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Striatal dopamine $D_{2/3}$ receptor binding following dopamine depletion in subjects at Ultra High Risk for psychosis ☆

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Striatum

Abstract
Altered striatal dopaminergic neurotransmission is thought to be fundamental to schizophrenia. Increased presynaptic dopaminergic activity ([^{18}F]-DOPA PET) may predate the onset of psychotic symptoms and correlates to clinical symptoms in subjects at Ultra High Risk (UHR) for developing psychosis. Postsynaptic dopaminergic neurotransmission has not been investigated yet in UHR patients. We hypothesized that synaptic dopamine concentration would be increased in UHR patients, and that synaptic dopamine concentration would be related to symptom severity. 14 UHR patients and 15 age and IQ matched controls completed an [^{123}I]-IBZM SPECT scan at baseline and again after dopamine depletion with alpha-methyl-para-tyrosine (AMPT). We measured changes in radiotracer binding potential, compared these between UHR patients and controls, and correlated these to symptom severity. The UHR group as a whole did not differ significantly from controls. AMPT significantly reduced symptom severity in the UHR group (p=0.014). Higher synaptic dopamine concentration predicted larger reduction of positive symptoms following depletion in the UHR group (p=0.01). In UHR patients, positive symptoms responded to dopamine depletion, comparable to observations in schizophrenia, suggesting a similar mechanism. Higher synaptic dopamine concentration was associated with more severe positive symptoms and a greater reduction of these symptoms following depletion.
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1. Introduction

Schizophrenia typically emerges in late adolescence, and is characterized by disturbances in perception, thought, volition

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and cognition. It is usually preceded by a prodromal period, with mild positive psychotic and negative symptoms, non-specific symptoms and a decline in psychosocial functioning. Researchers in Australia, USA and Germany developed instruments for assessment of symptoms and signs that predicted transition to psychosis prospectively (Klosterkotter et al., 2001; Miller et al., 2003; Yung et al., 2003). Recently, these findings were replicated with transition rates varying from 10% to 40% after a two-year follow-up (Cannon et al., 2008; Ruhrmann et al., 2010; Yung et al., 2008). Patients in these studies were described to have an *At Risk Mental State* (ARMS) or have an *Ultra High Risk (UHR)* to develop psychosis. Currently there is no proven therapy or strategy to prevent transition to psychosis (de Koning et al., 2009).

Dopamine receptors have been a focus in schizophrenia research as they are the target of anti-psychotic drugs. Imaging studies have shown direct evidence of disruption of dopaminergic neurotransmission in the striatum of patients with schizophrenia and this is thought to be fundamental to development of psychotic symptoms. More specifically, the majority of [^{18}F]-DOPA positron emission tomography (PET) studies showed increased striatal DOPA uptake (Howes et al., 2007) and dopamine depletion studies showed increased occupancy of striatal dopamine $D_{2/3}$ receptors by endogenous dopamine in patients with schizophrenia compared to controls (Abi-Dargham et al., 2000, 2009; Kegeles et al., 2010).

An increased presynaptic striatal [^{18}F]-DOPA uptake has recently been demonstrated in UHR patients (Howes et al., 2009), UHR patients that later develop psychosis (Howes et al., 2011a), and has been related to abnormal frontal brain function (Fusar-Poli et al., 2010) and hippocampal glutamate levels (Stone et al., 2010; Bloemen et al., 2011). Also presynaptic striatal [^{18}F]-DOPA has been reported to be increased after transition to psychosis (Howes et al., 2011b). However to our knowledge synaptic dopamine concentration using dopamine depletion has not yet been investigated in UHR patients.

