

## Sex Differences in Amphetamine-Induced Displacement of [<sup>18</sup>F]Fallypride in Striatal and Extrastriatal Regions: A PET Study

**Patrizia Riccardi, M.D.**

**David Zald, Ph.D.**

**Rui Li, M.S.**

**Sohee Park, Ph.D.**

**M. Sib Ansari, M.S.**

**Benoit Dawant, Ph.D.**

**Sharlet Anderson, M.A.**

**Neil Woodward, M.A.**

**Dennis Schmidt, Ph.D.**

**Ronald Baldwin, Ph.D.**

**Robert Kessler, M.D.**

**Objective:** The authors examined gender differences in *d*-amphetamine-induced displacements of [<sup>18</sup>F]fallypride in the stri-

atal and extrastriatal brain regions and the correlations of these displacements with cognition and sensation seeking.

**Method:** Six women and seven men underwent positron emission tomography (PET) with [<sup>18</sup>F]fallypride before and after an oral dose of *d*-amphetamine. Percent displacements were calculated using regions of interest and parametric images of dopamine 2 (D<sub>2</sub>) receptor binding potential.

**Results:** Parametric images of dopamine release suggest that the female subjects had greater dopamine release than the male subjects in the right globus pallidus and right inferior frontal gyrus. Gender differences were observed in correlations of changes in cognition and sensation seeking with regional dopamine release.

**Conclusion:** Findings revealed a greater dopamine release in women as well as gender differences in the relationship between regional dopamine release and sensation seeking and cognition.

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**S**tudies in animals suggest that estrogen significantly increases striatal dopamine synthesis, baseline dopamine release, *d*-amphetamine-induced dopamine release, and increased neuronal firing in substantia nigra (1). Both postmortem and neuroimaging studies suggest that there is increased dopamine release in women (2, 3).

Relative to men, women have higher frontal cortical dopamine 2 (D<sub>2</sub>) receptor levels (4), a slower decline in striatal and cortical D<sub>2</sub> receptor levels with age (5, 6), and higher striatal dopamine transporter levels (7). Previous studies report gender-related differences in dopaminergic neurotransmission (5–7).

Dopaminergic neurotransmission plays an important role in mental disorders (8), which show gender differences in their incidence, prevalence, clinical course, and treatment outcome (9). Given the evidence of gender differences in animals and humans and the sensitivity of [<sup>18</sup>F]fallypride to *d*-amphetamine-induced dopamine release (10), we used positron emission tomography (PET) with [<sup>18</sup>F]fallypride to evaluate whether there are gender differences in *d*-amphetamine-induced dopamine release and the relationship of dopamine release to cognition and sensation seeking in the striatal and extrastriatal brain regions.

