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Dopamine response to psychosocial stress in humans and its relationship to individual differences in personality traits

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ABSTRACT

Background: Previous studies have reported inter-individual variability in the dopamine (DA) response to stress. This variability might be related to individual differences in the vulnerability to experience the negative effect of stress.
Objective: To investigate whether personality traits as measured by the Revised NEO Personality Inventory explain variability in DA response to a psychosocial stress task.
Methods: Eleven healthy adults, mean age of 26 ± 3.87 underwent two Positron Emission Tomography (PET) scans using the dopamine $D_{2/3}$ agonist, [^{11}C]-(+)-PHNO under a control and stress condition. The Simplified Reference Tissue Model (SRTM) was used to obtain [^{11}C]-(+)-PHNO Binding Potential (BP_{ND}). Stress-induced DA response was indexed as a percent change in [^{11}C]-(+)-PHNO BP_{ND} between control and stress conditions. The regions of interest were defined into D_2-rich regions, which included the Associative and Sensorimotor Striatum (AST and SMST); $D_2/_3$ mixed regions, which included the Limbic Striatum (LST) and Globus Pallidus (GP); and D_3-rich region, which included the Substantia Nigra (SN).
Results: Several personality traits within the Neuroticism and Openness to Experience domain were significantly correlated with blunted DA response to stress. Specifically, the Angry-Hostility, Vulnerability, and Depression trait were associated with blunted DA stress response in the AST ($r = -0.645$, $p = 0.032$), LST ($r = -0.677$, $p = 0.022$) and GP ($r = -0.736$, $p = 0.010$), respectively. The Openness to Values was correlated with a decreased DA release in the SN ($r = -0.706$, $p = 0.015$).
Conclusion: Variability in DA stress response might be related to individual differences in personality.

1. Introduction

Exposure to stressful life events can precipitate mental illness in vulnerable individuals (Kendler et al., 2004). Individual differences in personality might represent an internal predisposition to react negatively toward stress and a greater risk to develop psychiatric illness (Bolger and Schilling, 1991; De Jong et al., 1999; Kendler et al., 2004; Larsen and Ketelaar, 1991; Weinstock and Whisman, 2006). Stress has been shown to affect the dopamine (DA) system in the striatum (Pani et al., 2000). Findings from preclinical studies suggested an opposite DA response to stress depending on the characteristic of the stressful stimuli. Specifically, an acute and controllable/escapable physical stress caused an enhanced DA efflux in the ventral striatum, whereas chronic and uncontrollable/inescapable exposure to the same stress attenuated the DA release (Abercrombie et al., 1989; Cabib and Puglisi-Allegra, 1994; Horvitz, 2000; Kalivas and Duffy, 1995; Lucas et al., 2007). In support to these preclinical findings, brain imaging studies in humans also reported stress-induced DA release in response to various stressful stimuli, including painful stimuli (Scott et al., 2006), metabolic stress (Adler et al., 2000), and psychosocial stress (Adler et al., 2000; Pruessner et al., 2004; Scott et al., 2006; Soliman et al., 2008). In all of these studies, the striatal DA system showed important inter-individual variability in its response to stress. In animals, acute and chronic social stress caused a significant elevation of mesolimbic DA D_2 receptor density in the subordinate, but not in the dominant rats (Lucas et al., 2004; Tidey and Miczek, 1996). Similarly, in humans, an increase in striatal DA response to stress was reported in subjects with a history of low maternal care, and those with negative schizotypy personality (Pruessner et al., 2004; Soliman et al., 2008).

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Personality plays an important role in determining individual differences in emotional health and psychological outcomes. In recent meta-analyses involving 175 studies published from 1980 to 2007, personality traits were highly correlated with anxiety, depressive, and substance use disorders, with the Neuroticism-related traits showing the strongest link to psychopathology (Kotov et al., 2011). Personality differences affect the stress experience, and it also influences how people cope with stress (Bolger and Schilling, 1991). Previous studies have reported a relationship between individual differences in D_2 receptor levels and personality traits. In-vivo PET and SPECT studies reported associations between the D_2 receptors availability in the striatum and the Detachment trait (Farde et al., 1997; Laakso et al., 2003; Wacker et al., 2005), Extraversion (Depue and Collins, 1999), Novelty-/Sensation-Seeking (Kaasinen et al., 2004; Suhara et al., 2001; Zald et al., 2008) and Neuroticism (Kestler et al., 2000; Lee et al., 2005; Wacker et al., 2005).

