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Sex Differences in the Relationship of Regional Dopamine Release to Affect and Cognitive Function in Striatal and Extrastriatal Regions Using Positron Emission Tomography and [^{18}F]Fallypride

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ABSTRACT The purpose of this study was to examine sex differences in the correlations of d-amphetamine (d-AMPH) induced displacements of [^{18}F]fallypride in striatal and extrastriatal regions in relation to affect and cognition. Seven male and six female healthy subjects, whose mean age was 25.9 years, underwent positron emission tomography (PET) with [^{18}F]fallypride at baseline and 3 h after a 0.43 mg/kg oral dose of d-AMPH. Percent displacements in striatal and extrastriatal regions were calculated using regions of interest (ROI) analysis and on a pixel-by-pixel basis. Subjects underwent neuropsychological testing prior to the baseline PET study and one hour after d-AMPH administration for the second PET. In order to examine the subjective effect of d-AMPH, subjects rated PANAS at baseline and after administration of amphetamine. Correlations of changes in cognition and affect with regional dopamine (DA) release revealed several significant sex related differences. The results of this study demonstrate in vivo sex related differences in the relationship of regional DA release to affect and cognitive function. **Synapse 65:99–102, 2011.**

INTRODUCTION

In the last two decades, sex differences have been extensively investigated in brain research. Animal studies have found that dopaminergic neurotransmission is modulated by sex steroids (Becker et al., 1990; Di Paolo, 1994). In particular, estrogen considerably enhances striatal dopamine (DA) synthesis, baseline DA release, d-amphetamine (d-AMPH) induced DA release, neuronal firing in substantia nigra and rapidly enhances the behavioral and neurochemical response to d-AMPH (Becker, 1990, 1999a, b; Chiodo and Caggiula, 1980). These findings suggest a sexual difference in the organization of the striatal DA system (Castner and Becker, 1996).

Studies in humans also have revealed sex differences in dopaminergic neurotransmission. Postmortem studies show lower striatal DA levels and a higher 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratio in the putamen of females compared to males suggesting increased DA turnover in women (Konradi et al., 1992).

A number of imaging studies of human striatal and extrastriatal DA D_2 receptors have reported sex differences (Kaasinen et al., 2001; Laakso et al., 2002; Munro et al., 2006; Pohjalainen et al., 1998).

Dopaminergic neurotransmission plays an important role in schizophrenia, major depression, Parkinson's disease, Tourette's syndrome, and attention deficit/hyperactivity disorder. These disorders all show sex differences in their incidence, prevalence, clinical

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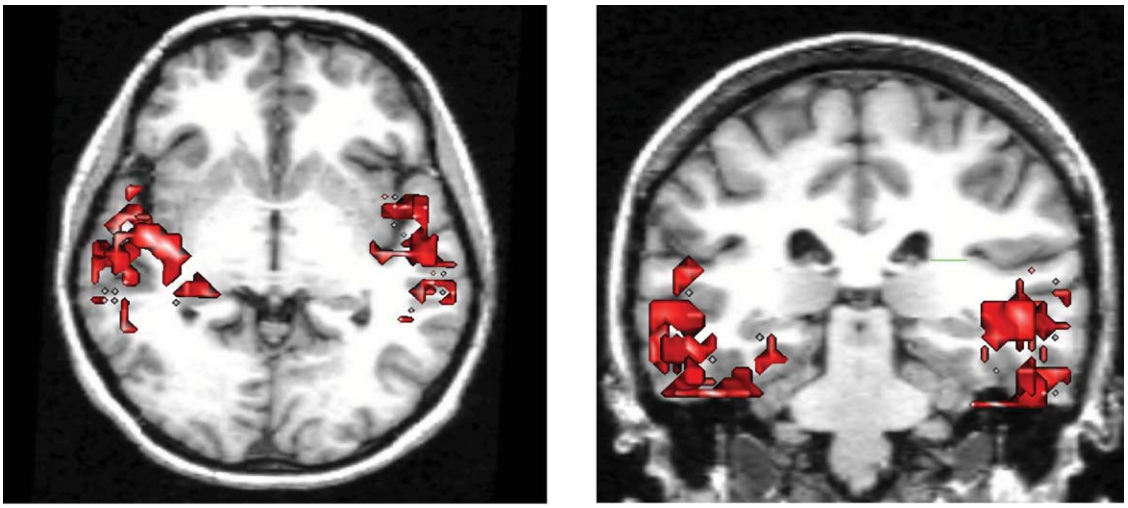