### Method

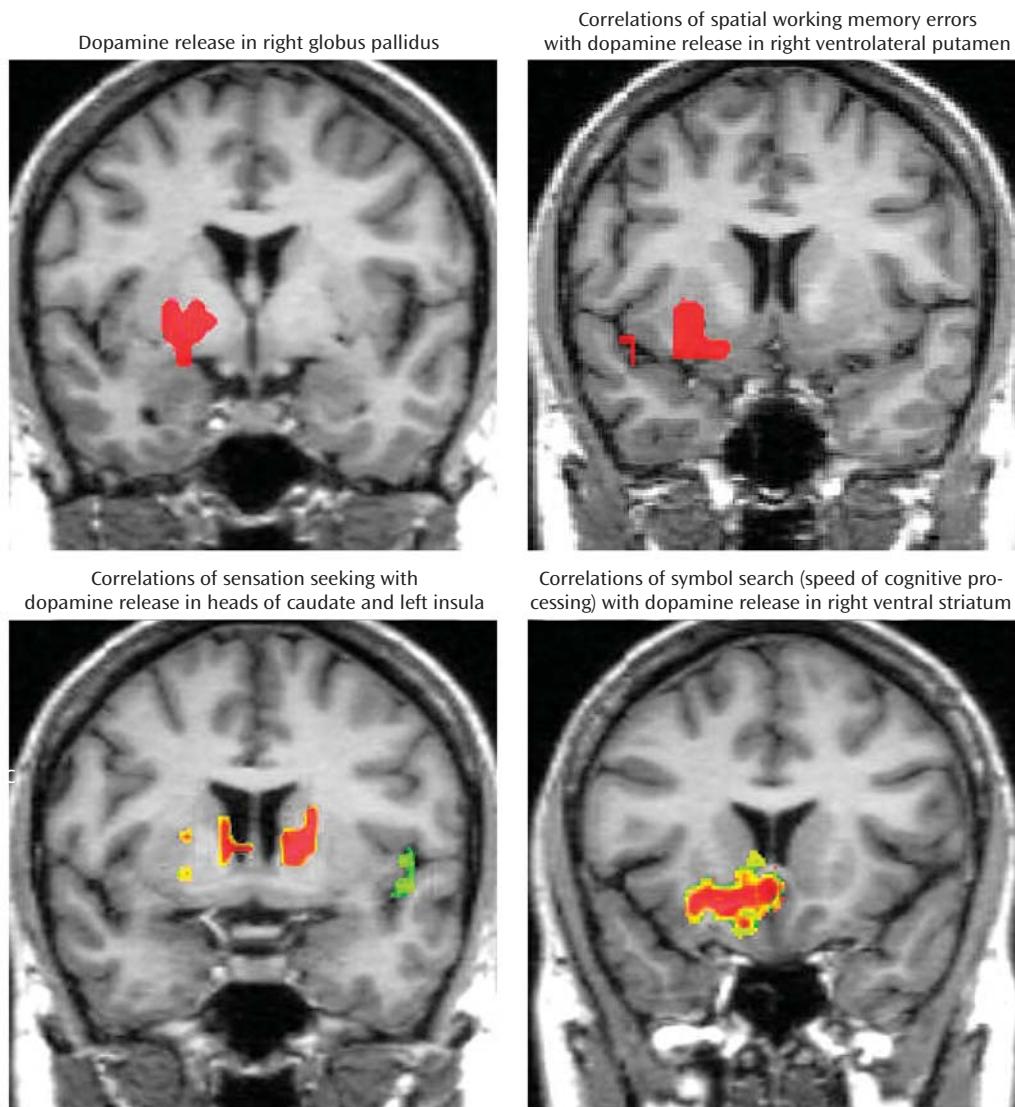
Thirteen healthy subjects (six women [mean age=24.8 years, range=21–29] and seven men [mean age=27.6 years, range=22–32]) without any history of psychiatric, neurological, or medical illness were recruited. Magnetic resonance imaging (MRI) scans were performed using a 1.5-T GE scanner. PET studies were performed us-

ing a GE Discovery LS PET scanner with a three-dimensional emission acquisition and a transmission attenuation correction. [<sup>18</sup>F]Fallypride PET scans (5.0 mCi, specific activity greater than 3,000 Ci/mmol) were conducted prior to and 180 minutes following a 0.43 mg/kg oral dose of *d*-amphetamine. The Sensation Seeking Scale-Form V (11) was also administered. Prior to the initial PET study and 60 minutes after *d*-amphetamine administration, subjects began a 75-minute neuropsychological battery, including a continuous performance task, digit symbol coding and symbol search (12), and spatial working memory (13). Serial scans were obtained for 3.5 hours. Blood samples were collected to determine the plasma level of *d*-amphetamine. Serial PET scans were coregistered to each other and to thin section T<sub>1</sub>-weighted MRI scans (14) and reoriented to the anterior commissure-posterior commissure line. The regions of interest, caudate, putamen, ventral striatum, medial thalamus, amygdala, temporal cortex, and substantia nigra were delineated on MRI scans of the brain and transferred to the coregistered PET scans. Regional D<sub>2</sub> receptor binding potential and parametric images of D<sub>2</sub> receptor binding potential were calculated using the reference region method (15). Percent displacement images were calculated on a pixel-by-pixel basis. Using an elastic deformation algorithm (16), mean parametric images of [<sup>18</sup>F]fallypride were also calculated. Correlations of changes in cognition and sensation seeking with parametric images of dopamine release were performed. Probability maps were calculated on a voxel-by-voxel basis using a two-tailed t test and corrected for multiple comparisons using the Forman method (17). Only clusters with significance exceeding p<0.001 after correction for multiple comparisons were examined. (See Figure 1.)

### Results

Parametric image analysis revealed significantly greater dopamine release in women in the right globus pallidus and right inferior frontal gyrus (p<0.001 [corrected for multiple

**FIGURE 1.** Coronal Images Demonstrating Significant Clusters of Gender Differences in (A) Dopamine Release in the Right Globus Pallidus, (B) Correlations of Spatial Working Memory Errors With Dopamine Release in the Right Ventrolateral Putamen, (C) Correlations of Sensation Seeking With Dopamine Release in the Heads of the Caudate and Left Insula, and (D) Correlations of Symbol Search (speed of cognitive processing) With Dopamine Release in the Right Ventral Striatum



comparisons]), while male subjects showed greater dopamine release in the dorsal striatum ( $p<0.1$ ). Differences in greater dopamine release in women relative to men were also observed in the temporal and parietal cortices ( $p<0.1$ ).

