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Nicotine usage is associated with elevated processing speed, spatial working memory, and visual learning performance in youth at ultra high-risk for psychosis

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Abstract

Research has stressed a link between nicotine and cognition in schizophrenia but this has not been examined in youth at ultra high-risk (UHR) for psychosis. A total of 35 UHR and 32 control participants were assessed for naturalistic nicotine-use and administered a cognitive battery. Smoking was reported more frequently in the UHR group (46%) than controls (22%). Frequent smoking was associated with elevated cognitive performance in the UHR group, highlighting a need for experimental investigations.

Keywords

Cognition; Nicotine; Prodrome

1. Introduction

It is estimated that 72%-90% of schizophrenia patients smoke cigarettes compared to 24% of the general population (Cather et al., 2008). Several studies have shown that nicotine use may help to improve cognitive deficits in this population (Wing et al., 2011). However, this is a complex issue as accumulating research also suggests that prolonged nicotine use may actually result in worsening cognitive functioning over time (Iasevoli et al., 2013). The present study investigates nicotine use and cognition in youth at ultra high-risk for psychosis

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Contributors

Ms. Gupta helped to design and run the study, prepare data and draft the manuscript. Dr. Mittal attained funding, conceptualized the study, conducted analyses, and drafted the manuscript.

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(UHR), a group exhibiting declining cognitive function as well as imminent risk for psychosis (Fusar-Poli et al., 2012). As nicotine may be an important modulator for select cognitive functions (Jacobsen et al., 2004), it is important to both quantify use and examine correlations with cognition in this critical population.

While researchers have observed that nicotine influences psychophysiological function in UHR and early psychosis populations (Cadenhead, 2011), it is surprising that there have been no studies examining associations with cognition in UHR youth. Patterns of addiction in adolescence (i.e., the typical UHR time period) set the stage for lifetime behavior and it is not yet entirely clear if these youth also show the high incidence of nicotine abuse seen in patients with formal psychosis (Cather et al., 2008). Further, new-targeted interventions are needed for this group who often exhibit mild-moderate cognitive deficits (Seidman et al., 2010; Fusar-Poli et al., 2012) and understanding the relationship between the nicotine system and cognitive function is a necessary first step in novel treatment development. In the present study, 35 UHR and 32 control participants were evaluated for naturalistic nicotine use and administered a battery of tests theoretically linked to nicotine function, as well as structured clinical interviews. Based on the literature in patients with formal psychotic disorders (Cather et al., 2008; Horan et al., 2008), we predicted that the UHR group would show significantly more frequent nicotine use and that this would be closely associated with higher scores on cognitive tasks including processing speed, working memory and visual learning.

2. Method

2.1 Participants

A total of 67 adolescents (mean=18.7; SD=1.9) were recruited through the Adolescent Development and Preventive Treatment (ADAPT) program, and were referred by community health care providers or self-referred in response to media announcements. UHR inclusion criteria included the presence of Attenuated Positive Symptom (APS) or Genetic Risk and Deterioration (GRD) prodromal syndromes (Miller et al., 2003). The exclusion criteria for all participants included history of significant head injury or other physical disorder affecting brain functioning, mental retardation, or history of a substance dependence disorder in the prior 6 months (excluding nicotine use). Additionally, UHR exclusion criteria included an Axis I psychotic disorder diagnosis, and control exclusion criteria included any Axis I diagnosis or a first-degree relative with psychosis.

2.2 Clinical Measures

The Structured Interview for Prodromal Syndromes (SIPS) was used to diagnose UHR syndromes, defined by moderate levels of positive symptoms and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of psychosis (Miller et al., 2003). The Structured Clinical Interview for the DSM-IV (SCID, research version) (First et al., 1995), was used to rule out Axis I psychotic disorders. Training of interviewers (advanced doctoral students) was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa≥80.

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2.3 Nicotine Usage

Nicotine usage was measured utilizing the Alcohol/Drug Use Scale (AUS/DUS) (Drake et al., 1996), a clinician-rating based inventory that measures frequency of tobacco use on a scale ranging from 0 (no use), 1(occasionally), 2 (less than 10 per day), 3(11-25 per day) and 4(more than 25 per day). The measure has been widely used in a number of psychosis spectrum studies (Cannon et al., 2008; Mittal et al., 2011; Mittal et al., 2012; Dean et al., 2014; Carol, E., and Mittal, V.M., under review) and shows excellent reliability (Long and Hollin, 2009; Moller and Linaker, 2010).

