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Prescription Stimulant Use is Associated with Earlier Onset of Psychosis

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Abstract

A childhood history of attention deficit hyperactivity disorder (ADHD) is common in psychotic disorders, yet prescription stimulants may interact adversely with the physiology of these disorders. Specifically, exposure to stimulants leads to long-term increases in dopamine release. We therefore hypothesized that individuals with psychotic disorders previously exposed to prescription stimulants will have an earlier onset of psychosis. Age of onset of psychosis (AOP) was compared in individuals with and without prior exposure to prescription stimulants while controlling for potential confounding factors. In a sample of 205 patients recruited from an inpatient psychiatric unit, 40% (n=82) reported use of stimulants prior to the onset of psychosis. Most participants were prescribed stimulants during childhood or adolescence for a diagnosis of ADHD. AOP was significantly earlier in those exposed to stimulants (20.5 vs. 24.6 years stimulants vs. no stimulants, $p<0.001$). After controlling for gender, IQ, educational attainment, lifetime history of a cannabis use disorder or other drugs of abuse, and family history of a first-degree relative with psychosis, the association between stimulant exposure and earlier AOP remained significant. There was a significant gender x stimulant interaction with a greater reduction in AOP for females, whereas the smaller effect of stimulant use on AOP in males did not reach statistical significance. In conclusion, individuals with psychotic disorders exposed to prescription stimulants had an earlier onset of psychosis, and this relationship did not appear to be mediated by IQ or cannabis.

Graphical abstract

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Keywords

attention deficit hyperactivity disorder; amphetamine; methylphenidate; schizophrenia

Introduction

Recent studies indicate rising rates of the diagnosis of attention deficit hyperactivity disorder (ADHD) and the use of prescribed stimulants for its treatment. In 2012, more than 5 million children and adolescents ages 3–17 years were diagnosed with ADHD, an increase from 4.4 million in 2002 (Chai et al. 2012; Bloom et al. 2013). In the year 2010 alone, 1.9 million pediatric patients were dispensed a prescription for methylphenidate and 1.2 million were dispensed amphetamine or dextroamphetamine (Chai et al. 2012). There has also been a concomitant increase in diversion and misuse of prescription stimulants in adolescents and young adults (Lakhan and Kirchgessner 2012; Hartung et al. 2013).

Stimulant induced psychosis was first described at length by Connell who reported a case series of individuals who developed psychosis in the context of amphetamine use (Connell 1958). Since then, numerous studies have described the development of psychosis in individuals abusing amphetamine and methamphetamine (Curran et al. 2004; McKetin et al. 2006). New onset psychosis has also been reported in children/adolescents prescribed amphetamine and methylphenidate for ADHD, although studies of the long-term risk of psychosis in this population are lacking (Cherland and Fitzpatrick 1999; Ross 2006).

Prescription stimulants are associated with long-term sensitization of dopaminergic release in the striatum (Vanderschuren et al. 1999; Vezina 2007). Increased presynaptic dopamine release is a replicated finding associated with psychosis (Laruelle et al. 1999; Howes et al. 2012). Therefore, through the process of sensitization, exposure to stimulants during childhood or adolescence could increase the risk for future psychosis. Consistent with this model, there is evidence that stimulants are associated with an increased risk of developing a psychotic disorder. Psychotic symptoms have been reported to persist in a significant percentage of individuals with methamphetamine-induced psychosis (Tatetsu et al. 1956; Sato 1992; Sato et al. 1992). Recent studies observed an increased risk of schizophrenia in individuals with methamphetamine and cocaine/amphetamine use disorders (Callaghan et al. 2012; Giordano et al. 2015).

One commonly employed method of evaluating psychosis risk is comparing age of onset of psychosis (AOP) in patients with and without an exposure while taking into account potential confounding factors. Multiple studies have shown that cannabis use, substance

abuse in general, male gender, family history of psychosis, low level of educational attainment and premorbid IQ are associated with earlier AOP (Gureje 1991; Suvisaari et al. 1998; Cantwell et al. 1999; Khandaker et al. 2011; Large et al. 2011; Liu et al. 2013). Controlling for educational attainment and IQ is of particular relevance for this study as cognitive impairment may increase the likelihood of being treated for a diagnosis of ADHD or using stimulants to compensate for cognitive deficits. The diagnosis of ADHD itself may also be a confounding factor, as recent prospective studies demonstrate that children with ADHD have an increased risk of developing schizophrenia (Dalsgaard et al. 2014; Maibing et al. 2014). In addition, the severity of ADHD symptoms has been associated with earlier AOP in individuals with schizophrenia with a history of childhood ADHD (Peralta et al. 2011).