[^{123}I]-IBZM Single Photon Emission Computed Tomography (SPECT) imaging measures the in-vivo binding of [^{123}I]-IBZM to striatal dopamine $D_{2/3}$ receptors not occupied by endogenous dopamine. Synaptic dopamine concentration, or occupancy of $D_{2/3}$ receptors by endogenous dopamine, can be estimated by employing a well-validated challenge paradigm (Bloemen et al., 2008), which combines a baseline scan with a second scan following dopamine depletion with alpha-methyl-*para*-tyrosine (AMPT). AMPT is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis. The percentage change in binding potential between the baseline and depletion is a proxy of baseline synaptic dopamine concentration.

We hypothesized that synaptic dopamine concentration is increased in UHR patients, as has been demonstrated in schizophrenia. We furthermore hypothesized that dopamine concentration is positively related to symptom severity.

2. Methods

2.1. Subjects

Help seeking UHR patients were recruited through our clinical early psychosis program (Academic Medical Centre, Amsterdam). Inclusion criteria were age between 18 and 35 years and fulfillment of UHR criteria (see below). Healthy control subjects were recruited through local advertisement.

Exclusion for all participants criteria were: (1) present treatment with antipsychotic or stimulant medication or previous treatment for longer than one week, (2) present use (checked by urine drug screen) or lifetime history of substance dependence or abuse, (3) neurological disorders, (4) pregnancy (checked by urine test), (5) participation in research with radioactive load in past year prior to study. Additional exclusion criteria for healthy controls were: present or past DSM-IV diagnosis or family history of psychotic illness. The study was approved by local and national medical ethics committees and all participants of the study gave written informed consent after the full procedure had been explained to them.

2.2. Clinical measures

All subjects were assessed by a psychiatrist and a research psychologist. UHR diagnosis was assessed with the "Comprehensive Assessment of At Risk Mental State" (CAARMS) (Yung et al., 2004). At the time of imaging all patients were assessed using the following instruments: the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia to assess symptom severity (Kay et al., 1987), Structured Clinical Interview for Diagnosis (SCID), sections B and C (Spitzer et al., 1992) to asses other DSM-IV diagnoses, the Comprehensive International Diagnostic Interview (CIDI), sections J and L to assess substance abuse (World Health Organization, 1993), and 7 subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) to assess full scale intelligence quotient (FSIQ) (Wechsler, 1987).

2.3. Depletion protocol

Dopamine depletion was induced by oral administration of AMPT over 24 h. The exact AMPT dose was calculated on a per weight basis (40 mg/kg body weight, with a maximum of 4 g). This dose was selected as it induces sufficient depletion while causing minimal adverse effects (Bloemen et al., 2008; Boot et al., 2008; Hasler et al., 2008). Three doses were given one day prior to imaging; at 10 a.m., 4 p.m. and 10 p.m. The last AMPT dose was given at 10 a.m., one hour prior to the acquisition of the second SPECT scan. To prevent the formation of AMPT crystals in the urine, subjects were instructed to drink plenty of fluids.

2.4. Spect protocol

Participants were not allowed to consume coffee, alcohol or nicotine on scan days (Kaasinen et al., 2004). All subjects took potassium iodide orally to block thyroid uptake of free radioactive iodide. Subjects underwent two SPECT scans with the selective dopamine $D_{2/3}$ receptor tracer iodine-123 labeled (S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide ([^{123}I]-IBZM), using the sustained equilibrium/constant infusion technique (Laruelle et al., 1995). A total [^{123}I]-IBZM dose (specific activity $>$200 MBq/nmol and radiochemical purity $>$95% produced according to GMP criteria at GE Healthcare, Eindhoven, The Netherlands) of approximately 80 MBq was given as a bolus, followed by continuous infusion of approximately 20 MBq per hour for the duration of the experiment. The bolus to hourly infusion ratio was approximately 4.0 (Booij et al., 1997). SPECT data were acquired for approximately 60 min, from 120 to 180 min after the initiation of [^{123}I]-IBZM administration. SPECT studies were performed using a brain-dedicated scanner (Neurofocus 810, upgrade of Strichmann Medical Equipment). Axial slices were acquired in 5 mm steps as earlier described (Boot et al., 1997a, 2008). The first scan was obtained in the absence of pharmacological intervention (baseline scan). The second scan was performed identically

following dopamine depletion. Eleven controls and UHR subjects participated in an earlier magnetic resonance spectroscopy study (Bloemen et al., 2011).