2.4 Cognitive Battery

Participants were administered the Wide Range Achievement Test-Word Reading Subtest Fourth Edition (WRAT) as a measure of general intelligence (Wilkinson and Robertson, 2006). Tests tapping into cognitive domains that have been found to be sensitive to nicotine use (Barr et al., 2008; Freedman et al., 2008; Deutsch et al., 2013) were selected from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; Nuechterlein and Green, 2006) battery including: Brief-Visuospatial-Memory-Task-Revised (BVMT-R: Benedict, 1997) (assesses visual learning; raw score reflects the total recall score of three trials), Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS; Keefe, 1999) (assesses processing speed; raw score reflects the total correct digits written), Trail Making Test: Part A (TMT-A; Tombaugh, 2004) (assesses processing speed; raw score reflects the total number of seconds), Wechsler Memory Scale-Third Edition Spatial Span (WMS-III; Wechsler, 1997b) (assesses nonverbal working memory; raw score reflects the sum of total correct responses forwards/backwards), and Letter-Number Sequencing (LNS: Wechsler, 1997a) (assesses verbal working memory; raw score reflects total correct responses of reordered numbers). Because the MATRICS norms do not fall below the age of 18, we used uncorrected t-scores (generated from the MATRICS scoring software).

2.5 Statistical Approach

Independent t-tests and chi-square tests were utilized to examine for any potential demographic differences between groups. Likewise, group differences in the cognitive variables were examined using independent t-tests. Because nicotine frequency was not normally distributed, group differences were evaluated utilizing the Mann-Whitney *U* test (non-parametric equivalent). Partial correlations (controlling for general intelligence) were used to examine relationships between the nicotine frequency and cognitive variables. As the results did not differ in terms of direction, magnitude, or significance from traditional bivariate tests, the results reported below reflect the bivariate correlation analyses. These analyses were repeated with spearman correlations as well. Two-tailed tests were employed for comparisons of demographic differences, whereas one-tailed test were used for analyses involving predicted outcomes. Because of the significantly lower rate of smoking reported in controls, the correlations were conducted by group independently.

3. Results

The nicotine assessment was administered to all 67 participants and cognitive data was not available for 2 participants in the UHR group. There were no significant differences between

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the UHR (n=35) and healthy control (n=32) groups on demographic characteristics including age, gender, general intelligence, and parental education (see Table 1 for group differences in demographics as well as target variables). The most prevalent comorbid disorders in the UHR group included a history of mood (50%), and anxiety (29%). A one-sample Kolmogorov-Smirnov test indicated that the nicotine frequency variable was positively skewed with a skew of 1.61(SE=0.29) and kurtosis of 2.40 (SE=0.58). Each of the other target variables was normally distributed. The UHR group showed significantly greater positive t(65)= 13.56, $p \leq 0.01$, as well as negative symptoms t(65)= 10.53, $p \leq 0.01$ when compared to controls.

A total of 46% of the UHR group reported nicotine use whereas only 22% in the controls did so, $\chi^2(1)=4.21$, $p \leq 0.05$. A Mann-Whitney *U* test indicated that the UHR group reported significantly more frequent nicotine use when compared with the healthy control group, $z= -2.19$, $p \leq 0.05$. Independent t-tests indicated that the UHR group showed significant deficits in trail making, t(63)=−2.02, $p \leq 0.05$, and letter-number-sequencing, t(63)=−2.14, $p \leq 0.05$, $p=0.35$. However, there were no differences between groups for visual learning, t(63)= −0.50, symbol coding, t(63)=−0.38 or spatial span, t(63)=0.57, $p=0.23$.

Bivariate correlations indicated that elevated nicotine use was tied to increased visual learning (r=0.33, $p \leq 0.05$), trail-making ($r=0.29$, $p \leq 0.05$), symbol coding ($r=0.36$, $p \leq 0.05$), and spatial span ($r=0.30$, $p \leq 0.05$) scores in the UHR group although there were no significant findings for letter-number-sequencing ($r=0.03$, $p=0.44$). Spearman associations were in the same direction as bivariate analyses, although these results for spearman associations were non-significant.

4. Discussion

Results indicating that individuals in the UHR group (46%) engaged in smoking behavior roughly twice as often as healthy controls (22%) present a striking picture of smoking behavior in this population. Findings that the UHR group showed lower scores in cognitive domains are consistent with the broader literature (Fusar-Poli et al., 2012). Observations that nicotine use was broadly associated with elevated cognitive performance provide an important new perspective for understanding the UHR period.