Examination of the correlations of sensation seeking with dopamine release in regions of interest demonstrated a striking gender difference in the left ventral striatum (men:  $r=0.898$  [ $p=0.006$ ]; women:  $r=-0.713$ ). This difference was significant at the  $p<0.005$  level, which was not corrected for multiple comparisons. Parametric image analysis demonstrated markedly different patterns of correlations between sensation seeking and *d*-amphetamine-induced dopamine release in male and female subjects, i.e., women but not men showed negative correlations with dopamine release in the heads of the caudate nuclei bilaterally ( $r=-0.84$ ), the

globus pallidus ( $r=-0.801$ ), and the left anterior cingulate ( $r=-0.757$ ,  $p<0.001$  [corrected for multiple comparisons]). In contrast, male but not female subjects demonstrated significant clusters of negative correlations ( $p<0.001$  [corrected for multiple comparisons]) in the left and right insular regions ( $r=-0.719$  and  $-0.771$ , respectively), bilateral inferior temporal cortex ( $r=-0.710$  on the left and  $-0.771$  on the right), and the left lateral thalamus ( $r=-0.746$ ). These differences in correlations were significant in the heads of the caudate nuclei bilaterally and the left insula.

Correlations of changes in spatial working memory errors with parametric images of dopamine release demonstrated a right ventral putamen cluster in male ( $r=-0.84$ ,  $p<0.001$  [corrected for multiple comparisons]) but not female subjects. Gender difference in the right ventral puta-

men correlations for spatial working memory was significant ( $p<0.001$  [corrected for multiple comparisons]).

Changes in performance on the symbol search task was significantly correlated in male subjects with dopamine release in the ventral and lateral striatal bilaterally and right hippocampus (range:  $-0.741$  to  $-0.829$  [ $p<0.001$ ]). Female subjects had positive correlation in the right ventral striatum ( $r=0.49$ ). A significant gender difference in correlations was observed in the right ventral and lateral striatum ( $p<0.001$  [corrected for multiple comparisons]). However, plasma levels of *d*-amphetamine were not significantly different in men and women ( $0.46$  [ $SD=0.26$ ] nM/ml and  $0.45$  [ $SD=0.23$ ] nM/ml, respectively).

## Discussion

While gender-related differences in dopaminergic neurotransmission have been reported in studies using PET and single photon emission computed tomography (SPECT), no previous studies of *d*-amphetamine-induced dopamine release, to our knowledge, have examined gender differences in humans. The greater dopamine release in the right globus pallidus and right inferior frontal gyrus in women is consistent with previous animal studies reporting greater *d*-amphetamine-induced dopamine release in women. These differences are not because of volumetric differences, since these structures are similar in size in both men and women (18). In addition, gender differences in dopamine release were observed in cortical regions and other striatal regions, suggesting increased dopamine release in female subjects. Sensation-seeking behavior, spatial working memory, and attention and speed of cognitive processing are all believed to be modulated by dopaminergic neurotransmission (19). Gender differences in the relationship of dopamine release to these behaviors suggest significant differences in regional dopaminergic function. The differences found in this study remained significant after correction for multiple comparisons for both within-image comparisons and multiple behavioral tests.

In summary, significant gender differences in regional dopamine release and the relationship of regional dopamine release to cognitive function and sensation seeking were observed. These differences are likely because of gonadal hormonal modulation of cerebral dopaminergic neurotransmission. To our knowledge, this is the first study to investigate gender-related differences in *d*-amphetamine-induced dopamine release in striatal and extrastriatal regions in humans. The results of this study, if confirmed, indicate the need to consider gender in studies of dopamine release and the need for further studies to consider the role of gender-related differences in dopaminergic neurotransmission in neuropsychiatric disorders.

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Received Feb. 4, 2005; revision received April 26, 2005; accepted May 11, 2005. From the Departments of Radiology, Computer Science, and Psychology, Vanderbilt University, Nashville. Address correspondence and reprint requests to Dr. Riccardi, Vanderbilt University

Medical Center, Department of Radiology, Nashville, T.N. 37232-2675; pitrizia.riccardi@vanderbilt.edu (e-mail).

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