2.5. Peripheral measures

Blood samples were taken at 9 a.m. (baseline) before administering [^{123}I]-IBZM on the baseline day and at 9 a.m. (pre-SPECT) and 12 a.m. (post-SPECT) on the depletion day for determination of plasma levels of prolactin and homovanillic acid. Urine samples were collected at the same times for determination of dopamine.

Prolactin was measured as earlier described (Boot et al., 2008). The total assay variation ranged from 5.8% to 7.6%. Homovanillic acid levels were measured as earlier described (Boot et al., 2008). Intra- and inter-assay variations, calculated on low, mid, and high levels, ranged from 1.2% to 7.8% (intra-assay) and 4.8–10.4% (inter-assay) respectively. Concentrations of dopamine in urine were determined as earlier described (Abeling et al., 1984; Stroomer et al., 1990). Dopamine variation ranged from 2.4% to 4.1% (intra-assay) and 2.7–6.7% (inter-assay). Plasma AMPT levels were measured using gas chromatography/mass spectrometry. Inter- and intra-assay coefficient of variation was less than 5%.

2.6. Image reconstruction and analysis

SPECT data were reconstructed and analyzed by a single blinded investigator. Images were corrected for attenuation and reconstructed in three-dimensional mode, as earlier described (Booij et al., 1997b). For quantification, region-of-interest (ROI) analyses were performed. Fixed ROI templates were used for left and right striatum and occipital cortex and placed on four consecutive axial slices containing the highest striatal binding. Individual variation required movement of the fixed ROIs, without changing size and shape, for optimal fitting.

Mean activation across all slices was calculated for the striatum (representing specific binding) and for the occipital reference region (representing non-specific/non-displaceable binding). The binding potential was calculated as the ratio of specific to non-specific activity (total activity in striatum minus activity in occipital cortex, divided by activity in occipital cortex) (BP_{ND}) (Innis et al., 2007). To assess the synaptic dopamine concentration (ΔBP_{ND}), the difference between BP_{ND} after depletion and BP_{ND} at baseline was expressed as percentage change in BP_{ND} compared to baseline BP_{ND} (Abi-Dargham et al., 2000).

2.7. Statistical analyses

Demographic variables were analyzed using independent *t*-tests or chi-square test as appropriate. All variables were tested for normality, and parametric or non-parametric tests were used as appropriate. A probability value of 0.05 (two-tailed) was selected for all tests. All statistical analyses were performed with SPSS, release 18.0.0 for Windows (SPSS Inc., Chicago, Illinois, USA, 2009). Peripheral measures were compared using repeated-measures analysis of variance (ANOVA). Between-group comparisons of BP_{ND} were done using repeated-measures ANOVA. The group differences were further explored "post-hoc" using paired-sample *t*-tests. AMPT effects on positive PANSS scores were tested with repeated-measures ANOVA. The relation between percentage change in BP_{ND} and change in positive symptoms (total score on positive subscales of the PANSS) following AMPT was tested using a linear regression analysis. Relationships between clinical measures and dopamine concentration were analyzed using Pearson correlation coefficient.

3. Results

3.1. Subjects and demographics

We recruited 16 UHR patients and 15 controls. Two UHR patients only completed baseline scanning and did not return for the depletion scan due to anxiety during baseline imaging and for unknown reason, respectively. Demographic characteristics and PANSS scores are listed in Table 1.

3.2. Adverse and clinical effects

None of the subjects had to be withdrawn due to side effects. One UHR subject experienced an anxiety attack after AMPT depletion, but completed the depletion SPECT on another day. Some UHR patients reported feeling better after taking AMPT. AMPT significantly decreased positive

Table 1 Demographic variables.

