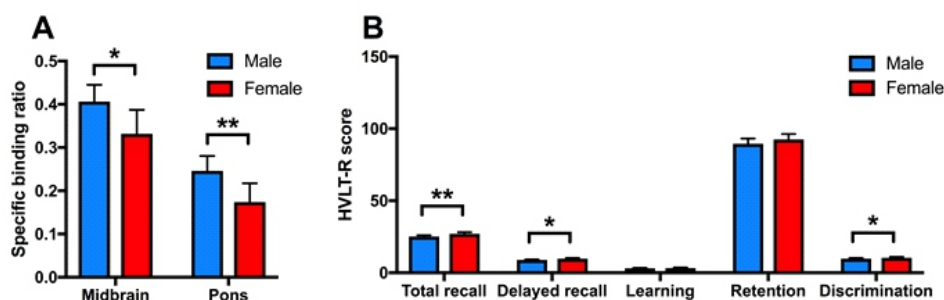


Figure 2. Comparison of SERT availabilities of midbrain and pons (A), and of HVLTR scores (B) according to sex: \* $P < 0.05$ , \*\* $P < 0.01$ .

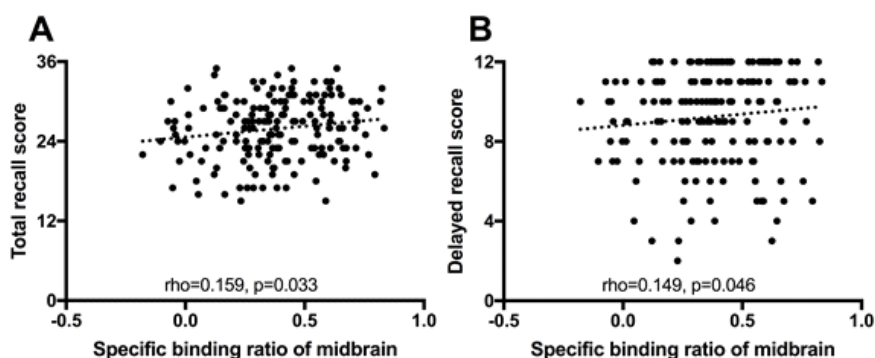
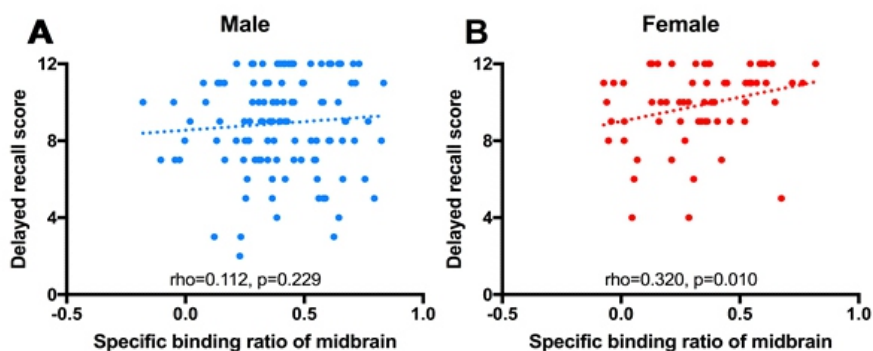


Figure 3. Scatterplots of specific binding ratio of midbrain with total recall score (A), and delayed recall score (B) in 181 healthy subjects.



**Figure 4.** Scatterplots of specific binding ratio of midbrain with delayed recall score in males (A) and females (B).

**Table 2.** Correlations of the availability of SERT with HVLt-R scores.

	Midbrain		Pons	
<b>HVLt-R</b>				
<b>Total recall score</b>	0.159	0.033	-0.017	0.820
<b>Delayed recall score</b>	0.149	0.046	-0.043	0.569
<b>Learning score</b>	0.037	0.618	0.072	0.337
<b>Retention score</b>	0.017	0.816	-0.127	0.089
	0.109	0.143	-0.058	0.435

\*HVLt-R; The Hopkins Verbal Learning Test-Revised

**Table 3.** Correlations of the availability of SERT with HVLt-R scores according to sex.

	Male				Female			
	midbrain rho	P	Pons rho	P	midbrain rho	P	Pons rho	P
<b>HVLt-R</b>								
<b>Total recall score</b>	0.178	0.054	0.025	0.786	0.229	0.068	0.026	0.841
<b>Delayed recall score</b>	0.112	0.229	-0.018	0.847	0.320	0.010	-0.037	0.770
<b>Learning score</b>	-0.022	0.818	0.109	0.241	0.146	0.250	0.022	0.861
<b>Retention score</b>	0.006	0.953	-0.128	0.168	0.079	0.534	-0.120	0.346
<b>Discrimination score</b>	0.178	0.055	-0.021	0.823	0.068	0.595	-0.050	0.694

\*HVLt-R; The Hopkins Verbal Learning Test-Revised, Rho; correlation coefficient

## Discussion

In this study, SERT availabilities of males were higher than those of females both in midbrain and pons. However, memory function of females was superior to males. In addition, SERT availability of midbrain correlated positively with total recall score, and delayed recall score. This positive correlation between SERT availability of midbrain and delayed recall score becomes stronger in females.

