Striatal dopamine D2/3 receptor regulation by stress inoculation in squirrel monkeys

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1. Introduction

Intermittent exposure to mildly stressful situations is a feature of stress inoculation training for people who work in conditions where performance in the face of adversity is required, e.g., medical and military personnel, police, firefighters, and rescue workers (Meichenbaum, 1993; Saunders et al., 1996; Stetz et al., 2007). Stress inoculation is further supported by evidence that mild but not minimal nor severe stress exposure promotes subsequent coping and emotion regulation as described by U-shaped functions (Russo et al., 2012; Sapolsky, 2015; Seery et al., 2010). Exposure psychotherapies likewise teach patients to imagine a graded series of stressful situations and encourage interaction with stressors in vivo (McNally, 2007). These procedures promote learning (Craske et al., 2008) and provide opportunities to practice acquired coping skills (Serino et al., 2014).

Previously, we showed that stress inoculation early in life enhances subsequent coping and emotion regulation modeled in mice (Broekhurst et al., 2015) and squirrel monkeys (Lyons et al., 2009; Lyons et al., 2010). In keeping with suggestions that emotion regulation is an aspect of cognitive control (Compton et al., 2011), we also found that stress inoculation enhances cognitive control of impulsive motivated behavior (Parker et al., 2005; Parker et al., 2012). Impaired cognitive control and dysregulation of motivation have been linked to low striatal dopamine D2 and/or D3 receptors (DRD2/3) levels in rodents, monkeys, and humans (Dalley et al., 2011; Groman et al., 2011; Nader et al., 2006; Trifiletti & Martinez, 2014; Volkow et al., 2011). Conversely, increased experimental expression of dopamine D2 receptors in ventral striatum enhances motivation in mice (Trifiletti et al., 2013). High striatal DRD2/3 availability in humans is associated with resilience against the development of addictions (Volkow et al., 2002; Volkow et al., 2006) and pharmacological DRD2/3 agonists decrease impulsive behavior in rats (Fernando et al., 2012). DRD2/3 agonists similarly improve reversal learning as an index of cognitive control in
humans dependent on psychostimulant drugs (Ersche et al., 2011).

Here, we examine striatal DRD2/3 regulation by stress inoculation in female squirrel monkeys. Females are studied because stress-related mental health disorders are 2–3 times more common in women than men (Altemus et al., 2014). Impaired cognitive control of thoughts, feelings, and behavior is a key dimension of various psychiatric disorders in humans (Groman & Jentsch, 2012) and neural mechanisms that mediate this dimension may provide novel targets for new treatment interventions. Based on our findings that cognitive control of impulsivity is improved in squirrel monkeys exposed early in life to stress inoculation (Parker et al., 2005; Parker et al., 2012), we test for increased striatal DRD2/3 availability in stress inoculated squirrel monkeys studied as adults by measuring \(^{11}\text{C}\)raclopride binding in vivo with positron emission tomography (PET).

2. Materials and methods

Female squirrel monkeys (Saimiri sciureus) that were born and raised at the Stanford University Research Animal Facility served as subjects. All squirrel monkeys were initially housed in undisturbed mixed-sex natal groups through 16 weeks of age. Group composition was determined by birth dates to minimize developmental differences between natal groups. Seasonal synchronous breeding facilitated the generation of age-matched groups.

