Reduced Dopamine Response to Amphetamine in Subjects at Ultra-High Risk for Addiction

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Background: Not everyone who tries addictive drugs develops a substance use disorder. One of the best predictors of risk is a family history (FH) of substance use problems. In part, this might reflect perturbed mesolimbic dopamine responses.

Methods: We measured amphetamine-induced changes in [^{11}C]raclopride binding in 1) high-risk young adults with a multigenerational FH of substance use disorders ($n = 16$); 2) stimulant drug-naïve healthy control subjects with no known risk factors for addiction ($n = 17$); and 3) subjects matched to the high-risk group on personal drug use but without a FH of substance use problems ($n = 15$).

Results: Compared with either control group, the high-risk young adults with a multigenerational FH of substance use disorders exhibited smaller [^{11}C]raclopride responses, particularly within the right ventral striatum. Past drug use predicted the dopamine response also, but including it as a covariate increased the group differences.

Conclusions: Together, the results suggest that young people at familial high risk for substance use disorders have decreased dopamine responses to an amphetamine challenge, an effect that predates the onset of addiction.

Key Words: Dopamine, PET, [^{11}C]raclopride, stimulants, substance dependence, vulnerability

A dense family history of drug and alcohol dependence is a risk factor for addiction (1–3). The neurobiology of this association, though, is poorly understood. One longstanding hypothesis is that disturbances in mesolimbic dopamine system reactivity might be involved. This proposal is based on the following: dopamine system activations elicit approach toward rewards (4–7); most drugs of abuse, particularly psychostimulants, increase mesolimbic dopamine transmission (8); animals selectively bred for drug preference have shown altered dopamine responses to a range of drugs (9–13); and humans with drug addictions are reported to have lower striatal dopamine receptor concentrations and blunted dopamine responses to drug challenges (14–18). This noted, direct evidence of a preexisting dopamine disturbance in people vulnerable to addiction is lacking.

One corollary of the high-risk proposal is that not all selected individuals will actually carry the trait or express the premorbid differences. Given this, we measured amphetamine-induced dopamine responses with positron emission tomography (PET) and [^{11}C] raclopride in young people with an extensive multigenerational family history of substance dependence and who had started exhibiting high-risk behavior themselves through current nondependent use of cocaine or amphetamine (FH + exposed) (19). This high-risk group was compared with 1) stimulant drug-naïve healthy control subjects with no known risk factors for addiction (Ctls_naive) and 2) subjects matched to the high-risk group on personal drug use but without a family history of substance use problems (Ctls_exposed).

We hypothesized that FH + exposed would show a distinct dopaminergic response to drug challenge as compared with the control groups. By including a Ctls_exposed group matched on personal drug use with the high-risk subjects, it was proposed that this would allow us to separate contributions of familial risk versus prior drug exposure (20). A smaller dopamine response would suggest that the blunted dopamine response seen in drug-addicted populations (14,16,17) exists before the development of the disorder. A larger dopamine response could suggest a preferential recruitment of the brain's incentive motivation system in response to drugs in this vulnerable group. Either higher or lower dopamine responses in FH + exposed would represent a novel risk marker for addiction.

Methods and Materials

Subjects were recruited by advertisements in newspapers and on websites. Volunteers who passed a telephone screen completed a semistructured clinical interview for DSM-IV [Structured Clinical Interview Axis I Disorders, Nonpatient Edition (21)] for assessment of present and past Axis I disorders. Based on this interview and the Family Interview for Genetic Studies (22), subjects were divided into three groups (Table 1). Family history positive drug users (FH + exposed) were healthy men and women aged 18 to 25 who reported current occasional use of psychostimulant drugs (cocaine, amphetamines) and had a multigenerational family history of substance dependence as defined by a minimum of one affected first-degree relative, at least one affected second-degree relative, and a minimum of three affected first-degree or second-degree relatives. All subjects were free of any current or past dependence on substances other than tobacco or caffeine (those meeting criteria for abuse were included), current Axis I psychiatric disorder other than substance use disorder (SUD), and past or current treatment with methylphenidate or other stimulants. Exclusion criteria included cardiovascular, neurological, or other disorders that might be aggravated by study participation or complicate interpretation of the results, planning to quit drug use during the next month, a seropositive pregnancy

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Table 1. Subject Demographic Characteristics

