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Sex Differences in the relationship of regional Dopamine release to affect and cognitive function in Striatal and Extrastriatal Regions using PET and [^{18}F]Fallypride

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Keywords

Dopamine; PET; humans; [^{18}F]Fallypride; amphetamine challenge

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 andneurochemical response to d-AMPH (Becker, 1990; 1999; Chiodo *et al*, 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 course, and treatment outcome (Hartung and Widiger, 1998). As there are sex-related differences in neuropsychiatric disorders in which dopaminergic neurotransmission is

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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 whetherthere 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, 6 females (ages 21 to 29 years, mean age 24.8 years) and 7 males (ages 22 to 32 years, mean age 27.6 years), were recruited by advertisement. All were non smokers. 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 minutes following a 0.43 mg/kg oral dose of d-AMPH.

Approximately 60 minutes 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). In order 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 (Figure 1). In regard to Stroop interference, female subjects performed better than male subjects at baseline but demonstrated deterioration in performance following d-amphetamine administration, while male subjects improved (Figure 2). This resulted in a significant interaction between gender and change in the interference score following d-AMPH administration ($F(1,9) = 6.78$, $p<0.03$).

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 the present 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 versus 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 indopaminergic function may play a role in the observed sex differencesin 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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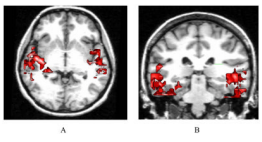

Figure 1.
Sex Differences in Correlations with changes in Stroop (A &B)

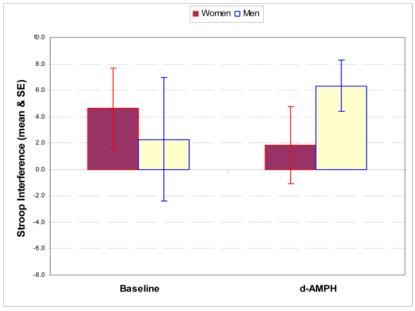

Figure 2.
Stroop interference in male and female subjects at baseline and following d-AMPH administration demonstrates a significant interaction of gender and state ($F [1,9] = 6.78, p<0.03$)