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Stress-Induced Dopamine Release in Humans at Risk of Psychosis: a [^{11}C]Raclopride PET Study

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Drugs that increase dopamine levels in the brain can cause psychotic symptoms in healthy individuals and worsen them in schizophrenic patients. Psychological stress also increases dopamine release and is thought to play a role in susceptibility to psychotic illness. We hypothesized that healthy individuals at elevated risk of developing psychosis would show greater striatal dopamine release than controls in response to stress. Using positron emission tomography and [^{11}C]raclopride, we measured changes in synaptic dopamine concentrations in 10 controls and 16 psychometric schizotypes; 9 with perceptual aberrations (PerAb, ie positive schizotypy) and 7 with physical anhedonia (PhysAn, ie negative schizotypy). [^{11}C]Raclopride binding potential was measured during a psychological stress task and a sensory-motor control. All three groups showed significant increases in self-reported stress and cortisol levels between the stress and control conditions. However, only the PhysAn group showed significant stress-induced dopamine release. Dopamine release in the entire sample was significantly negatively correlated with smooth pursuit gain, an endophenotype linked to frontal lobe function. Our findings suggest the presence of abnormalities in the dopamine response to stress in negative symptom schizotypy, and provide indirect evidence of a link to frontal function.

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INTRODUCTION

Stressful stimuli lead to dopamine (DA) release in the brains of animals (Abercrombie *et al*, 1989; Rouge-Pont *et al*, 1993) and humans (Adler *et al*, 2000; Pruessner *et al*, 2004). Considerable evidence links psychotic states and a hyperdopaminergic response to physiological or psychological stressors (Moore *et al*, 1999). In schizophrenia, a prototypical psychotic illness, there is clinical evidence of abnormal DA response to pharmacological challenge, metabolic stressor, and psychological stressor. For example, schizophrenic patients have a higher DA response to amphetamine than controls as measured by receptor binding studies (Laruelle *et al*, 1996; Breier *et al*, 1997), and do not show the expected decrease in plasma homovanillic acid (HVA, a DA metabolite) in response to a mental stressor (Sumiyoshi *et al*, 1999). Schizotypal personality disorder patients also show greater amphetamine-induced DA release than controls, though less than that seen in acute schizophrenic patients (Abi-Dargham *et al*, 2004). A metabolic stressor, 2-deoxy-glucose, induced significantly larger increases in plasma HVA in schizophrenic patients than controls (Elman *et al*, 2003). Interestingly, the same stressor produced HVA elevation in schizotypal personality disorder patients only equivalent to controls, along with a blunted cortisol response, possibly indicating that these patients possess a buffering mechanism against hypothalamic–pituitary–adrenal axis stress activation (Mitropoulou *et al*, 2004). Stress, like DA agonist drugs, can trigger relapse in schizophrenic patients (Norman and Malla, 1993; Nuechterlein *et al*, 1994). It has been proposed that exaggerated responses to stress are key in the etiology of psychosis in vulnerable individuals (Thompson *et al*, 2004). However, it is not clear whether differences in dopaminergic responsiveness precede psychosis or develop subsequent to onset.

In the current study, we compared acute stress-related DA release in healthy individuals at elevated risk for psychosis and demographically similar normal controls. High-risk subjects were two groups of 'psychometric schizotypes' with elevated scores on either positive or negative symptom dimensions. Recent research on schizotypy indicates that schizotypal symptoms divide into the same three factors found in schizophrenia, ie positive, negative, and disorganized (Reynolds *et al*, 2000; Suhr and Spitznagel, 2001). Here, we chose to focus on the positive and negative

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dimensions of schizotypy, since these have been associated in longitudinal studies with elevated rates of psychosis and social dysfunction (Erlenmeyer-Kimling *et al*, 1993; Chapman *et al*, 1994; Kwapil *et al*, 1997; Freedman *et al*, 1998). We identified positive and negative symptom schizotypy using the perceptual aberration (PerAb) and physical anhedonia (PhysAn) scales, respectively (Chapman *et al*, 1976, 1978). These scales have a low intercorrelation, suggesting the two groups represent divergent aspects of vulnerability to psychosis (Chapman *et al*, 1980).