Groups were housed indoors in 1.8 × 1.2 × 1.8 m species appropriate cages that were cleaned daily. Housing and testing occurred in climate controlled rooms with a ambient temperature of 26 °C. Light/dark cycles were 12:12 h with lights on at 0700 h. All squirrel monkeys were provided unrestricted access to fresh drinking water and monkey chow with fruit and vegetable supplements. Various toys, swinging perches, and simulated foraging activities were provided for environmental enrichment. To facilitate husbandry-related activities and experimental manipulations, squirrel monkeys were trained to leave the home cage through a small sliding door connected to a transport box used for capture and transportation. All procedures were approved by Stanford University’s Administrative Panel on Laboratory Animal Care and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.1. Experimental design

Squirrel monkeys were randomized to one of three 10-week treatment conditions that occurred between 17 and 27 week of age as described elsewhere in detail (Parker et al., 2004; Parker et al., 2006). In the no-stress (NS) control condition, squirrel monkeys were continuously maintained in undisturbed natal groups. In the stress inoculation (SI) condition, squirrel monkeys were individually removed from natal groups once each week for 10 total 1-hr separation sessions (Parker et al., 2004). In the SI + Mom condition, squirrel monkeys were treated identically except that each monkey along with its mother was removed together from natal groups once each week for 10 total 1-hr sessions (Parker et al., 2006). After each social separation in the SI and SI + Mom conditions, squirrel monkeys were returned to the home cage and reunited with the natal group. All separations occurred between 1200 and 1800 h and no more than one squirrel monkey from each natal group was separated on a given day.

After completion of the treatment conditions at 27 week of age, behavioral measures of coping and emotion regulation were collected from all squirrel monkeys in the presence of mothers during involuntary exposure to a novel environment at 9 months of age (Parker et al., 2004; Parker et al., 2006). Mothers were then permanently removed and their offspring were housed with peers.

2.2. \(^{11}\text{C}\)Raclopride radiosynthesis

\(^{11}\text{C}\)Raclopride was prepared in a GE TRACERlab FX C Pro module (GE Healthcare) using previously published methods (Langer et al., 1999) with the following modifications. Briefly, \(^{14}\text{C}\) carbon dioxide was delivered from a GE PETtrace cyclotron (GE Healthcare) into the synthetic module, where the methylating agent \(^{11}\text{C}\)methyl triflate, was formed from \(^{11}\text{C}\)carbon dioxide via reduction, halogenation, and triflation. \(^{11}\text{C}\)Methyl triflate was bubbled with a flow rate of 20 mL/min into solution containing acetone (300 μl), 0-Desmethyl free base precursor (1 mg, 3.3 μmol, ABX), and NaOH (3 μL, 1 N) at ~20 °C. The reaction mixture was warmed to room temperature within 1 min, diluted with 1 mL water, and loaded on a semi-preparative HPLC column for purification (Phenomenex Luna C18 5 μm, 250 × 10 mm, 30% acetonitrile, 70% 0.1 M NH₄HCO₃ with 0.5% AcOH, 7 mL/min). The fraction corresponding to \(^{11}\text{C}\)Raclopride (Rt = 9.2 min) was collected in a round flask preloaded with 20 mL water. Mobile phase was removed using a solid phase extraction (SPE) process, then \(^{11}\text{C}\)Raclopride was eluted from the SPE cartridge with ethanol and subsequent dilution with saline (ethanol < 10% v/v). Final \(^{11}\text{C}\) raclopride for imaging was sterilized by passing it through a 0.22 μm Millex MP (33 mm) sterile filter. Overall synthesis time was 45 min and radiochemical yield of \(^{11}\text{C}\)Raclopride was 2.0 ± 0.6% (n = 40). Analytical HPLC (Phenomenex Gemini C18 5 μm, 250 × 4.6 mm, 60% acetonitrile, 40% 0.1 M NH₄HCO₃ with 0.5% AcOH, 1 mL/min) showed the final product (Rt = 7.8 min) to have >99% radiochemical and chemical purities and high specific activity (10.6 ± 3.9 Ci/μmol; n = 40). Both radiochemical yield and specific activity were decay-corrected to the end of synthesis.