The purpose of this study is to test the following hypotheses: 1) A history of premorbid exposure to prescription stimulants is associated with an earlier onset of psychotic disorders. 2) The relationship between prescription stimulant use and earlier AOP will persist after adjusting for gender, cannabis and other substance use disorders, history of first degree relative with psychosis, educational attainment and IQ.

Material and Methods

Study Sample and Clinical Assessments

Two hundred and thirty-nine individuals with psychotic disorders (diagnosed with schizophrenia, schizoaffective disorder, psychotic bipolar disorder, psychotic depression or psychosis not-otherwise specified) were recruited from an inpatient psychiatric unit specializing in the treatment of individuals with schizophrenia and bipolar affective disorder as part of a genetic association study used in prior studies (Ongür et al. 2009). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was reviewed by McLean Hospital Institutional Review Board. Informed consent of participants was obtained after the nature of the procedures had been fully explained. The Structured Clinical Interview for DSM-IV (SCID-IV) was used to diagnose psychotic, mood and substance use disorders. The Chronology of Psychotic Symptoms from the SCID-IV Psychosis Module was used to determine AOP. Patient interviews, review of medical records, and information from family members and outside providers were used to determine psychiatric diagnoses and AOP. Please see Ongür et al., for further details (Ongür et al. 2009).

All participants completed a questionnaire which asked about prior use of prescription stimulants, age of onset of stimulant use, type of stimulant(s) used, whether stimulants were prescribed or not, and self-reported diagnosis of ADHD (yes or no). Premorbid IQ was estimated using the North American Adult Reading Test (Crawford et al. 2001). Because IQ was not collected at study initiation and was added at a later time point, IQ was missing in a subset of patients (n=63).

Statistical Analysis

Demographic characteristics in the stimulant vs. non-stimulant groups were compared using t-tests or χ^2 -square tests. Correlation coefficients evaluated the relationship between age of onset of stimulant use and AOP. Non-parametric tests were used when appropriate. All tests of hypotheses were two-sided with a significance level of 0.05. STATA was used for all analyses.

Primary Analysis

Unadjusted AOP was first compared in the two stimulant groups using independent sample t-test. The *a priori* primary analysis was to assess the effect of prior stimulant use on AOP using a multiple regression model controlling for gender, lifetime cannabis use/dependence, other lifetime substance abuse/dependence, presence of first-degree relative with psychosis and educational attainment (years of education completed). We combined presence of lifetime history of opioid, cocaine, sedative/hypnotic, hallucinogen and polysubstance use disorders as diagnosed using SCID-IV into a single dichotomous variable since the number of subjects with individual use disorders (besides cannabis) was small and not sufficiently powered for individual analyses. Because we restricted the primary analysis to variables for which all subjects had complete data, IQ was not included.

Secondary Analyses

As secondary analyses, 1) we first repeated the primary analysis comparing individuals without a history of stimulant use to the subset of individuals prescribed stimulants and to the subset of individuals not prescribed stimulants separately. 2) We next used exploratory multiple regression analyses to look for interactions between stimulant use and each of the potential confounding factors, and repeated the primary analysis with the addition of any significant interaction terms that were identified. Robust standard errors were used for all regression models to correct for departure from the assumption of homoscedasticity of residuals (Hayes and Cai 2007). 3) We also used a multiple imputation approach that allowed inclusion of subjects with missing IQ data (van Buuren et al. 1999). This approach is commonly used to allow inclusion of observations with missing independent variable data in multiple regression models (Horton and Kleinman 2007). One hundred copies of the dataset were created with imputed values for missing IQ. Next, complete-case analyses of these datasets were performed independently. Beta values were averaged to provide a single parameter estimate. Standard errors were calculated accounting for within-imputation and between-imputation variability in the parameter estimates.