Measure	Ctls_naive	Ctls_exposed	FH + Exposed
n	17	15	16
Sex (M/F)	10/7	9/6	6/10
Age (Years)	20.5 ± 2.1	22.1 ± 1.8	21.3 ± 2.4
Beck Depression Inventory[a]	1.8 ± 2.2	3.6 ± 3.4	5.0 ± 4.6[c]
Years of Education	15.2 ± 2.0	15.0 ± 1.5	14.4 ± 1.6
First-Degree Relatives with SUD[b]	.0 ± .0	.0 ± .0	1.6 ± .6[c,d]
Second-Degree Relatives with SUD[b]	.0 ± .0	.0 ± .0	2.9 ± 1.1[c,d]
Weighted Total Relatives with SUD[b]	.0 ± .0	.0 ± .0	3.1 ± .7[c,d]
First-Degree Relatives with Axis I[b]	.1 ± .3	.6 ± .7	1.5 ± 1.0[c,d]
Second-Degree Relatives with Axis I	.4 ± .7	.5 ± .9	1.1 ± 1.2
Weighted Total Relatives with Axis I[b]	.3 ± .4	.8 ± 1.0	2.0 ± 1.1[c,d]
Alcohol[b]	138.1 ± 134.1	401.2 ± 361.8[c]	417.9 ± 300.7[c]
Cannabis[b]	23.6 ± 28.6	423.8 ± 586.4[c]	713.6 ± 936.4[c]
Cocaine[b]	0 ± 0	12.5 ± 15.1[c]	30.4 ± 46.9[c]
Amphetamines[b]	0 ± 0	16.7 ± 23.8[c]	11.1 ± 13.1[c]
MDMA[a]	.1 ± .5	14.7 ± 19.9[c]	8.8 ± 16.6
Opiates	0 ± 0	.5 ± 1.5	1.6 ± 5.7
Psilocybin[b]	.2 ± .6	6.9 ± 7.1[c]	13.3 ± 18.1[c]
Ketamine	0 ± 0	17.7 ± 62.5	2.4 ± 6.3
Tobacco[b]	81.1 ± 259.9	1039.3 ± 1172.0[c]	591.6 ± 703.8[c]

Mean ± SD by group for demographic variables/self-reported lifetime days of drug use (see Table S5 in Supplement 1 for additional detail). Groups are well matched on age and education. Ctls_naive and Ctls_exposed with any family history of SUD were not included in the sample. Due to comorbidity of other psychiatric disorders with SUD, we expected to find group differences in family history of Axis I disorder, as well as subclinical depressive symptoms (Ctls_naive = Ctls_exposed) < FH + exposed. Ctls_naive subjects had never used amphetamines or cocaine and reported very little other drug use. All Ctls_exposed and FH + exposed were current occasional users. Group differences in drug use reflect Ctls_naive < (Ctls_exposed = FH + exposed).

Ctls_exposed, family history negative drug users; Ctls_naive, stimulant drug-naïve healthy control subjects; F, female; FH + exposed, family history positive drug users; M, male; MDMA, 3,4-methylenedioxymethamphetamine; SUD, substance use disorder.

[a] $p \leq .05$.

[b] $p \leq .01$.

[c] > Ctls_naive.

[d] > Ctls_exposed.

test, adoption, or being unable to provide a complete family history. Healthy control subjects (Ctls_naive) were matched on age to FH + exposed, were all psychostimulant naïve, and reported minimal exposure to other drugs of abuse except occasional consumption of alcohol, marijuana, or tobacco. They were also free of first-degree or second-degree relatives with current or past substance use problems. All other exclusion criteria were identical to FH + exposed. Family history negative drug users (Ctls_exposed) were matched on age and personal drug use history to FH + exposed and were current nonabusive occasional users of psychostimulant drugs (cocaine, amphetamines) but free of first-degree or second-degree relatives with current or past substance use problems. All other exclusion criteria were identical to FH + exposed.

The study was carried out in accordance with the Declaration of Helsinki and approved by the Research Ethics Board of the Montreal Neurological Institute. All participants gave written informed consent.

Procedure

All subjects underwent two PET scans on separate days (average 18.3 ± 22.7 days between scans, minimum interval 72 hours, no group difference was observed [$F_{2,45} = .73$, $p = .487$]), with the tracer [^{11}C]raclopride following ingestion of either *d*-amphetamine (.3 mg/kg, by mouth, 60 minutes before scanning) or a lactose placebo given in a double-blind, fully randomized, counterbalanced design. This procedure provides a reliable [^{11}C]raclopride change signal (23) that can be increased (24) and decreased (25) by experimental manipulations. On each test day, subjects arrived at the lab in the morning after 2 hours of fasting. Before each test session, subjects abstained from tobacco for at least 12 hours, from alcohol for at least 24 hours, and were asked to abstain from all other drugs for 7 days (those reporting no use within 48 hours, with negative urine screens were tested). Regular cannabis users were asked to abstain for up to 1 month or until they could provide a negative drug screen. On the morning of each test day, all tested negative on a urine drug screen sensitive to cocaine, opiates, phencyclidine, barbiturates, Δ9-tetrahydrocannabinol, benzodiazepines, and amphetamines (Triage Panel for Drugs of Abuse, Biosite Diagnostics, San Diego, California). Women were tested during the follicular phase and provided a negative urine pregnancy screen on the morning of each PET scan (Assure FastRead hCG Cassette, Conception Technologies, San Diego, California).

Sixty minutes before PET scanning (time 0), a baseline blood sample was drawn (collected via venipuncture directly into an ethylenediaminetetraacetic acid vacutainer for determination of plasma amphetamine concentration) and a set of visual analogue scales (VAS) assessing subjective stimulant and pleasurable effects of the drug was administered. Subjects then ingested either *d*-amphetamine (.3 mg/kg, by mouth) or a lactose placebo. At time 30 minutes, subjects completed another VAS, were installed