Variable	UHR group	S.D.[e]	Controls	S.D.[e]	*p*-Value
N	14[f]		15		
Gender (M/F)[a]	12/4		13/2		0.65
Age in years (average ± S.D.)	21.99	3.94	22.17	3.54	0.75
Weight in kg (average ± S.D.)	77.32	17.55	77.73	15.05	0.97
FSIQ (average ± S.D.)[b]	104.67	12.51	111.47	18.62	0.31
PANSS positive total[c] baseline	12.36	2.90	7.07	0.28	<0.001*
PANSS positive total[d] depletion (*N*=14)	10.43	3.18	7.00	0.00	0.001*
PANSS total baseline	50.29	13.57	30.79	2.16	<0.002*
PANSS total depletion (*N*=14)	47.43	14.66	31.14	2.00	0.003*

[a]M=male, F=female.
[b]Full-scale intelligence quotient measured by seven subtests of the abbreviated Wechsler adult intelligence scale-III.
[c]Total of the positive symptom sub-scores of the PANSS.
[d]Total of all sub-scores of the PANSS.
[e]Standard deviation.
[f]For the demographics 14 subjects were used, because for analysis using depletion scan data only 14 subjects had data available.
*Significantly different between UHR and controls.

PANSS scores in the UHR group (mean=1.92, S.D.=2.56, p=0.014, eta^2=0.38).

We found a significant main effect of AMPT on positive PANSS scores in the UHR group (F(1,12)=10.38, p=0.007, partial eta^2=0.46). High striatal synaptic dopamine concentration predicted good response of positive symptoms to AMPT in the UHR group (r^2=0.56, p=0.01).

3.3. $D_{2/3}$ receptor binding

There was no statistically significant AMPT x group interaction (F(1,27)=1.25, p=0.27) for BP_{ND}. The main effect of AMPT on BP_{ND} was significant (F(1,27)=5.09, p=0.03, partial eta^2=0.16), but there was no significant effect of group on BP_{ND} (F(1,27)=0.001, p=0.976). Percentage change in BP_{ND} was 5.20% (S.D.=21) for UHR patients and 10.94% (S.D.=13) for controls, but did not differ significantly between the two groups (t(20.7)=0.87, p=0.394). There was no significant difference between groups in BP_{ND} at baseline (t(29)=−0.45; p=0.66) or after depletion (t(27)=0.64; p=0.53) (Table 2). Levene's Test for Equality of Variances indicated unequal variances in the percentage change in BP_{ND} (F=4.40, p=0.046).

Percentage change in BP_{ND} was significantly correlated to baseline total CAARMS positive subscale scores (r=0.78, p=0.001), baseline PANSS total (r=0.57, p=0.032), baseline PANSS positive subscales (r=0.75, p=0.002) (Figure 1) in the UHR group, whereas there was no significant correlation between percentage change in BP_{ND} and baseline PANSS positive subscales (r=0.09, p=0.77) and baseline PANSS total scores (r=0.06, p=0.84) in the control group.

3.4. Peripheral measures

There was a statistically significant decrease of dopamine and homovanillic acid and an increase of prolactin after AMPT, but no between-group differences (Table 3), dopamine: AMPT × group interaction (F(1,24)=1.36, p=0.25), main effect of AMPT on dopamine (F(1,24)=298.55, p=<0.001, eta^2=0.93), main effect of group on dopamine (F(1, 24)=4.08, p=0.055). Homovanillic acid: AMPT × group interaction (F(1,25)=1.90, p=0.18), main effect of AMPT on homovanillic acid (F(1,25)=80.80, p=<0.001, eta^2=0.76), main effect of group on homovanillic acid (F(1, 25)=0.52, p=0.48). Prolactin: AMPT × group interaction (F(1,26)=0.36, p=0.55), main effect of AMPT on prolactin (F(1,26)=50.50, p=<0.001, eta^2=0.67), main effect of group on prolactin (F(1, 26)=0.94, p=0.34).