Results

Sample Characteristics

Out of 239 patients with psychotic disorders, 113 (47.2%) reported a history of use of stimulants. Because we were testing the hypothesis that premorbid use of stimulants is associated with earlier onset of psychosis, we excluded 31 subjects from analysis who reported age of onset of stimulant use after onset of psychosis (mean $\pm$ SD: 10.4 $\pm$ 9.1 years after AOP). An additional three subjects with stimulant-induced psychosis were eliminated

from analysis: one with repeated hospitalizations for methamphetamine-induced psychosis and two subjects with a single isolated episode of stimulant-induced psychosis at study entry. Out of the final sample (n=205), 82 (40%) reported stimulant use prior to the onset of psychosis. Demographic and baseline characteristics of patients with and without a history of prescription stimulant use are presented in Table 1. There were no significant differences in diagnosis, family history, educational attainment or IQ between the two groups. Individuals exposed to stimulants were significantly more likely to be younger, male, and have a history of a lifetime cannabis use disorder.

Stimulant Use Characteristics

AOP was significantly earlier in individuals with a history of stimulant use (20.5 ± 6.4 years stimulant group vs. 24.6 ± 9.0 years non-stimulant group; $t=3.7$, $p<0.001$). Type of stimulant(s) used was as follows: methylphenidate (n=27; 33%), amphetamine salts (n=22; 27%), a history of both methylphenidate and amphetamine use (n=27; 35%) and atomoxetine (n=1). There was no significant effect of type of stimulant on AOP (20.1 ± 4.2 amphetamine alone or combined with methylphenidate vs. 20.8 ± 8.5 methylphenidate; $t=0.4$, $p=0.7$).

A majority of patients with stimulant exposure reported that stimulants had been prescribed (n= 66; 80.5%), whereas 16 (19.5%) were never prescribed stimulants. Of those prescribed, 71% (n=44) reported a diagnosis of ADHD and the remaining 29% (n=19) were prescribed stimulants for unknown reasons. The distribution of age of onset of stimulant use was positively skewed with 25% of individuals prescribed stimulants between the ages of 6 – 12 and 86% of participants prescribed stimulants during childhood/adolescence (ages 6 – 19). The mean age of onset of stimulant use was 15.8 ± 5.3 years (median 16). The onset of stimulant use preceded cannabis use by an average of 2.6 ± 3.3 years, and the majority (70%) of individuals in our sample had an earlier age of onset of stimulant than cannabis use. Importantly, age of onset of stimulant use was significantly correlated with AOP ($\rho=0.45$, $p<0.001$).

Gender × Stimulant Interaction

Males had a significantly earlier AOP than females (21.5 ± 6.2 male vs. 25.8 ± 10.9 female; $t=3.0$, $p=0.003$). Males were significantly more likely to have a history of lifetime cannabis abuse/dependence (54.4% male vs. 24.6% female, $\chi^2=16.4$, $p<0.001$) but not other drugs of abuse ($\chi^2=2.0$, $p=0.16$). In a model with gender, stimulant use and their interaction ($F_{3,201}=6.1$, $p<0.001$), we found a significant gender × stimulant use interaction ($\beta=6.1$, $p=0.02$). The effect of stimulant use on AOP was most pronounced in females (20.2 ± 8.0 stimulant use vs. 28.0 ± 11.1 no stimulant use; $t=2.8$, $p=0.006$), whereas the effect in males did not reach statistical significance (20.6 ± 5.9 vs. 22.3 ± 6.3 ; $t=1.6$, $p=0.1$).

There were no significant interactions between stimulant use and cannabis use, other substance use, family history of psychosis, or education (all $p>0.2$).

Regression Models

Primary Analysis—The final results of the primary *a priori* analysis can be found in Table 2 (Model 1). In this model ($F_{6,198}$, $p<0.001$), we found significant effects of gender, family history of psychosis as well as a lifetime history of cannabis abuse/dependence (all $p<0.05$) but not education. After controlling for all potential confounding factors, the effect of stimulant use on AOP remained significant ($p=0.007$).