2.3. Neuroimaging

Whole brain anatomical and \(^{11}\text{C}\)Raclopride data were acquired with established methods. Each squirrel monkey was fasted overnight and then sedated with an intramuscular injection of 10 mg/kg ketamine hydrochloride. Atropine sulfate was subcutaneously administered at 0.04 mg/kg. Ophthalmic ointment was placed in both eyes and anesthesia was induced with ~1% isoflurane gas. Heart rate, respiration, body temperature, and blood oxygen...
saturation were continuously monitored. An intravenous catheter was placed using aseptic technique in either the cephalic or saphenous vein. The radiotracer was produced to provide ~2.0 mCi of $^{11}$C]raclopride in a volume no greater than 0.75 mL injected at 0.2 mL per 30 s at ~10:00 h. The mass (0.17 ± 0.02 μg; mean ± SEM) and specific activity (4.3 ± 0.3 Ci/μmol) of $^{11}$C]raclopride administered to each monkey did not differ significantly across the three treatment conditions. After administration, the catheter was flushed with an amount of heparinized saline equivalent to the volume of the catheter.

Fully three-dimensional dynamic emission data were then collected for 60 min on a microPET R4 (Siemens Preclinical Solutions, Knoxville, TN) using an energy window of 250–750 keV and 137 successive time frames of increasing duration (14 at 5 s, 29 at 10 s, 45 at 20 s, 30 at 40 s, 19 at 60 s). The microPET scanner has 96 scintillation detector modules compactly arranged in a 14.8 cm diameter ring with an axial length of 7.8 cm. The tomograph has a spatial resolution of 1.85 mm full-width at half-maximum (FWHM) in the axial direction and 1.66 mm FWHM in the transaxial direction, which provides linear resolution of ~2.5 mm in all three dimensions. Resulting emission data were used to compute $^{11}$C]raclopride binding for each voxel with a simplified kinetic model that uses the cerebellum as a reference brain region devoid of DRD2/3 (Gunn et al., 1997).

Whole brain anatomical data were acquired with MRI in separate sessions on a Signa 3T scanner (General Electric, Milwaukee, WI) at 9.5 years of age (range 8.4–10.3 years). Squirrel monkeys were sedated as described above and MRI was conducted with the following three-dimensional inversion recovery prepared fast spoiled gradient pulse sequence: TR = 12 ms, TE = 3 ms, TI = 300 ms, flip angle = 15, NEX = 4, matrix = 160 x 160, FOV = 8 cm, voxel size = 0.5 x 0.5 x 0.5 mm, slice thickness = 0.5 mm, gap = 0 mm, total scan time = 18 min. PET data were spatially co-registered to MRI data (Fig. 1) using SPM8 software (www.fil.ion.ucl.ac.uk/spm/). $^{11}$C]raclopride binding measures (BP$_{ND}$) were determined for dorsal caudate nucleus, dorsal putamen, and ventral striatum as defined elsewhere (Mawlawi et al., 2001).

2.4. Data analysis

Mixed factor analysis of variance (ANOVA) was used to assess BP$_{ND}$ measures. Stress inoculation (NS, SI, SI + Mom) was considered a between-subjects factor with striatal region (caudate, putamen, ventral striatum) and brain side (left, right) considered within-subjects factors. Body weight was included as a statistical covariate in keeping with suggestions for small primate PET neuroimaging (Morris et al., 1998).

Post hoc pairwise comparisons with the NS control treatment condition were conducted with Dunnett tests. Post hoc comparisons between striatal regions were conducted with Bonferroni corrections and comparisons between SI and SI + Mom treatment conditions were conducted with t-tests. Effect sizes were determined using Cohen’s $d$ and associations between DRD2/3 BP$_{ND}$ measures and previously reported cognitive control errors (Parker et al., 2012) were assessed with Pearson correlation coefficients. All test statistics were evaluated with two-tailed probabilities at $P < 0.05$.