We performed [^{11}C]raclopride positron emission tomography (PET) while exposing subjects to a psychological stressor previously shown to induce significant striatal DA release in healthy volunteers with poor maternal care (Pruessner *et al*, 2004). Because of these previous findings, we also assessed maternal care using the Parental Bonding Inventory (Parker *et al*, 1979). We hypothesized that schizotypal individuals would show greater striatal DA responses than control subjects. Finally, because theoretical models have linked DA release with frontal lobe dysfunction in schizophrenia (Davis *et al*, 1991), smooth pursuit eye movements were measured as an index of frontal lobe function (O'Driscoll *et al*, 1999; Bagary *et al*, 2004).

MATERIALS AND METHODS

Subjects

The individuals who participated in the current study are a subgroup of participants recruited for a larger study (Holahan and O'Driscoll, 2005). Students in 10 of the largest undergraduate classes at McGill University completed a 300-item questionnaire on 'perceptions and experiences' consisting of 35 items from the PerAb Scale (Chapman *et al*, 1978), 61 items from the PhysAn Scale (Chapman *et al*, 1976), and 204 distracter items from the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Hathaway and McKinley, 1989). Elevated scores on the MMPI Social Desirability Scale (scores >2 SD above the control mean) were used to exclude subjects with a test-taking style that could invalidate results. A total of 1914 questionnaires were completed for a 60% return rate. Potential schizotypal subjects were individuals who scored >1.95 SD above the mean of their sex on only one of the two schizotypy scales while potential control subjects scored 0.5 SD below the mean on both scales. Cutoffs used were similar to those reported in previous college samples (O'Driscoll *et al*, 1998; Gooding *et al*, 2000). Subjects were screened for Axis I diagnoses using the computerized Diagnostic Interview Schedule Screening Instrument (Robins *et al*, 1981). When this yielded Axis I diagnoses, subjects were interviewed by one investigator (AVH) using the Structured Clinical Interview for DSM-IV (First *et al*, 1996) and excluded if they met criteria. Additional exclusion criteria included any neurological condition, use of prescription medication other than oral contraceptives, pregnancy, claustrophobia, metal in the body, or radiological procedures in the past year.

The Chapman questionnaires identify subjects based on their reported experience of different classes of subclinical symptoms hypothesized to be related to schizophrenia. Individuals with elevated scores on the PerAb scale have an elevated risk of psychosis (Chapman *et al*, 1980, 1994), an elevated rate of schizophrenia in first-degree relatives (Lenzenweger and Loranger, 1989) and a myriad of cognitive and psychophysiological deficits that are associated with schizophrenia (Simons, 1982; Allen *et al*, 1987; Jutai, 1989; Lenzenweger, 1991; Simons and Giardina, 1992; Kwapil *et al*, 1996; Suhr, 1997; Nuchpongsai *et al*, 1999; Gooding *et al*, 2001). Elevated PhysAn scores in the adolescent offspring of schizophrenic patients are associated with increased rates of psychosis and poorer social adjustment in young adulthood (Erlenmeyer-Kimling *et al*, 1993; Freedman *et al*, 1998). Healthy individuals with elevated scores on the PhysAn scale also show many attributes of a high-risk population: they have an increased incidence of the cognitive, behavioral, and social abnormalities associated with schizophrenia, including impaired attention (Jutai, 1989; Wilkins and Venables, 1992; Erlenmeyer-Kimling *et al*, 1993), reaction time crossover (Simons, 1982), abnormal P300 amplitude (Miller, 1986), skin conductance nonresponsiveness (Dawson and Nuechterlein, 1984), and poorer social competence (Garnet *et al*, 1993; Blanchard *et al*, 1998). Further, PhysAn scores may have a familial component as they are higher in schizophrenic patients and their relatives than controls (Katsanis *et al*, 1990; Clementz *et al*, 1991; Franke *et al*, 1993), and are higher in individuals with schizophrenia-related personality disorders who have a genetic loading of schizophrenia than in those without it (Thaker, 2000).

Twenty-eight healthy volunteers participated in the imaging study: 10 controls, 10 PerAb, and 8 PhysAn subjects. The three groups were demographically similar (Table 1). The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. After complete description of the study to the subjects, written informed consent was obtained. Subjects were compensated for their participation.