Secondary Analyses—1) We repeated the primary analysis comparing those not exposed to stimulants to the subset of individuals who were prescribed stimulants ($F_{6,182}=5.0$, $p<0.001$). We again found significant effects of gender, family history and cannabis use ($p<0.05$), and the effect of stimulant use on AOP was significant for stimulant users who were prescribed stimulants ($\beta = -3.1$, $p=0.02$). Using the model for the primary analysis comparing individuals without a history of stimulant use to those who were *not* prescribed stimulants ($F_{6,132}=3.5$, $p=0.003$), we also found a significant effect of stimulant use on AOP with a similar effect size ($\beta = -3.1$, $p=0.02$).

2) Because we found a significant gender x stimulant interaction using exploratory models, we repeated the primary model adding the interaction term ($F_{7,197}=4.7$, $p<0.001$; Table 2: Model 2). After controlling for potential confounders, the gender x stimulant interaction remained significant ($p=0.008$). Because main effects are difficult to interpret in the setting of an interaction, we performed the primary analysis in females and males separately. In females, after controlling for potential confounders, the effect of stimulant use on AOP remained significant ($F_{5,63}=3.9$, $p=0.004$; stimulant exposure $\beta = -7.5$, $p=0.003$). However, stimulant effect on AOP was not significant in males ($\beta = -1.2$, $p=0.32$).

3) We used multiple imputation to account for missing IQ data ($n=63$; 31% missing) for multiple regression using a model that included the same explanatory variables for the primary analysis except educational attainment. Since IQ and educational attainment were correlated in this dataset ($r=0.47$, $p<0.001$), we excluded educational attainment to avoid collinearity. Using this model, we found similar findings ($F_{6,195}=5.5$, $p<0.001$) of significant effects of gender, family history and cannabis abuse/dependence on AOP (all $p<0.05$). Controlling for these variables and IQ did not alter the significance of the effect of stimulant use on AOP ($\beta = -3.0$, $p=0.01$). Importantly, there was no significant effect of IQ on AOP ($\beta = -0.05$, $p=0.55$).

As a post-hoc sensitivity analysis, we included the 31 participants who were excluded from analysis because of onset of stimulant use after onset of psychosis to ensure removing these participants did not bias our results. Because this study tests the hypothesis that *prior* stimulant history is associated with earlier AOP, we added these participants to the *non-stimulant* group (i.e., no history of stimulant use prior to onset of psychosis). Using the final regression model ($F_{6,229}=5.3$, $p<0.001$), we found significant effects of cannabis use and family history ($p<0.05$) and a significant effect of stimulant use on AOP ($\beta = -2.1$, $p=0.04$).

Individuals exposed to stimulants were significantly younger than those without a prior history of stimulant use. We therefore performed a post-hoc analysis by randomly selecting a subset of the individuals who were not exposed to stimulants such that the two exposure

groups were matched in age (both groups 28.1 years). We repeated the primary analysis in this subset ($F_{6,138}=4.3$, $p<0.001$). We still found a significant effect of stimulant use ($\beta=-2.6$, $p=0.04$), albeit of a smaller effect size, suggesting that the age difference between the two groups did not explain the association between stimulant use and earlier AOP.

Discussion

In this study, we demonstrate the novel finding that prior exposure to prescription stimulants is associated with an earlier onset of psychosis while controlling for potential confounding factors. Our sample was largely prescribed stimulants during childhood and adolescence, and the majority of participants were prescribed stimulants for ADHD. Importantly, stimulant exposure was associated with earlier AOP in the subset of individuals prescribed stimulants. Therefore, although there have been many prior studies showing an association between cannabis and other drugs of abuse and earlier AOP (Cantwell et al. 1999; Large et al. 2011), this is the first study demonstrating an earlier AOP for medications *prescribed* for comorbid psychiatric disorders. We identified a significant gender x stimulant interaction in which the effect of stimulant use on AOP was most pronounced in female patients. We also replicated previous findings of earlier AOP in males, individuals with a history of cannabis use and a family history of psychotic disorders (Gureje 1991; Suvisaari et al. 1998; Large et al. 2011).