3. Results

Significant stress inoculation ($F(2,20) = 4.01, P = 0.034$) and striatal region ($F(2,40) = 37.61, P < 0.001$) main effects were discerned in the 3-way ANOVA. As expected, DRD2/3 BP$_{ND}$ was greater in caudate and putamen compared to ventral striatum ($P < 0.001$). Across striatal regions, DRD2/3 BP$_{ND}$ was respectively 9.3% and 10.7% greater in SI and SI + Mom squirrel monkeys compared to NS controls. Laterality main effects and all of the interactions were not statistically significant.

The 3-way ANOVA was decomposed to separately examine each striatal region with left and right brain sides combined (Fig. 2). Significant stress inoculation effects were discerned for ventral

![Fig. 1. Axial (top) and coronal (bottom) images of neuroanatomy (MRI) and DRD2/3 availability (PET) detected in vivo by $^{11}$C]raclopride binding in squirrel monkey brain.](image)
correlated with fewer cognitive control errors (Fig. 3) and the DRD2/3 availability were detected in the ventral striatum. DRD2/3 availability in ventral striatum was also greater in caudate and putamen compared to NS controls (Fig. 2). Dunnett tests likewise established that DRD2/3 BPND was greater for SI + Mom squirrel monkeys compared to NS controls (P < 0.038) but not putamen. Squirrel monkeys from the SI condition did not differ from SI + Mom squirrel monkeys in any of the striatal regions. Post hoc Dunnett tests established that DRD2/3 BPND was greater in ventral striatum for both SI (P = 0.041) and SI + Mom (P = 0.037) squirrel monkeys compared to NS controls. Dunnett tests likewise established that DRD2/3 BPND was greater for SI + Mom squirrel monkeys compared to NS controls in caudate (P = 0.038) but not putamen (Fig. 2).

Effect size estimates confirmed that DRD2/3 regulation by stress inoculation varied systematically across striatal regions. For the SI and SI + Mom conditions combined, treatment effects relative to the NS condition were greatest in ventral striatum (d = 1.41) followed by caudate (d = 1.07) and putamen (d = 0.78). Differences between regions diminished the overall increase described above for stress inoculation main effects across striatal regions. Effects in ventral striatum were the most robust with DRD2/3 BPND measures respectively 22.1% and 21.8% greater in SI and SI + Mom squirrel monkeys compared to NS controls.

Behavioral assessments of cognitive control from an earlier study (Parker et al., 2012) were completed for 6 of 7 SI squirrel monkeys and 7 of 9 NS squirrel monkeys. Cognitive control tests were not conducted with any of the SI + Mom squirrel monkeys. Similar DRD2/3 BPND measures in SI and SI + Mom squirrel monkeys suggest that increased DRD2/3 availability relative to NS controls (Fig. 2) reflects stress inoculation and not subsequent testing effects. Cognitive control errors for SI and NS squirrel monkeys analyzed together were inversely correlated with bilateral measures of DRD2/3 availability in ventral striatum (r = −0.62, df 11, P = 0.02) but not caudate (r = −0.45, df 11, P = 0.12) nor putamen (r = −0.32, df 11, P = 0.29). Higher DRD2/3 availability in ventral striatum correlated with fewer cognitive control errors (Fig. 3) and the correlation largely reflects group differences between SI and NS squirrel monkeys. The correlation was nearly significant, however, for NS squirrel monkeys analyzed alone (r = −0.71, df 5, P = 0.076) but not for SI squirrel monkeys with higher overall levels of DRD2/3 availability and fewer cognitive control errors.

4. Discussion

Significant stress inoculation and striatal region main effects for DRD2/3 availability were detected in vivo by neuroimaging. DRD2/3 availability was greater in caudate and putamen compared to ventral striatum. DRD2/3 availability in ventral striatum was also consistently greater in stress inoculated squirrel monkeys compared to no-stress controls. Squirrel monkeys exposed to stress inoculation in the presence of their mother did not differ from squirrel monkeys exposed to stress inoculation without maternal companionship. Similar effects in different social contexts extend the generality of our findings and together suggest that stress inoculation increases striatal DRD2/3 availability as a correlate of cognitive control in squirrel monkeys.