Previous brain imaging studies of personality have used nonselective D_2/D_3 PET radioligands such as the antagonists [^{11}C] Raclopride, [^{18}F]fallypride, and [^{11}C]FLB-457, giving some insight into the influence of personality on the D_2 receptor status. In the present study, we used [^{11}C]-(+)-PHNO to elucidate the differential effect of psychosocial stress on the DA system, taking into account individual's differences in personality traits. [^{11}C]-(+)-PHNO is a DA $D_{2/3}$ agonist radioligand, with a higher affinity to the D_3 receptors (Narendran et al., 2006; Rabiner et al., 2009; Searle et al., 2010; Tziortzi et al., 2010). In the brain, D_3 receptors are found to co-localize with D_2 receptors, with high levels of the D_3 receptors detected in the ventral striatum (Murray et al., 1994; Seeman et al., 2006). More recently, Tziortzi reported that the D_3 receptors contributed to ~100% of the [^{11}C]-(+)-PHNO binding in the substantia nigra, ~26% of binding in the limbic striatum, ~6% in the putamen, ~0% in caudate and ~65% in the globus pallidus (Tziortzi et al., 2010). Based on these relative contributions of D_2 and D_3 binding of [^{11}C]-(+)-PHNO, we aimed to study the influence of personality on dopamine response to stress in the D_2-rich regions, D_2/D_3-mixed regions, and the D_3-rich regions in healthy individuals. Using [^{11}C]-(+)-PHNO as a radioligand, we have a unique opportunity to study the effect of psychosocial stress on D_2 and D_3 receptors in the same subject. Although (Mizrahi et al., 2011) used [^{11}C]-(+)-PHNO to study the effect of psychosocial stress in humans, this is the first study that investigates the effect of stress on D_3-rich region and takes into account the influence of personality traits on both D_2 and D_3 receptors system.

2. Materials and methods

2.1. Subjects

Study participants were recruited through advertisements posted within the greater Toronto area. Potential subjects were screened to rule out any Axis I disorders using the Structured Clinical Interview for DSM-IV by the study psychiatrist (RM). In addition, pregnancy, claustrophobia or metal in the body were exclusion criteria. Urine toxicology screening was done in two parts: an alcohol dehydrogenase enzyme assay was used to screen for ethanol and a combination of gas- and liquid-chromatography mass-spectroscopy (GC/MS and LC/MS) was used to screen for drugs, which is sensitive to cocaine, amphetamine, MDMA, ketamine, Δ9-tetrahydrocannabinol, opiates, anxiolytics, antidepressants, and anti psychotics. The GC/MS was analyzed using the ThermoFisher DSQ 2, and the LC/MS was analyzed using the ThermoFisher LTW. The sample preparation, the instrument methodology, and the drug libraries set up in these instruments were all developed and validated in-house at the Centre for Addiction and Mental Health (CAMH) Clinical Laboratory.

A written informed consent was obtained from each study participant after the study was fully explained. The study and recruitment procedures were approved by the Research Ethics Board for Human Subjects at CAMH. The sample in this study is the same as the healthy control presented in a recent study (Mizrahi et al., 2011).

2.2. Personality assessment

Personality traits were assessed with the Revised NEO Personality Inventory (Costa and McCrae, 1992). The NEO Personality Inventory is a 240-item self-report questionnaire that measures five broad dimensions of personality factors: Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C) (Costa and McCrae, 1992). The NEO PI-R is emerged from factor-analytic research on normal personality descriptors. It can be used to describe any personality from normal to pathological (Costa and McCrae, 1992). The NEO Pi-R has been shown to have high internal consistency (coefficient alpha range: 0.56–0.81) and test–retest reliability (coefficient alpha range: 0.66–0.92 for facet scales), as well as strong convergent and discriminant validity (Costa and McCrae, 1992).

The five factors are each differentiated into 6 subscales or "facets" that represent groups of inter-correlated traits. Respondents have five choices, ranging from 'strongly agree' to 'strongly disagree'. Raw scores were transformed to *T*-scores to correct for age and gender using the published normative data (Costa and McCrae, 1992). Standardized *T*-scores < 45 are considered in the low range, those 45–55 in the average range, and those >55 in the high range (Costa and McCrae, 1992).

2.3. Stress task

Psychological stress was induced using the Montreal Imaging Stress Task (MIST), which has been validated in previous functional MRI and PET studies (Dedovic et al., 2005; Pruessner et al., 2004). A recent study has also shown its specificity to induce psychosocial stress in humans (Lederbogen et al., 2011; Mizrahi et al., 2011). Although this task is sufficient to elicit a significant hormonal stress response in humans, it is considered to be a moderate stressor in comparison to the more widely used public speaking task with regard to cortisol stress response and self-reported levels of discomfort (Pruessner et al., 1999). In this study, subjects performed mental arithmetic tasks under two conditions while lying in the PET scanner: the control non-stress and stress conditions. The arithmetic task was displayed on a computer screen, which also displayed information about the total number of errors, expected average number of errors, time spent on the current problem, and performance feedback for each problem (correct, incorrect, time out). The arithmetic task consisted of 6 blocks of mental arithmetic segment, with each block lasted for 6 min. During the stress PET condition, subjects completed each segment under time pressure and received verbal negative feedback from investigators for approximately 2 min between each segment, telling them that they needed to improve their performance to each minimum performance requirement. Additionally, to maintain constant difficulty, the time constraint was adjusted to be slightly above each individual's abilities. Because of the manipulation of the difficulty level, the average performance was set at 20–30% correct answers. The non-stress PET scan condition is a sensory motor control PET session, which involved a similar arithmetic task but without time constraints or negative verbal feedback. The non-stress control was also administered as a practice trial on a separate day outside the PET scan room, prior to the day of PET scan visits. This session served to reduce the effect of novelty. All non-stress PET scans were