Numerous studies have demonstrated that cannabis and substance abuse in general are associated with an earlier AOP (Large et al. 2011). However, there has only been one small study of earlier AOP associated with stimulant use in individuals with childhood-onset schizophrenia that did not control for other factors associated with AOP (Karatekin et al. 2010). Since individuals who use illicit drugs often initiate substance abuse with cannabis ("gateway drug"), many previous studies included a substantial number of individuals that abused cannabis and no other drugs, making it easier to detect an effect of cannabis on AOP (Baeza et al. 2009). In studies where stimulant abuse was reported, stimulant use rates were substantially lower than cannabis use and usually associated with polysubstance abuse, making it difficult to detect a specific effect of stimulants on AOP (Cantwell et al. 1999; Bersani et al. 2002; Baeza et al. 2009). For example, an Australian study found an association between age of stimulant onset and AOP that was interpreted as a spurious effect of earlier AOP due to cannabis use (Power et al. 2014). In their sample, almost all stimulant users (98%) abused cannabis, and cannabis use preceded onset of amphetamine by 2–3 years. Several unique characteristics of our sample enabled detection of an effect due to stimulants: 1) Our sample had a high base rate of stimulant use (40%), which in itself is supportive of a potential link with psychosis. The high rate may be in part attributed to the substantially higher prescribing rates for stimulants for ADHD in the United States compared to other countries (Scheffler et al. 2007; Knopf et al. 2012). However, the rate of 40% is markedly higher than usual rates of prescription stimulant use for ADHD (3.5% in population under age of 19) and misuse of prescription stimulants in the U.S. (highest rate reported in literature 17%; Hall et al. 2005; Zuvekas and Vitiello 2012). 2) Stimulants were mostly prescribed in childhood and adolescence prior to usual onset of substance use disorders. Most patients (70%) began taking stimulants prior to onset of cannabis use,

allowing detection of an effect of earlier AOP with stimulant use independent of the effect of cannabis use disorder on AOP.

One interesting finding was that the significant reduction in AOP with stimulant use was largely due to the greater effect size in females, effectively closing the gender gap in AOP: male stimulant users had a similar AOP to female stimulant users (20.6 years male vs. 20.2 years female). Participants with stimulant exposure were more likely to be male than individuals without stimulant exposure, consistent with reports that the majority of individuals diagnosed with ADHD or prescribed stimulants are male (Cox et al. 2008). Importantly, the greatest rate of increase in prescription stimulants in recent years is in females (Cox et al. 2008). Previous reports in the literature have shown a similar pattern in which females with a history of cannabis use, family history of psychotic disorders or treatment-resistant schizophrenia have similar AOP to males (Gorwood et al. 1995; Meltzer et al. 1997; Rabinowitz et al. 1998; Compton et al. 2009). One interpretation is that other exposures or clinical factors have stronger effects that outweigh the impact of gender on AOP. Another possibility is that there are gender-specific effects of stimulants. Preclinical studies indicate that dopamine release in the nucleus accumbens is modulated by estrogen and progesterone, and estrogen enhances amphetamine-stimulated dopamine release (Becker 1999). Female adolescent rats show stronger behavioral sensitization to methylphenidate than males (Roeding et al. 2014).

A plausible mechanism for earlier AOP in those exposed to stimulants is stimulant-induced sensitization of striatal dopamine release. In animal studies, exposure to stimulants has long-term effects on behavior corresponding with increased dopamine release. Even a single dose of amphetamine leads to time-dependent enhancement of dopamine release with subsequent amphetamine challenge (Vanderschuren et al. 1999). After exposure to several doses of amphetamine, subsequent amphetamine challenge leads to increased dopamine in the nucleus accumbens that progressively increases over time (Hamamura et al. 1991; Vezina 2007). In humans, increased dopamine release in the striatum has been demonstrated one year after initial pre-treatment with amphetamine (Boileau et al. 2006). Likewise, individuals with schizophrenia show increased dopamine release in response to amphetamine, and the magnitude of dopamine release is correlated with severity of amphetamine-induced psychotic symptoms (Laruelle et al. 1996, 1999). Increased presynaptic dopamine storage capacity in the striatum has been demonstrated in at risk, drug-naïve and patients with chronic schizophrenia (Howes et al. 2009, 2012). This constellation of findings suggests that a putative mechanism of prior prescription stimulants reducing AOP may be the induction of long-term sensitization of striatal dopaminergic function, leading to changes in dopaminergic systems that parallel abnormalities seen in psychotic disorders.