In natural and semi-natural conditions squirrel monkey mothers and other group members intermittently leave newly weaned offspring beginning at 3–6 months of age to forage for food on their own (Boinski & Fragaszy, 1989; Lyons et al., 1998). Initially, brief intermittent separations studied in controlled experimental conditions elicit distress peep-calls and increase plasma levels of the stress hormone cortisol with partial habituation of these

**Fig. 2.** Stress inoculation effects on DRD2/3 availability in ventral striatum, caudate, and putamen. Data from individual squirrel monkeys are plotted for the no-stress control (NS), stress inoculated alone (SI), and stress inoculated with mother (SI + Mom) treatment conditions. Horizontal bars signify treatment condition means and asterisks represent significant Dunnett test comparisons with the NS control condition (P < 0.05). DRD2/3 BPND measures reflect left and right brain sides combined. Note different y-axis measurement scales for ventral striatum compared to caudate and putamen.

**Fig. 3.** Correlation between DRD2/3 availability in ventral striatum and cognitive control errors (r = −0.62, df 11, P = 0.02) for squirrel monkeys from the no-stress control (NS, triangles) and stress inoculated alone (SI, squares) treatment conditions. Cognitive control errors were assessed as described elsewhere (Parker et al., 2012) and represent the number of straight reaches on test trials with the box opening oriented left or right. DRD2/3 BPND for ventral striatum reflects left and right brain sides combined. Linear regression and 95% confidence intervals are depicted.
measures observed over repeated separations (Coe et al., 1983; Hennessy, 1986). Later in life, squirrel monkeys exposed to intermit-
tent separations show fewer behavioral indications of anxiety,
diminished stress levels of cortisol, and enhanced sensitivity to
 glucocorticoid feedback regulation of the hypothalamic–pituitary–
adrenal (HPA) axis compared to squirrel monkeys not exposed to prior separations (Lyons et al., 2009; Lyons et al.,
2010). Whereas severe forms of chronic stress impair HPA axis regulation and induce anxiety in macaque monkeys (O’Connor &
Cameron, 2006; Sanchez, 2006), intermittent separations that
simulate naturally occurring but stressful conditions mimic the
effects of stress inoculation in humans.

In an earlier study of cognitive control conducted at 1.5 years of
age, stress inoculated squirrel monkeys exposed to prior intermit-
tent separations performed significantly better than control squirrel
monkeys not exposed to prior separations (Parker et al., 2005).
Performance on the same cognitive test in marmoset monkeys and macaque monkeys is impaired by lesions of prefrontal cortex
(Diamond, 1990; Dias et al., 1996; Wallis et al., 2001) but not lesions of
hippocampus (Diamond et al., 1989). In a different sample of
squirrel monkeys from those examined here, stress inoculation early in life increased ventromedial prefrontal cortical volumes
control over prefrontal cortex control (Diamond, 1990; Hennessy,
2006). Larger volumes do not reflect increased cortical thickness but instead represent surface area expansion of ventromedial prefrontal cortex due to growth and maturation of underlying white matter (Katz et al., 2009).

To determine whether improvements in cognitive control of
impulsivity continue on into adulthood, we tested a subset of the
same squirrel monkeys as those examined here using different
procedures at 3.5 years of age to assess inhibition of a motivated
prepotent response (Parker et al., 2012). Stress inoculated squirrel
monkeys exposed to prior intermittent separations again per-
formed better than control squirrel monkeys not exposed to prior separations (Parker et al., 2012). Moreover, performance at 3.5
years correlated with cognitive control measures collected at 1.5
years of age (Parker et al., 2012). These findings suggest that stress
inoculation early in life induces enduring trait-like transformations in cognitive control of impulsivity.