Table 1 Subject Characteristics and Results

	Control	PhysAn	PerAb
Mean age (years) ± SD	22.0 ± 1.1	21.3 ± 1.4	21.7 ± 1.8
Sex (female, male)	9, 1	6, 1	7, 2
Mean PhysAn score ± SD	10.1 ± 0.74	32.4 ± 5.3[a]	7.1 ± 3.6
Mean PerAb score ± SD	3.3 ± 0.48	4.6 ± 1.5	19.5 ± 2.9[b]
Maternal care score ± SD	30 ± 5.1	22 ± 6.0[c]	24 ± 7.7[c]
Maternal care (low, high)	1, 9	5, 2	4, 4
Nonstress BP ± SD	1.56 ± 0.34	1.79 ± 0.36	1.61 ± 0.26
Stress BP ± SD	1.60 ± 0.43	1.63 ± 0.44[d]	1.63 ± 0.22
Pursuit gain ± SD	0.95 ± 0.03	0.93 ± 0.03	0.95 ± 0.04

Abbreviation: BP, binding potential; PerAb, perceptual aberrations; PhysAn, physical anhedonia.
The [^{11}C]raclopride BP values were extracted from a region of interest in the striatum (see text).
[a]PhysAn subjects differed significantly from Controls ($p<0.001$), whereas PerAb subjects did not ($p>0.14$).
[b]PerAb subjects differed significantly from Controls ($p<0.001$), whereas PhysAn subjects did not ($p>0.17$).
[c]Both groups differed significantly from Controls ($p<0.04$) but not from each other.
[d]Significant difference between stress and nonstress ($p<0.05$).

Stress Task

Psychological stress was induced using a mental arithmetic task similar to that used in a previous PET study (Pruessner *et al*, 2004). The task consists of arithmetic problems that have to be answered under time pressure. Subjects were trained outside the scanner prior to the first PET session. For the stress PET condition, the time constraint was set slightly below the average time needed during the pre-scan session. During the scan, the time constraint was adjusted for each 3-min segment based on performance in the previous segment, to maintain constant difficulty. This ensures that all subjects perform the same number of problems with the same success rate. Arithmetic questions were presented in the scanner via a computer screen and answered using a computer mouse. The same computer screen also displayed information about the total number of errors, the expected average number of errors, the time spent on the current problem, and the performance feedback for each problem (*correct*, *incorrect*, *timeout*). There were three blocks of 12 min each (in four 3-min segments) of mental arithmetic. A confederate, blinded to each individual's group membership, wearing a lab coat and standing beside the scanner, gave the subject negative feedback after each 3-min segment. Feedback included a report of the subject's inferior standing with regard to 'expected' performance and a recommendation to improve their score. This task has been shown to induce behavioral and physiological stress and anxiety responses (Pruessner *et al*, 1999) and DA release in the ventral striatum as measured by [^{11}C]raclopride PET (Pruessner *et al*, 2004). After the end of the testing session, subjects were debriefed and told that the task was designed to be impossible to accomplish and that it did not assess their ability to perform mental arithmetic. During the nonstress control PET session, subjects performed a similar arithmetic task, but without time constraints, visible progress bar, or negative verbal feedback.

PET Procedure

Each subject underwent two [^{11}C]raclopride PET scans, one during the stress task, and one during the control task, conducted on different days with the order counterbalanced across subjects and groups. For the stress scanning session, subjects performed the mental arithmetic task continuously from approximately 10 min before until 20 min after the [^{11}C]raclopride injection, except for the verbal feedback blocks in between each 3-min arithmetic task block. The control session was identical except that there was no contact with the confederate and no time limit. The two scans were done at the same time of day, within four weeks of each other. The groups did not differ in inter-scan interval. PET scans were obtained with a CTI/Siemens HR + tomograph. Ten minutes after beginning the stress or control task 8–10 mCi of [^{11}C]raclopride was injected into an antecubital vein over 60 s and emission data were then acquired over a period of 60 min. Two subjects were excluded from analysis—one from the PerAb group due to an interstitial raclopride injection during one of the PET scans, the other from the PhysAn group due to a serious traumatic personal event that occurred just prior to the nonstress PET session.

Each subject underwent a T1-weighted magnetic resonance imaging (MRI) scan for anatomical localization. PET emission frames were summed, registered to the individual MRI (Woods *et al*, 1993), and transformed into Montreal Neurological Institute space (Collins *et al*, 1994). We also used an automated head movement detection and correction procedure described previously (Zald *et al*, 2004).