Potential hypotheses about the relationship of stimulant use and psychosis include: 1) prescription stimulants may contribute to AOP in those who would ultimately go on to develop a psychotic disorder; 2) stimulant use itself does not contribute to an earlier onset of psychosis, but rather earlier AOP is due to other factors such as cognitive impairment or a diagnosis of ADHD (i.e., confounding). Cognitive deficits precede the onset of psychosis, and prodromal difficulties with attention and executive function could lead to a diagnosis of

the inattentive subtype of ADHD or stimulant use (Kahn and Keefe 2013). Factors that make it less likely our findings are secondary to cognitive impairment include the lack of significant differences in measures of cognitive status between the two groups: educational attainment and IQ. Controlling for educational attainment and IQ did not alter the significance of the finding of earlier AOP in individuals with a history of stimulant use. Furthermore, there was a significant correlation between age of onset of prescription stimulant use and AOP. These findings, as well as a plausible mechanism of action, suggest that stimulant use may be at least in part responsible for earlier AOP. Because IQ data was missing in a significant percentage of patients, these findings will require replication.

We did not conduct standardized interviews for the diagnosis of ADHD nor did we use rating scales to assess ADHD severity. ADHD diagnosis was obtained by self-report, which limits our ability to exclude the possibility that our findings are due to a history of ADHD or severity of ADHD symptoms. It is likely that individuals prescribed stimulants for “unknown” reasons may have received treatment for an ADHD diagnosis or symptoms of ADHD. The finding of a significant reduction in AOP in the subset of patients who abused/misused stimulants that were not prescribed supports the association of AOP with stimulant use, although these individuals may also have had undiagnosed ADHD or symptoms of ADHD. However, there were no significant differences in educational attainment and IQ in the two exposure groups. If the association between stimulant use and AOP is due to confounding with ADHD, one would expect lower levels of educational attainment or IQ in the stimulant exposed group, as lower IQ and lower levels of educational attainment are associated with a diagnosis of ADHD (Polderman et al. 2010; Biederman et al. 2012; Rommel et al. 2015; Soendergaard et al. 2015). This study will require replication using standardized ADHD diagnostic tools in individuals exposed and not exposed to stimulants.

Other limitations of this study include lack of data on cumulative dose and duration of treatment, as a dose-response relationship would strengthen support of our hypothesis. The lack of data on obstetric and development factors is another limitation as schizophrenia and ADHD are both neurodevelopmental disorders. Individuals with schizophrenia with a history of childhood ADHD have more developmental abnormalities and have a worse prognosis compared to their counterparts without ADHD (Elman et al. 1998). In addition, since participants were recruited from an acute inpatient unit, the findings may not be generalizable to individuals with psychotic disorders in the community. Inpatients with psychotic disorders are more likely to have comorbid substance use disorders (Zeidler et al. 2012) and worse long-term outcome (Wolter et al. 2010).

Conclusion

This study presents the novel finding of an association between prescription stimulant use and an earlier onset of psychosis. The potential public health impact of this association is amplified by increasing prescribing rates of stimulants to millions of children and adolescents in the United States. An earlier onset of psychosis is associated with poor long-term function and a worse prognosis (Lay et al. 2000; Rabinowitz et al. 2006). The identification and prevention of risk factors that lead to an earlier age of onset has the potential to decrease morbidity associated with psychotic disorders.