4. Discussion

This is the first study to use the dopamine depletion paradigm to measure baseline striatal dopamine neurotransmission in drug-naïve UHR patients. Our results demonstrate that the AMPT depletion paradigm achieved sufficient depletion; AMPT induced (1) a statistically significant increase in BP_{ND} in the combined sample and in controls, (2) significant symptom reduction on the PANSS in UHR patients, (3) a significant

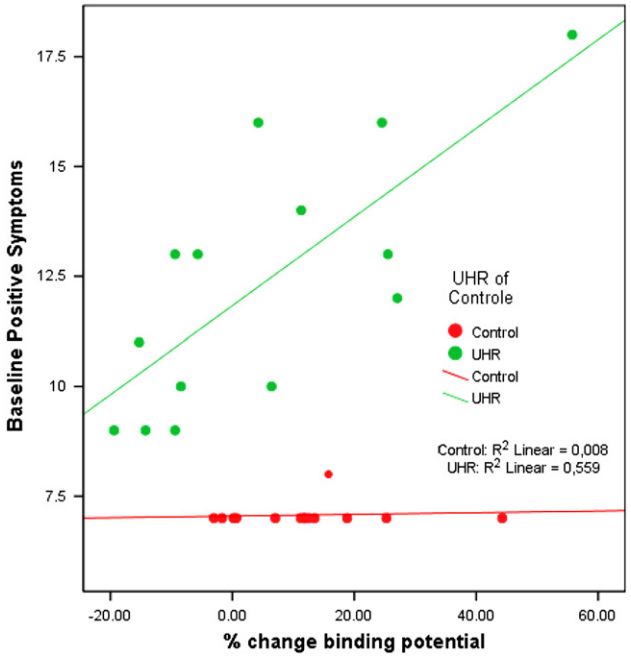

Figure 1 Correlation PANSS positive symptom scores and the percentage change in binding potential (BP_{ND}) in the UHR and the control group.

Table 2 [^{123}I]-IBZM binding potential (BP_{ND}) at baseline and following AMPT administration.

	Group	n	Mean[a]	S.D.[b]	p-Value
Baseline condition	Control group	15	0.82	0.12	
	UHR group	16	0.84	0.15	0.66[c]
Depletion condition	Control group	15	0.90	0.11	
	UHR group	14	0.87	0.13	0.53[c]
Percentage change after depletion	Control group	15	10.94	12.60	
	UHR group	14	5.20	21.47	0.39[c]

[a]Mean binding potential.
[b]Standard deviation.
[c]p-Value for the comparison between UHR patients and controls.

Table 3 Pharmacological measures taken from blood and urine samples of participants.

Variable	Baseline[e]	S.D.[h]	Pre-SPECT[f]	Mean value ± S.D.		S.D.[h]
				S.D.[h]	Post-SPECT[g]	
AMPT[a]	-	-	8.34	2.01	15.37	3.45
Dopamine[b]	145.58	29.60	79.3	23.68	76.77	27.13
Prolactin[c]	14.31	5.79	24.93	6.90	38.21	17.48
Homovanillic acid[d]	68.62	30.39	33.54	15.02	21.25	9.99

[a]Alpha-methyl-para-tyrosine, measured in mg/L in plasma.
[b]Dopamine measured in nmol/mmol kreatinine in urine.
[c]Prolactin measured in μg/L in plasma.
[d]Homovanillic acid nmol/L in plasma.
[e]Baseline=day 1 at 9 a.m.
[f]Pre-SPECT=day 2 at 9 a.m.
[g]Post-SPECT=day 2 at 12 a.m.
[h]Standard deviation.

correlation between PANSS scores and synaptic dopamine concentration in UHR patients, (4) high synaptic dopamine concentration predicted good response of positive symptoms to AMPT in UHR patients, and (5) a significant increase in prolactin and significant decrease in dopamine and homovanillic acid. However, our results suggest that UHR patients are a heterogeneous group and that this may partially explain why we did not find between-group differences in dopaminergic neurotransmission.