Voxel-wise [^{11}C]raclopride binding potential (BP) was calculated using a simplified reference tissue compartmental model (Lammertsma and Hume, 1996; Gunn *et al*, 1997) to generate statistical parametric images of change in BP (Aston *et al*, 2000). The reference method assumes that nonspecific binding of the tracer is equivalent in the striatum and reference region. Raclopride has been shown to have negligible nonspecific binding (Farde *et al*, 1985). We have demonstrated that this method is insensitive to changes in cerebral blood flow (Aston *et al*, 2000). There is considerable evidence from studies in nonhuman primates that the reduction in [^{11}C]raclopride binding is proportional to DA release (Endres *et al*, 1997; Hartvig *et al*, 1997; Laruelle *et al*, 1997). Only peaks within the striatum were considered, since this is the only brain structure where receptor-specific [^{11}C]raclopride binding is detected with certainty. T-maps of the change in BP were thresholded at a level of $t > 3.8$, which corresponds to $P < 0.05$, corrected for multiple comparisons (Worsley *et al*, 1996). The t threshold is based on a search volume for striatum of 37 264 mm^3, an effective image filter of 12 mm full width at half maximum, and 230 degrees of freedom (Worsley *et al*, 1996; Aston *et al*, 2000). The search volume was set as the total number of striatal voxels with BP >1 in the averaged (across subjects) [^{11}C]raclopride BP map. A mask was made of all striatal voxels with a T >3.2 to extract BP values from each individual's parametric images. These values were compared with pairwise t-tests between groups, and correlated with the smooth pursuit data (see below).

Psychological and Physiological Measures

Subjects completed the Spielberger State-Trait-Anxiety inventory (Spielberger *et al*, 1977), the questionnaire for competence and control for the assessment of self-concept related self-esteem (Krampen, 1991) and the parental bonding index (PBI), a well-validated self-report scale of parenting style (Parker *et al*, 1979; Parker, 1981). The last two measures were included because they were linked to stress response in our previous study (Pruessner *et al*, 2004). Assignment to the 'high' or 'low' maternal care category was based on a cutoff score of 27.0 (Parker *et al*, 1979). Perception of stress was assessed after each PET session by asking subjects to complete a state anxiety questionnaire (Spielberger *et al*, 1977) and visual analogue scales (VAS) (Pruessner *et al*, 2004) to assess feelings of negativity and uncontrollability at the end of the PET scan, prior to debriefing.

Saliva samples were collected every 12-min throughout the experiment. Saliva-derived cortisol was analyzed using a time-resolved fluorescence immunoassay (Dressendorfer *et al*, 1992) and the area under the curve (AUC; μg/dl/min) was calculated for each subject and each scanning

session (Pruessner *et al*, 2003). Heart rate, electromyography (EMG), and skin conductance were measured throughout each PET session by electrodes placed on the left arm and chest (F1000 system, Focused Technology, Ridgecrest, CA 93556). Quantification of autonomic data was done using AUC calculations for each measure (Pruessner *et al*, 2003, 2004).

Smooth pursuit eye movements, a putative endophenotype for schizophrenia (Gottesman and Gould, 2003), were measured in 23 of the 26 subjects as part of a larger study (Holahan and O'Driscoll, 2005). Subjects were asked to follow the movement of a small square ($0.5^\circ \times 0.5^\circ$) that moved across 20° of visual angle with a sinusoidal velocity profile at 0.4 Hz (for more details see Holahan and O'Driscoll, 2005). Eye movements were monitored using an Eyelink infrared video-based tracking system (SR Research, Mississauga, Canada) and data were analyzed with custom software (Holahan and O'Driscoll, 2005). The dependent measure was peak pursuit gain, a measure previously found to be correlated with frontal activation (O'Driscoll *et al*, 1999) and frontal structural integrity (Bagary *et al*, 2004). Pursuit gain was compared across groups with a one-way ANOVA. Correlations with were assessed with Pearson's *r*.

RESULTS

Behavioral Measures

A multivariate general linear model showed no group differences in self-esteem or trait anxiety scores. Subjects reported higher state anxiety scores ($F = 13.5$, $df = 1$, $p < 0.001$) and higher VAS scores ($F = 16.749$, $df = 1$, $p < 0.001$) after the stress session than after the nonstress session. There was no main effect of Group, and Group did not interact with Condition.