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Highlights

- A history of prior exposure to prescription stimulants was associated with an earlier age of onset of psychosis
- The majority of participants were prescribed stimulants for attention deficit hyperactivity disorder
- The association between prescription stimulant exposure and age of onset of psychosis remained significant after controlling for male gender, cannabis use, other substance abuse, family history of a first-degree relative with psychosis, educational attainment and IQ

Table 1

Demographic and Clinical Characteristics

	No History of Prescription Stimulant Use (n = 123)	History of Prescription Stimulant Use (n = 82)	Test Statistic	p Value
Age, years (mean $\pm$ SD)	38.1 $\pm$ 12.6	28.0 $\pm$ 9.5	t=6.5	<0.001
Early-stage illness, n(%) ¹	50 (40.7%)	43 (52.4%)	$\chi^2=2.8$	0.10
Gender, n (%)				
Male	74 (60.2%)	62 (75.6%)	$\chi^2=5.3$	0.02
Female	49 (39.8%)	20 (24.4%)		
Diagnosis, n (%)				
Schizophrenia	73 (59.4%)	37 (45.1%)	$\chi^2=7.8$	0.10
Schizoaffective Disorder	39 (31.7%)	34 (41.5%)		
Bipolar Disorder (psychotic features)	1 (0.8%)	2 (2.4%)		
Major Depression (psychotic features)	3 (2.4%)	0 (0.0%)		
Psychosis NOS	7 (5.7%)	9 (11.0%)		
Psychiatric family history (first degree relative):				
Psychosis	17 (13.8%)	6 (7.3%)	$\chi^2=2.1$	0.15
Bipolar Disorder	17 (13.8%)	12 (14.6%)	$\chi^2=0.03$	0.87
Depression	30 (24.4%)	27 (32.9%)	$\chi^2=1.8$	0.18
Substance abuse	24 (19.5%)	22 (26.8%)	$\chi^2=1.5$	0.22
Any diagnosis	71 (57.7%)	50 (61.0%)	$\chi^2=0.2$	0.64
Education	13.8 $\pm$ 2.4	13.5 $\pm$ 2.4	t=0.8	0.41
IQ	108.8 $\pm$ 8.4	107.7 $\pm$ 9.4	t=0.66	0.51
History of Lifetime Cannabis Abuse or Dependence, n (%)	39 (31.7%)	52 (63.4%)	$\chi^2=20.0$	<0.001
History of Lifetime Abuse or Dependence of Other Drugs, n (%)	20 (16.3%)	22 (26.8%)	$\chi^2=3.4$	0.07
Sedative/Hypnotic	3 (2.4%)	6 (7.3%)		
Cocaine	11 (8.9%)	10 (12.2%)		
Opioid	2 (1.6%)	6 (7.3%)		
Hallucinogen/PCP	1 (0.8%)	9 (11.0%)		
Polysubstance	8 (6.5%)	2 (2.4%)		

¹ Early phase of illness defined as duration of psychosis < 5 years (Breitborde et al. 2009).

Table 2

Regression Analyses for Variables Predicting Age of Onset of Psychosis

Variable	Model 1: $R^2 = 0.16$ (<i>a priori</i>)				Model 2: $R^2 = 0.20$ (Gender x Stimulant Interaction)			
	β	t	p	95% Confidence Interval	β	t	p	95% Confidence Interval
Stimulant Exposure	-3.1	-2.8	0.007	-5.3 -0.9	-7.9	-3.4	0.001	-12.5 -3.3
Gender	-2.9	-2.0	0.04	-5.7 -0.1	-5.2	-2.9	0.004	-8.8 -1.7
Gender x Stimulant	-	-	-	-	6.9	2.6	0.008	1.8 11.9
Lifetime Cannabis Abuse/Dependence	-2.6	-2.2	0.03	-4.8 -0.3	-2.5	-2.7	0.03	-4.8 -0.3
Other Drugs: Lifetime Abuse/Dependence	1.6	1.1	0.27	-1.2 4.4	1.6	1.2	0.25	-1.2 4.4
First Degree Relative with Psychosis	-3.8	-2.4	0.02	-7.1 -0.6	-4.2	-2.6	0.009	-7.3 -1.0
Educational Attainment (years)	0.4	1.5	0.15	-0.1 1.0	0.4	1.6	0.11	-0.1 1.0
Intercept	21.7	4.8	<0.001	12.7 30.7	22.7	4.9	<0.001	13.5 31.8

Indicator variables for presence of stimulant exposure, cannabis abuse, other drugs of abuse, first-degree relative with psychosis and male gender coded as 1; not present or female gender = 0.