Sex Differences in Amphetamine Induced Displacement of $[^{18}F]$ Fallypride in Striatal and Extrastriatal Regions: A PET Study

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Abstract

OBJECTIVE: This study examined sex differences in d-amphetamine induced displacements of $[^{18}F]$fallypride in striatal and extrastriatal regions and the correlations of these displacements with cognition and sensation seeking. METHOD: Six females and seven males underwent positron emission tomography with $[^{18}F]$fallypride before and after an oral dose of d-amphetamine. Percent displacements were calculated using regions of interest and parametric images of DA D$_2$ receptor binding potential (b.p.). RESULTS: Parametric images of DA release suggest that women have greater DA release than men in the right globus pallidus and right inferior frontal gyrus. Sex differences were seen in correlations of changes in cognition and sensation seeking with regional DA release. CONCLUSIONS: This study demonstrates greater DA release in women and sex differences in the relationship of regional DA release to sensation seeking and cognition.
Introduction

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

Women have higher frontal cortical DA D₂ receptor levels (4), a slower decline in striatal and in cortical DA D₂ receptor levels with age (5, 6), and higher striatal DA transporter levels than men (7). The above studies indicate gender related differences in dopaminergic neurotransmission. Dopaminergic neurotransmission plays an important role in mental disorders (8) which show sex differences in their incidence, prevalence, clinical course, and treatment outcome (9). Given the evidence of sex differences in animals and humans and the sensitivity of [¹⁸F]fallypride to d-AMPH induced DA release (10), we used PET with [¹⁸F]fallypride to evaluate whether there are sex differences in the d-AMPH induced DA release and the relationship of DA release to cognition and sensation seeking in striatal and extrastriatal regions.

Methods

Thirteen normal subjects, 6 females (ages 21 to 29 years, mean age of 24.8 years) and 7 males (ages 22 to 32 years, mean age of 27.6 years) without any history of psychiatric, neurological or medical illness were recruited. MRI scans were performed using a 1.5 T GE scanner. PET studies were performed using a GE Discovery LS PET scanner using a 3-D emission acquisition and a transmission attenuation correction. [¹⁸F]fallypride PET scans (5.0 mCi, specific activity greater than 3000 Ci/mmol) were performed prior to and 180 minutes following a 0.43mg/kg oral dose of d-AMPH. Sensation Seeking Scale-Form V (11) was performed. Prior to the initial PET study and 60 minutes after d-AMPH 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 for determination of plasma level of d-AMPH. Serial PET scans were coregistered to each other and to thin section T1 weighted MRI scans (14) and reoriented to the ACPC line. Regions of interest, caudate, putamen, ventral striatum, medial thalamus amygdala, temporal cortex, substantia nigra were delineated on MRI scans of the brain and transferred to the coregistered PET scans. Regional DA D<sub>2</sub> receptor b.p. and parametric images of DA D<sub>2</sub> receptor b.p 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 calculated. Correlations of changes in cognition and sensation seeking with parametric images of DA release were performed. Probability maps were calculated on a voxel basis using a two tailed t-test and corrected for multiple comparisons using the method of Forman (17). Only clusters with a significance greater than p>0.001, corrected for multiple comparisons, were examined.

RESULTS

Parametric image analysis revealed significantly greater DA release in the right globus pallidus and right inferior frontal gyrus due to higher DA release for female subjects (p<0.001, corrected for multiple comparisons). Trend levels differences (p<0.1) for greater DA release in females than males were seen in temporal and parietal cortex.

Examination of the correlations of sensation seeking with DA release in ROIs demonstrated a striking sex difference in the left ventral striatum; men had an r= 0.898, p= 0.006, while women had an r= -0.713. This difference was significant at the p<0.005 level uncorrected for multiple comparisons. Parametric image analysis demonstrated markedly different patterns of correlations
between sensation seeking and d-AMPH induced DA release in male and female subjects, i.e. females but not males having negative correlations with DA release in the heads of the caudate 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, males but not females 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), inferior temporal cortex bilaterally (r = -0.710 on the left and -0.771 on the right), and the left lateral thalamus (r = -0.746). These differences in correlations reached significance in the heads of the caudate bilaterally and left insula.

Correlations of changes in spatial working memory errors with parametric images of DA release demonstrated a right ventral putamenal cluster in males (r = -0.84, p<0.001, corrected for multiple comparisons) but not in female subjects; the sex difference in right ventral putamen correlations for spatial working memory was significantly different (p<0.001, corrected for multiple comparisons).

Changes in performance on the symbol search task was significantly correlated in male subjects with DA release in the ventral and lateral striatum bilaterally and right hippocampus (r’s ranging from -0.741 to -0.829; p<0.001). Female subjects had positive correlation in the right ventral striatum (r=0.49). A significant difference in correlations was seen in the right ventral and lateral striatum (; p<0.001 corrected for multiple comparisons).

Plasma levels of d-AMPH were not significantly different in males and females being 0.46 ± 0.26 nM/ml and 0.45 ± 0.23 nM/ml respectively.

**DISCUSSION**
While sex related differences in dopaminergic neurotransmission have been reported in humans using PET and SPECT, no previous studies of d-AMPH induced DA release have examined gender differences in humans. The greater DA release in the right globus pallidus and right inferior frontal gyrus in women is consistent with previous animal studies reporting greater d-AMPH induced DA release in females. These differences are not due to volumetric differences as these structures are similar in size in men and women (18). Trend level differences in DA release were seen in cortical regions and other striatal regions suggesting increased DA release in female subjects. Sensation seeking behavior, spatial working memory, attention and speed of cognitive processing are all believed to be modulated by dopaminergic neurotransmission (19). The finding of sex differences in the relationship of DA release to these behaviors suggests significant sex differences in regional dopaminergic function. The differences seen in this study remained significant after correction for multiple comparisons both for within image comparisons and for multiple behavioral tests.

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


FIGURE LEGENDS

Figure 1: Coronal images demonstrating significant clusters of sex differences in (A) DA release in the right globus pallidus, (B) correlations of spatial working memory errors with DA release in the right ventrolateral putamen, (C) correlations of sensation seeking with DA release in the heads of the caudate and left insula, (D) correlations of symbol search (speed of cognitive processing) with DA release in the right ventral striatum.