Although the software is designed to continuously vary task time constraints to ensure the same success rate and number of problems attempted for each subject, we calculated the rate of correct responses since differences in performance and feedback might influence the neural response. The success rate was $43 \pm 5\%$ (mean $\pm$ SD) and there were no differences between groups ($F = 0.13$, $df = 2,22$; $p = 0.88$). There were also no significant group differences in percent correct during the nonstress session, or in total number of problems attempted or solved in either session.

D2 Binding Potential Maps

There was a significant reduction in [^{11}C]raclopride BP in the stress condition compared to the control condition, indicative of DA release, only in the PhysAn group (peak $t = 7.8$). The area of significantly reduced BP included bilateral ventral striatum, putamen, and caudate, with the highest *t* values located in the ventral striatum (Figure 1). There were no significant BP reductions in either the Control (peak $t = 3.0$) or PerAb (peak $t = 2.89$) groups.

Region of interest data drawn from the area of significant DA release confirmed the t-map findings (Table 1; Figure 2). The reduction in BP from nonstress to stress was $9.8 \pm 13.6\%$ in the PhysAn group (control BP and SD: 1.79 ± 0.36, stress BP: 1.63 ± 0.44, $p = 0.03$). In the other two groups there was no evidence of DA release; indeed there was a slight nonsignificant increase in BP (control group nonstress: 1.56 ± 0.34, stress: 1.60 ± 0.44, 2.67% increase, $p > 0.2$; PerAb group control: 1.61 ± 0.26, stress: 1.63 ± 0.22, 2.57% increase, $p > 0.2$). We performed pairwise group comparisons on the region of interest data. Given our directional hypothesis that schizotypes would show greater

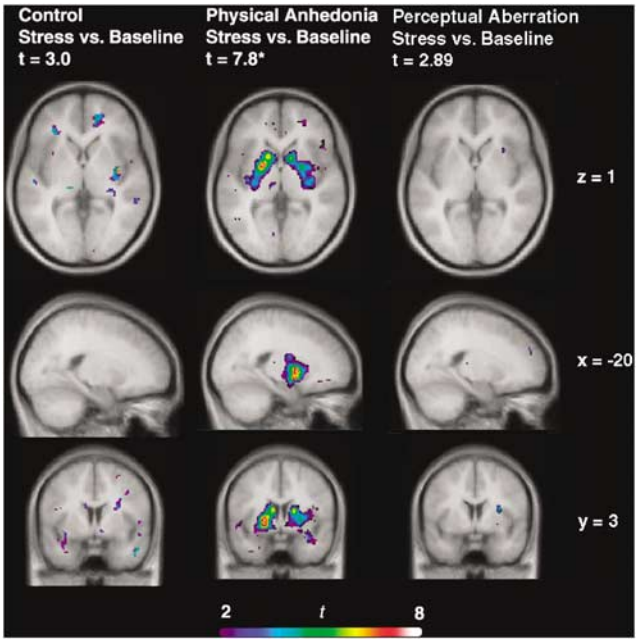

Figure 1 Negative and positive schizotypy and stress-dopamine response. Decrease in binding potential (BP) during the stress condition compared to nonstress (indicative of dopamine release) in control and schizotype groups. One axial, one sagittal, and one coronal section of the statistical parametric map of the change in [^{11}C]raclopride BP overlaid on the average MRI of all subjects in stereotaxic space. The color scale represents the *t*-statistic. (*$p < 0.001$)

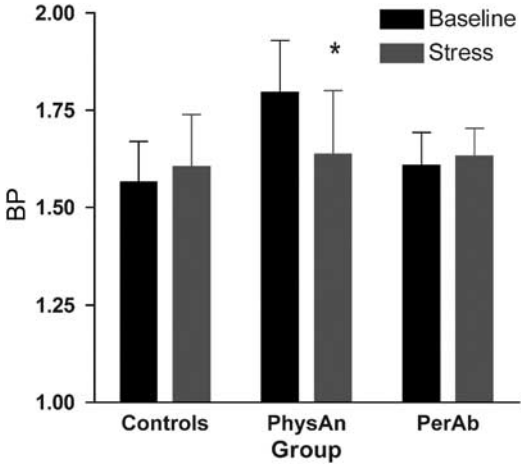

Figure 2 Binding potential (BP) in each condition. Mean [^{11}C]raclopride BP extracted from the region of interest in the ventral striatum (see Materials and Methods). There was a significant difference in [^{11}C]raclopride BP between stress and nonstress in the PhysAn group ($p = 0.03$, one-tailed), but not in the other two groups.