Cognitive control of impulsive behavior is a complex function
mediated by multiple neural mechanisms. Larger ventromedial
prefrontal size in humans predicts diminished impulsivity (Matsumo et al., 2009) and prefrontal cortical regions interact with striatal
dopamine systems to regulate cognitive control (Jentsch &
Pennington, 2014). Studies of rats, monkeys, and humans have
found that impulse motivation for psychostimulant drugs is
associated with low striatal DRD2/3 measures (Dalley et al., 2011;
Nader et al., 2006; Triffleff & Martinez, 2014; Volkow et al., 2011)
and high striatal DRD2/3 availability in humans has been linked to
resilience against addictions (Volkow et al., 2002; Volkow et al.,
2006). Pharmacological DRD2/3 agonists decrease impulse
behavior in rats (Fernando et al., 2012) and improve reversal
learning as an index of cognitive control in humans dependent on
psychostimulant drugs (Erche et al., 2011).

We found that DRD2/3 availability was greater in squirrel
monkey caudate and putamen compared to ventral striatum as
observed in PET studies of humans (Mawlawi et al., 2001) and other
non-human primates (Groman et al., 2011). DRD2/3 availability
was also greater in stress inoculated squirrel monkeys compared to
stress controls. Stress inoculation effects were greatest in ventral
striatum followed by caudate and putamen. Differences between
striatal regions in neuroanatomical connections and functions
(Haber & Knutson, 2010; Choi et al., 2012) support our finding that
enhanced cognitive control correlated with higher DRD2/3 avail-
ability in ventral striatum. Pharmacological mimicry of increased
DRD2/3 availability by stress inoculation may therefore provide a
novel target for new treatments of psychiatric disorders in humans
that involve deficits in cognitive control.

Our results should be interpreted in the context of potential
limitations. Findings from females may or may not hold true for
males. Behavioral measures of cognitive control were not collected
from all monkeys which limited the size of samples used for cor-
relations but allowed assessment of stress inoculation versus sub-
sequent testing effects. The [11C]raclopride PET radiotracer
primarily binds dopamine D2 receptors (Narendran et al., 2006) but
also D3 receptors in ventral striatum (Gurevich & Joyce, 1999) and
does not distinguish pre-versus post-synaptic locations. DRD2/3
BPND measures also reflect receptor availability and not receptor
densities because in vivo dopamine levels affect [11C]raclopride
binding (Laruelle, 2000). Nevertheless, in vivo PET measures of
DRD2/3 availability correlate with in vitro estimates of striatal
DRD2/3 densities in vervet monkeys (Groman et al., 2014). More-
over, cerebrospinal fluid levels of the dopamine metabolite
homovanillic acid do not differ significantly in stress inoculated
squirrel monkeys compared to controls (Parker et al., 2007). Lastly,
the search for drugs that mimic increased DRD2/3 signaling as a
target for new clinical interventions must contend with unwanted
side effects (Jentsch & Pennington, 2014).

5. Conclusions

We found stress inoculation and striatal region main effects for
DRD2/3 availability in squirrel monkeys. DRD2/3 availability was
greater in caudate and putamen compared to ventral striatum.
DRD2/3 availability in ventral striatum was also consistently
greater in stress inoculated squirrel monkeys compared to no-
stress controls. Squirrel monkeys exposed to stress inoculation in
the presence of their mother did not differ from squirrel monkeys
exposed to stress inoculation without maternal companionship.
Similar effects in different social contexts extend the generality
of our findings and together suggest that stress inoculation increases
striatal DRD2/3 availability as a correlate of cognitive control in
squirrel monkeys.

Conflict of interest

Dr. Schatzberg reports equity in Merck, Pfizer, Neurocrine,
XHale, and Corcept Therapeutics (co-founder). Dr. Schatzberg has
received lecture fees from Merck and consulted to Takeda/Lund-
beck, Pfizer, Depomed, and Neurotechnics. Drs. Lee, Nechvatal, Shen,
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