Previous studies showed discrepancies in gender effects on SERT availabilities. Ryding et al. (2004) reported that SERT availability of brainstem was not different between

males and females using <sup>123</sup>I-β-CIT SPET [21]. However, females had higher SERT availabilities of thalamus than males, not those of pons using <sup>123</sup>I-FP-CIT SPET according to Koch et al. (2014) [7]. In contrast, those of cortical and subcortical regions were higher in males in a study using <sup>11</sup>C-MADAM PET [22], consistent with this study. The study of Ryding et al. (2004) enrolled only 23 normal subjects. The small number of subjects might affect the results. Koch et al. (2014) showed higher SERT availability in the pons in males, even though the difference was not statistically significant [7]. Moreover, the study of Booij et al. (2007) reported that the suppression of SERT availability in midbrain by selective serotonin reuptake inhibitors was more decreased than



diencephalon (hypothalamus/thalamus) [11]. Approximately 70% of  $^{123}\text{I}$ -FP-CIT uptake in thalamus was by the SERT binding [7]. Koch et al. (2014) also mentioned the possibility that DAT uptake in thalamus could affect the SERT uptake. These results might explain the discrepancy. However, in majority of studies, memory function of females were superior to that of males [23-25]. Chronological aging is associated with changes of brain from molecular change to anatomical change [26]. Neurotransmitters regarding aging are dopamine and serotonin [26]. Approximately 4.2% of SERT availabilities are decreased per a decade [27]. However, the association between age and SERT availability was not prominent in this study.

The association between SERT availability and memory function was reported previously. In SERT knockout rats, impaired object memory function was observed comparing with controls [12]. In a rat injected with a serotonin neurotoxin, decreased SERT binding in cortex and hippocampus were observed, and both short- and long-term memory were impaired [13]. In 3,4-methylenedioxymethamphetamine ("ecstasy") users, lower SERT availabilities were observed [28-30], which was correlated with memory impairment [29]. In addition, patients with MCI also showed lower SERT availabilities in cortical, striatal, thalamic, and limbic regions, which were associated with memory impairment [14]. In patients with Alzheimer's disease, lower binding potential of  $^{11}\text{C}$ -DASB in midbrain, nucleus accumbens, putamen, and thalamus was reported [31]. In addition, post-mortem studies reported lower SERT in frontal, temporal lobes, entorhinal cortex, hippocampus, and dorsal raphe nucleus of patients with Alzheimer's disease [32-34].

In this study, we demonstrated the positive correlation between SERT availability of midbrain and verbal memory function in healthy subjects. However, when our subjects were categorized according to sex, the association was prominent in females but not in males. Changes of SERT availabilities were observed in females treated with estrogen and testosterone after surgically menopausal [35]. Manipulation of sex hormone in healthy females induced changes in SERT availabilities of neocortex [36]. Estrogen is known to affect cognition and interact with serotonergic system [37, 38]. The association between estrogen, memory, and serotonergic system might explain the correlation between SERT availability and memory in females.

This is the first study that investigated the correlation between SERT availability and memory function in health subjects. However, there are several limitations in this study. First, although PPMI is designed for development of biomarkers in Parkinson's disease, it may not be suitable best for this study. Because the mean age of enrolled normal subjects was 60, the young normal subjects were not enrolled. Second, as PPMI database was collected from multiple institutes, the difference in image acquisition may have affected the results. Third, the correlation between SERT availability of midbrain and delayed recall score was weak. The scores of eight subjects were below 8. The score range of remaining subjects was between 8 and 12. The delayed recall score can be affected by education. This might affect the weak correlation.

*In conclusion*, SERT availability was associated with memory function in healthy subjects. In subgroup analysis, in females, the association between SERT availability of midbrain and delayed recall score was significant, however, not in males. Further studies are needed to clarify underlying mechanisms of this phenomenon.

*The authors declare that they have no conflicts of interest*

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