Doses of AMPT used in challenge studies have been variable. Some groups used relatively high AMPT doses (Abi-Dargham et al., 2009; Martinez et al., 2009; Verhoeff et al., 2001), which may lead to more pronounced side-effects and may cause subjects to drop out of the study (Bloemen et al., 2011; de Haan et al., 2005). We have shown previously that lower doses (40 mg/kg) of AMPT achieve a satisfactory central and peripheral dopaminergic depletion with few side effects (Boot et al., 2008). In the present study depletion of dopamine with AMPT significantly decreased dopamine in urine and homovanillic acid in plasma, and significantly increased plasma prolactin. Homovanillic acid was decreased by approximately 70% in both UHR and controls, in line with previous AMPT depletion literature (Laruelle et al., 1997; Martinez et al., 2009; Verhoeff et al., 2001). AMPT caused a statistically significant increase in BP_{ND} of 10% in controls, which is comparable to findings of previous depletion studies (Abi-Dargham et al., 2000, 2009; Martinez et al., 2009; Riccardi et al., 2008).

Variance in BP_{ND} was significantly larger in the UHR group (as shown by Levene's Test for Equality of Variance), which underlines the heterogeneity of the group. This increased variance is also observed in schizophrenia patients (Abi-Dargham et al., 2000).

There was no significant difference in percentage change in BP_{ND} between UHR patients and healthy controls. A possible explanation for this is the heterogeneity of the UHR group, as only 10–40% develop subsequent psychosis. The heterogeneity of the UHR group is inherent to its concept but decreases our power to detect differences in BP_{ND}. Another speculative explanation is that the postsynaptic dopaminergic abnormalities seen in schizophrenia (Abi-Dargham et al., 2000, 2009) may be a later phenomenon caused by the psychosis, following presynaptic abnormalities that have been reported in UHR patients (Howes et al., 2009).

The dopaminergic abnormalities we observed were significantly correlated to the amount of positive symptoms they experience on the CAARMS, and to positive PANSS and to total PANSS, but not to total CAARMS. Howes and colleagues reported a correlation between presynaptic striatal dopamine levels and total CAARMS, but not to positive subscale totals (Howes et al., 2009). Abi Dargham and colleagues reported no relation between PANSS scores and striatal dopamine in schizophrenia (Abi-Dargham et al., 2000). This suggests that presynaptic dopamine may be more related to overall functioning whereas postsynaptic dopaminergic neurotransmission may be more related to positive symptoms. The reason that in schizophrenia this relationship is lost is unclear, but may be due to longer duration of symptoms, having had frank psychotic symptoms, or to possible ceiling effect of high dopamine and symptomatology.

It is also interesting that UHR patients with milder symptoms appear to have a low percentage change in BP_{ND}. Martinez et al. (2009) recently showed low striatal receptor occupancy in abstinent cocaine users. Although the patients in our sample had no history of drug abuse, a similar effect of AMPT was seen in the striatum. This finding suggests that low striatal receptor occupancy may not be specific for addiction. In this context it is of interest that all dopaminergic depletion imaging studies showed clear variations in striatal receptor occupancy, also in controls. Future studies should focus on etiological factors and clinical correlates of this variation.