DA release than controls, and the existing literature supporting this hypothesis (Breier *et al*, 1997; Abi-Dargham *et al*, 1998, 2004), *t*-tests between schizotypes and controls were one-tailed. PhysAn showed a trend toward a difference compared to the controls ($p = 0.08$) but there was no difference between PerAb and controls ($p = 0.43$). PhysAn demonstrated a trend toward greater DA release than PerAb ($p = 0.08$, two-tailed). The PhysAn had higher nonstress BP than the other two groups but this did not reach statistical significance ($p = 0.1$ compared to controls; $p = 0.12$ compared to PerAb). There was a small (0.4 cm^3) negative peak (greater BP in the stress condition) in the control group ($t = -5.3$) located in the left posterior putamen, but there were no negative peaks in either of the schizotypy groups. Although order was counterbalanced (stress or nonstress scan first) we confirmed that there were no order effects on stress-induced DA release ($F = 2.70$; $df = 1,26$; n.s.).

We also measured parental bonding (Parker *et al*, 1979) based on our previous work (Pruessner *et al*, 2004). Changes in [^{11}C]raclopride BP were significantly related to maternal care score across all subjects ($r = -0.719$; $p < 0.001$). Subjects reporting low maternal care showed the greatest stress-induced reduction in BP, replicating our previous finding (Pruessner *et al*, 2004).

Relationship between Schizotypy And Maternal Care

ANOVA revealed a significant main effect of Group on maternal care scores ($F = 6.84$; $df = 2,23$; $p = 0.015$). Contrasts indicated that both schizotypy groups reported significantly lower maternal care than controls ($p < 0.04$) but did not differ from each other.

We did a stepwise discriminant function analysis of the data to predict membership in the three groups (PhysAn, PerAb, and control) using all the self-report measures, physiological measures of stress, and change in D2 binding. The best-fit two functions grouped 72% of the original cases correctly, even when adjusting for group size ($df = 4,25$, Wilks' Lambda = 0.437, $p = 0.003$). The two significant predictors of group membership were change in D2 BP between control and stress sessions and perceived maternal care; the functions classified 100% of controls, 71.4% of PhysAn subjects, and 44.4% of PerAb subjects correctly. No misclassified schizotype subjects were assigned to the control group.

Endocrine and Physiological Stress Response

The stress session resulted in significant increases in salivary cortisol compared with the nonstress session (AUC units, μg/dl/min: mean difference 0.62 ± 0.07; $F = 85.51$; $df = 1,22$; $p < 0.001$). There were no group differences in cortisol response between the two schizotype and control groups nor between the two maternal care groups, and DA release was not correlated with cortisol levels. The stress paradigm also resulted in higher heart rate (mean difference 102.8 ± 21.2 beats/min^2; $F = 10.64$; $df = 1,22$; $p = 0.004$), and EMG response (mean difference 32.8 ± 12.1 contractions/min^{-2}; $F = 6.99$; $df = 1,22$; $p = 0.015$) but not skin conductance. There was no main effect of Group on any physiological variables and no Group–Condition interactions.

Smooth Pursuit Gain

There was no main effect of Group on pursuit gain in this small sample (Table 1). Smooth pursuit gain was significantly correlated with measures of [^{11}C]raclopride BP; nonstress BP was correlated with pursuit gain ($r = -0.43$, $n = 23$, $p = 0.04$) as was stress-induced change in BP ($r = -0.41$, $n = 23$, $p = 0.05$) (Figure 3).

DISCUSSION

Negative symptom psychometric schizotypes showed significant striatal DA release in response to stress. This effect was not observed in the PerAb group or in controls.

Previous studies have shown that schizophrenic and schizotypal personality disorder patients have an exaggerated DA response to amphetamine (Laruelle *et al*, 1996; Breier *et al*, 1997; Abi-Dargham *et al*, 2004). Our data extend these findings by showing an elevated DA response to an ecological social stress as opposed to a pharmacological challenge. Moreover, this increased DA response occurred in a group at elevated risk for psychosis that had no Axis I psychopathology.