A B

Fig. 1. Sex Differences in Correlations with changes in Stroop (**A** and **B**).

course, and treatment outcome (Hartung and Widiger, 1998). As there are sex-related differences in neuropsychiatric disorders in which dopaminergic neurotransmission is believed to play an important role, it is important to understand whether there are sex differences in the relationship of regional DA release to cognitive function and affect.

We used PET with [^{18}F]fallypride to evaluate whether there are sex differences in d-AMPH-induced DA release (Riccardi et al., 2006b). We report here the relationship of DA release in striatal and extrastriatal regions to cognition and affect, to further elucidate the impact of sex in DA release and its relation to behavior.

METHODS

For a full explanation of methods see Riccardi et al. (2006a, b). Briefly, 13 normal right hand subjects, six females (ages 21 to 29 years, mean age 24.8 years) and seven males (ages 22 to 32 years, mean age 27.6 years), were recruited by advertisement. All were nonsmokers. Five of the six females were on oral contraceptives (OC). After an initial assessment, the study was explained to subjects and informed consent was obtained in writing. This study was approved by the Vanderbilt Institutional Review Board.

All subjects received a physical and neurological examination and SCID (Williams et al., 1992) to rule out Axis I psychopathology. MRI scans were performed using a GE 1.5 T scanner with echospeed gradients. PET scans were performed using a GE Discovery LS PET scanner following a 5.0 mCi slow bolus injection of [^{18}F]fallypride prior to and 180 min following a 0.43 mg/kg oral dose of d-AMPH.

Approximately 60 min after d-AMPH administration (and at the equivalent point in time at baseline) subjects began a neuropsychological battery which included the Stroop task, a measure of attention (Stoelting Co., 2000). To examine the subjective effect of d-AMPH, subjects completed the positive affect negative affect scales (PANAS). The scale has been found to be reliable, conforms to a clear factor structure of affect, and pilot data makes clear that it is sensitive to the activating effects of d-amphetamine (Watson et al., 1988). The differences in Positive Affect observed during baseline and after d-AMPH administration were correlated with the amount of DA release in the ROIs examined.

RESULTS

Examination of correlations of changes in Stroop interference with regional DA release in ROIs revealed that male subjects had a significant negative correlation between Stroop score and left medial thalamic DA release ($r = -0.81$, $P = 0.05$) which was not seen in female subjects ($r = 0$). Male subjects had negative correlations between temporal cortical DA release and Stroop interference. For males, temporal cortex had an $r = -0.90$, $P = 0.05$, on the left and an $r = -0.87$, $P = 0.05$, on the right. In the female subjects, no association between temporal DA release and Stroop scores were observed (Fig. 1). In regard to Stroop interference, female subjects performed better than male subjects at baseline but demonstrated deterioration in performance following d-AMPH administration, while male subjects improved (Fig. 2). This resulted in a significant interaction between gender and change in the interference score following d-AMPH administration ($F(1,9) = 6.78$, $P < 0.03$).