Dopamine depletion with AMPT significantly decreased positive symptoms in UHR patients as measured by the total score on the subscales for positive symptoms on the PANSS. This novel finding adds to evidence that the positive symptoms that UHR patients experience are related to dopamine. This was strengthened by the fact that some of the UHR patients asked if they could continue AMPT medication (see also "patient perspectives"). Furthermore high synaptic dopamine concentration predicted good response of positive symptoms to dopamine depletion. This has also been reported in schizophrenia, and also predicted response to antipsychotic treatment (Abi-Dargham et al., 2000). This is interesting, in particular regarding the ongoing discussion about treatment of

UHR symptoms (de Koning et al., 2009; McGorry et al., 2009), as our results suggest there might be a subgroup of UHR patients with high synaptic dopamine concentration who could benefit from antipsychotics to treat their current positive symptoms. Our current data do not allow any conclusions with regard to transition to psychosis and at this time we are unable to determine which patients might possibly profit from medication, although our results suggest some may.

It is unlikely that the greater increase in BP_{ND} in UHR patients with higher positive symptoms is caused by up-regulation of $D_{2/3}$ receptors after acute dopamine depletion with AMPT as previous studies have shown that the duration of treatment is too short to induce detectable up-regulation (Laruelle et al., 1997). We can therefore assume that comparing baseline and depletion BP_{ND} is an indirect measure of the proportion of $D_{2/3}$ receptors occupied by dopamine in the baseline state. So what would explain higher synaptic dopamine concentration? Increased affinity of the receptors for dopamine could explain this, although this is not supported by a recent [^{11}C]-(+)-PHNO PET study (Graff-Guerrero et al., 2009). Graff and colleagues reported no evidence for elevated D_2 receptor affinity in schizophrenia patients, although depletion studies are needed to confirm this was not masked by endogenous dopamine. Alternatively increased synaptic dopamine concentration could be caused by increased activity of presynaptic dopaminergic neurons levels, which is supported by recent findings in UHR patients (Howes et al., 2009).

Furthermore the strong link between positive symptoms and dopamine in our study suggests that increased synaptic dopamine concentration may not be a risk factor for psychosis but is co-occurring with increased psychotic symptomatology. Thus, it may be more indicative of state than of trait of the UHR patients and these findings are in line with a dimensional approach of psychiatric disorders.

This study has several strengths. As the first depletion study in UHR patients studying dopaminergic neurotransmission it provides unique data about synaptic dopamine concentration in the striatum, and its relation to symptoms. Furthermore all subjects were drug-naïve and comparable in age, weight, FSIQ and sex. We achieved significant depletion with a relatively low AMPT dose and subjects had very little side effects. Limitations of this study are the small sample size, the inclusion of mainly male patients, and the failure of two subjects to complete the depletion scan. Furthermore, although we achieved depletion as explained above, the modest dose of AMPT and hence possibly a less complete depletion may have influenced our results. We did not measure activity of dopamine transporters which could have influenced synaptic dopamine concentration as well.

In conclusion, the results of this first depletion study in UHR patients suggest that UHR patients with high scores on positive symptom scales may already have abnormalities in dopaminergic neurotransmission. Dopamine depletion leads to significant positive symptom reduction in UHR patients, and synaptic dopamine concentration predicted good response of positive symptoms to AMPT in UHR patients. Furthermore the results show that positive symptoms respond to dopamine depletion in the UHR group as they do in schizophrenia. Our sample was not assessed longitudinally and therefore transition into psychosis is not known yet. However, follow-up studies are now ongoing and will provide information on transition to psychosis in the UHR group. These data may elucidate the relation between transition to psychosis and striatal synaptic dopamine concentration and may eventually answer the relevant question whether dopamine depletion studies can predict the transition to psychosis.

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Contributors

TvA and JB designed and funded the study. OB, MdK, and JM collected the data. OB and TG analyzed the data. OB, TvA, and JB wrote the manuscript. LdH and DL advised on the study and edited the manuscript.

Conflict of interest

Dr. Bloemen, Dr. de Koning, Mr. Gleich, Dr. Meijer, Prof. de Haan, Prof. Linszen, Prof. Booij and Prof. van Amelsvoort report no competing interests. This study is supported by a personal grant to TvA from the Dutch Organisation for Health Research and Development (200 Mw) (NWO-Veni grant 2006 (916.76.048)).

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