We found the two psychometric schizotype groups to differ in their stress-induced DA release, with only the PhysAn group (negative schizotypy) showing an exaggerated DA response. In schizophrenic patients, increases in striatal DA release have generally been associated with the presence of positive symptoms (Laruelle *et al*, 1996, 1999; Abi-Dargham *et al*, 1998). However, the genetic liability for schizophrenia is thought to be better indexed by negative than positive symptom schizotypy (Tsuang *et al*, 1991). For example, PhysAn scores are elevated in the relatives of schizophrenic patients while PerAb scores are not (Katsanis *et al*, 1990; Clementz *et al*, 1991) and lifetime risk of schizophrenia-spectrum disorders is higher in relatives of anhedonic schizophrenia probands than in nonanhedonic probands (Schurhoff *et al*, 2003). Negative, but not positive, symptoms are also elevated in schizophrenia families (Tsuang *et al*, 1991), and PhysAn is a major component of the stable familial set of traits referred to as 'schizotaxia', which is observed in a subset of relatives (Tsuang *et al*, 2002). That PhysAn but not PerAb subjects showed an elevated DA response to stress is consistent with

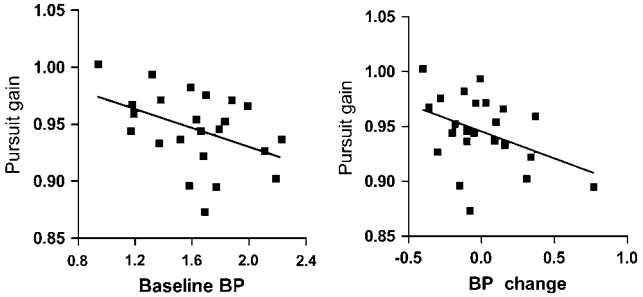

Figure 3 Smooth pursuit and dopamine function. Correlations between smooth pursuit gain (eye velocity/target velocity) and nonstress [^{11}C]raclopride binding potential (BP) (left panel, $p = 0.04$) and stress-induced change in [^{11}C]raclopride BP (nonstress—stress, right panel, $p = 0.05$). The subjects with lower smooth pursuit gain had greater nonstress BP and greater stress-induced dopamine release.

the idea that positive and negative schizotypy represent different forms of risk that may follow divergent paths to symptom development (Fanous *et al*, 2001).

A possible neural basis for the striatal DA hyperreactivity in our PhysAn group is reduced frontal lobe function (Davis *et al*, 1991). A large body of literature has linked negative symptoms with poor frontal function, and impaired frontal activation is associated with elevated striatal DA neurotransmission in schizophrenic patients (Meyer-Lindenberg *et al*, 2002). Grace's revision of the classic DA hypothesis (Grace, 1991, 2003) differentiates between phasic and tonic DA release in the striatum, and posits that low tonic activity is associated with the expression of negative symptoms. Compensatory changes resulting from low tonic DA, such as reduced stimulation of presynaptic DA receptors, are hypothesized to produce a heightened phasic DA response to stressors, which may be associated with psychosis. In this model, the abnormalities in subcortical DA are a downstream effect of reduced activity in prefrontal cortex, and in particular hypoactivity of prefrontal glutamatergic neurons (Moore *et al*, 1999). The reduction of frontal excitatory input to mesolimbic and mesocortical DA neurons could reduce tonic activity, while also resulting in an excessive mesolimbic response to exogenous stimuli such as stress (Moore *et al*, 1999; Laruelle *et al*, 2003). This model is consistent with our findings, as it predicts that psychosis-susceptible individuals will have higher [^{11}C]raclopride BP, reflecting low tonic DA, as shown here (Figure 2), larger stress-induced DA release (Figures 1 and 2), and that these should be associated with measures of frontal dysfunction (Figure 3).