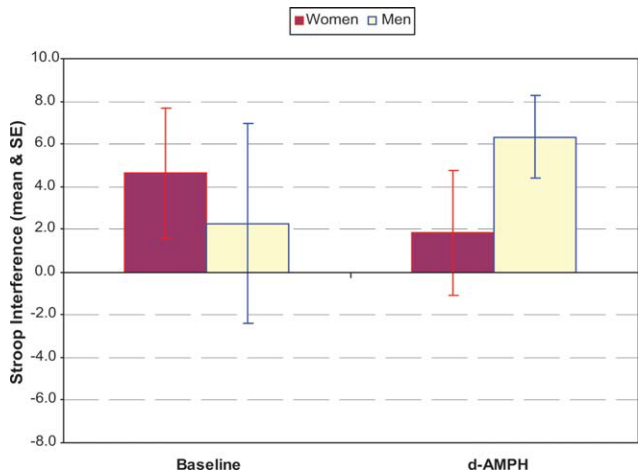

Fig. 2. Stroop interference in male and female subjects at baseline and following d-AMPH administration demonstrates a significant interaction of gender and state (F [1,9] = 6.78, $P < 0.03$).

Significant sex differences were seen in correlations between changes in positive affect with DA release in ROIs. D-AMPH-induced DA release in the left substantia nigra was correlated with change in positive affect in male subjects ($r = 0.84$, $P = 0.04$) but not in female subjects ($r = -0.13$). There was no significant correlation between right ventral striatal DA release and positive affect in men ($r = 0.757$, $P = 0.08$), or women ($r = 0.441$). Sex differences in the relationship of positive affect to regional DA release suggest the need to analyze males and females separately (Riccardi et al., 2006a). Plasma levels of d-AMPH were not significantly different in males (0.46 ± 0.26 nM/ml) compared with females (0.45 ± 0.23 nM/ml).

DISCUSSION

Our previous studies of d-AMPH induced DA release have reported sex differences in DA release in humans (Riccardi et al., 2006b). In this study, we further elucidate the sex differences seen in d-AMPH induced regional DA release and in the relationships of regional DA release to cognition and affect.

Dopaminergic neurotransmission has been shown to modulate attention, speed of cognitive processing, working memory, and positive affect (Nieoullon and Coquerel, 2003). It is also believed to be involved in the pathophysiology of schizophrenia, psychostimulant drug abuse, and attention deficit disorder in extrastriatal brain regions (Arnsten and Dudley, 2005; Koob and Le Moal, 2001; Weinberger et al., 2001). Furthermore, schizophrenia, major depression, Parkinson's disease, Tourette's syndrome, and ADHD all show sex differences in their incidence, prevalence, clinical course, and treatment response.

In this study, the sex related change in performance on the Stroop task following d-AMPH administration is consistent with higher baseline extracellular levels of DA in women in regions mediating this task, consistent with the hypothesized inverted U-shaped curve of DA levels vs. performance on cognitive tasks (Arnsten and Li, 2005). These observations, while preliminary, are consistent with animal data indicating both higher baseline levels of cortical DA and higher d-AMPH-induced DA release in females. Our results also are consistent with differential involvement of dopaminergic circuits in mediating cognition and affect in men and women.

It is noteworthy that in male subjects positive affect had correlations with DA release in the substantia nigra, suggesting an important role for this region in mediating dopaminergic function with affect. This is the first time that a correlation between positive affect and substantia nigra has been reported. We believe this finding to be unique in that none of the other currently available methods for imaging the dopamine system are capable of measuring changes in DA release in this area; furthermore, it indicates an association of Positive Affect with extrastriatal regions other than the ventral striatum, which has been the focus of previous studies (Drevets et al., 2001).

The correlation between positive affect and DA release in the substantia nigra is intriguing because dopaminergic projections from the substantia nigra modulate both striatal and limbic function. This places the substantia nigra in a critical position to affect information processing from the limbic system to the striatum.

In conclusion, sex differences in the relationship of regional DA release to cognitive function and affect were seen. Sex related differences in dopaminergic function may play a role in the observed sex differences in the vulnerability to neuropsychiatric disorders in which DA is believed to play an important role. The results of the current study, if confirmed, indicate the need for further study of the role of sex related differences in modulating dopaminergic neurotransmission in neuropsychiatric disorders.

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