We do not have direct measures of frontal function in this population. However, it has been reported that smooth pursuit quality (measured by pursuit gain or catch-up saccade rate) is significantly associated with measures of frontal structural integrity (Bagary *et al*, 2004) and frontal activation in schizophrenic patients (Ross *et al*, 1995; Hong *et al*, 2005; Keedy *et al*, 2006) and unaffected relatives (O'Driscoll *et al*, 1999). Although the PhysAn group did tend towards poorer pursuit gain, the small number of subjects made these results insignificant here. Nonetheless, in the larger samples tested (Holahan and O'Driscoll, 2005), schizotypes did have significantly lower pursuit gain than controls, and this was most significant for the PhysAn group In the current study, we correlated smooth pursuit gain with [^{11}C]raclopride BP measures and found the hypothesized significant association with both nonstress BP and stress-induced DA release (Figure 3), with subjects with lower pursuit gain having higher nonstress BP (ie lower tonic DA activity) and higher DA release (ie higher phasic DA activity). This evidence, although indirect, supports the notion of a link between frontal dysfunction and striatal DA function.

We should highlight our study limitations. First, since the parametric images shown represent thresholded statistical maps, the area of DA release might have been larger than that displayed in the figures. Moreover, because we report PET data to minimize false-positive results, we cannot exclude the presence of small changes in [^{11}C]raclopride undetected by our method. Also, we cannot exclude the possibility that variations in cerebral blood flow during the scan could have affected our measurement of [^{11}C]raclopride BP (Slifstein *et al*, 2004), since our simulations showing that the compartmental model used here adequately separates tracer delivery from binding to receptors were made under the assumption of constant blood flow (Aston *et al*, 2000). Second, the tracer [^{11}C]raclopride only displays specific binding in subcortical areas. Though the striatum is thought to be a critical region for DA dysfunction in schizophrenia, there may also be differences in frontal cortical DA systems that our method could not detect. Third, although our particular interest is in schizophrenia vulnerability, our personality measures of vulnerability are sensitive to risk for psychosis, including affective psychosis (Erlenmeyer-Kimling *et al*, 1993; Chapman *et al*, 1994). Increased DA release in response to stress may represent a risk factor for psychosis in general, rather than a risk factor for schizophrenia *per se* (Yui *et al*, 2004). Fourth, we did not find DA release to be correlated with cortisol levels, as was found in our previous study (Pruessner *et al*, 2004), nor did we observe differences in cortisol between groups, a result likely due to our low number of participants. Fifth, it is possible that factors other than schizotypy influenced the stress-induced DA and neuroendocrine responses we observed. The exclusion of schizotypal individuals meeting Axis 1 criteria, albeit to remove possible confounds, might have eliminated some 'true positive' individuals, and thus could have reduced our ability to find dopaminergic abnormalities in the PerAb group. Moreover, since groups were composed primarily of females, neuroendocrine responses to psychosocial stress could have been influenced by the sex composition of the groups (Kirschbaum *et al*, 1992). Differences between the stress and nonstress conditions may also have been a factor; the conditions were balanced for motor and visual stimuli, but only the stress condition involved contact with a confederate. Although unlikely, the possibility that nonstressful aspects of the interaction (eg attention, auditory input) could have caused DA release cannot be excluded. Besides these limitations, our data do not address the question of causality and mechanism. For example, it is unclear to what extent stress-induced differences in DA release seen in the PhysAn group are attributable to the differences in the distribution of low/high maternal care in the different groups, since in a previous study (Pruessner *et al*, 2004) low maternal care participants showed greater stress-induced DA release. However, the discriminant function analysis showed that both DA release and maternal care score independently predicted schizotypy group membership, indicating that DA release improves the identification of PhysAn subjects beyond that provided by maternal care scores. The cross-sectional design and the low number of subjects in this imaging study preclude speculation about the basis of the relationship between maternal care and schizotypy.

Notwithstanding, this is to our knowledge the first demonstration of increased stress-induced DA release in a population at risk for any psychotic disorder; future work will be necessary to determine to what extent it may be relevant for one disorder more than others. Our stimulus, stress, is distinctive and relevant in two ways: it is associated with psychosis-onset (Norman and Malla, 1993; Nuechterlein *et al*, 1994; Walker and Diforio, 1997) and it is not a pharmacological challenge. Additional strengths of the

study include individual adjustment of the stress paradigm to produce performance matching in the scanner across groups, and that the task produced the expected physiological, endocrine, and self-report changes associated with stress in all the three groups. Thus our findings of increased stress-related DA release in the PhysAn group cannot be attributed to methodological confounds such as clinical manifestation of disease, comorbidity, performance differences, or differences in perceived stress or state anxiety.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare that, except for income received from a primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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