The present findings suggest that nicotine use is associated with improved processing speed, spatial working memory, and visual learning amongst the UHR group. Similar findings in patients with schizophrenia have lead researchers to suggest that nicotine intake helps to compensate for a decreased number of nicotinic acetylcholine receptor (nAChRs) in the hippocampus that contribute to a failure of cholinergic activation of GABA (Freedman et al., 1995). It is also noteworthy that both glutamate and dopamine can be affected by nicotine intake and this may also contribute to the increased prevalence of smokers diagnosed with schizophrenia (Dalack et al., 1998). The non-significant correlation with verbal working memory and smoking, while spatial working memory was closely related, also supports the notion that nicotine intake effects specific functions. One possibility is that letter-number-sequencing draws heavily on executive function (Miyake et al., 2000), relying less prominently on the nicotine system. Another possibility is the study may have been too

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underpowered to detect verbal working memory results. However, it is also possible that non-verbal cognitive deficits are more prominent in UHR populations than verbal deficits, allowing for more room to improve following nicotine intake (Bora et al., 2014).

We observed several instances in which cognitive scores were not different between groups, but were associated with nicotine use in the UHR group. It is also interesting that significant nicotine-cognition correlations were present in the UHR group alone. This is consistent with findings that smoking may impair cognition and that enhancement is only likely under specialized conditions in healthy individuals (Newhouse et al., 2004). However, the null findings in controls could also be because reduced rates of smoking in the control group (restricting variability and power). It is also important to consider that there have been studies to suggest patients with schizophrenia smoke more intensely and frequently than healthy subjects (Strand and Nyback, 2004; Williams et al., 2011,) and control smokers may not be activating nicotine receptors (Olincy et al., 1997). Future investigation is needed in order to better understand nicotine use in clinical and healthy populations.

The current design does not allow for conclusions about causality and further, the frequency of smoking is not a perfect index of nicotine consumption as individuals may be utilizing other methods (e.g., vaping, chewing tobacco) or a range of dosages and quality. It is also important to note that while we observed correlations between smoking and cognitive functioning, the complex neurological underpinnings behind cognition are likely driven by additional factors beyond the nAChR system. Although there were not any significant group differences on demographic variables, the gender discrepancy did approach significance $\chi^2(1)=3.21$, $p=0.07$, and exploring gender differences will be an important future direction. While this naturalistic design provides a real-life view of smoking behavior, experimental designs (i.e., placebo or open-label) will be integral to further our understanding and highlight treatment targets. Future replications with larger sample sizes (allowing for more sophisticated analyses) and more specialized batteries (including assessments of other critical domains linked to the nicotine system saccadic eye movements and motor functioning; Sherr et al., 2002) are sorely needed. Finally, longitudinal designs will be important for examining issues pertaining to causality and for determine nicotine effects on clinical outcome. Taken together, the present results will be important for future efforts to promote psychoeducation (for limiting harmful smoking behavior in this population) and for novel cognitive treatment development targeting the nAChR system.

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Highlights

- The ultra high risk (UHR) group showed lower scores in cognitive domains than control participants.
- Smoking was reported more frequently in the UHR group (46%) than control participants(22%).
- Frequent smoking was associated with elevated cognitive performance in the UHR group compared to control participants.

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Table 1

Group Differences in Demographics, Cognitive Performance, and Nicotine Usage

	Healthy	Ultra High-Risk	Total Differences	
Gender				
Males	13(41.0%)	22(63.0%)	35(52.0%)	*N.S.*
Females	19(59.0%)	13(37.0%)	32(48.0%)	
Total	32	35	67	
Age				
Mean Years (SD)	18.8(1.7)	18.6(2.1)	18.7(1.9)	*N.S.*
Parent Education				
Mean Years (SD)	15.6(2.9)	16.2(2.5)	15.9(2.7)	*N.S.*
SIPS Scores				
PositiveSymptoms				
Mean (SD)	0.59(1.38)	11.63(4.59)	6.26(6.53)	$p \leq 0.001$
Negative Symptoms				
Mean (SD)	0.72(1.33)	11.25(1.38)	6.22(7.29)	$p \leq 0.001$
WRAT				
Mean (SD)	103.2(12.4)	108.4(14.5)	106.1(13.8)	*N.S.*
Cognitive Functions				
Brief Visuospatial Memory Test-Revised				
Mean (SD)	55.7(7.0)	54.6(10.2)	55.1(8.8)	*N.S.*
Trail Making Test A				
Mean (SD)	58.2(8.8)	53.2(10.6)	55.6(10.0)	$p \leq 0.05$
Symbol Coding				
Mean (SD)	55.0(8.1)	53.8(16.3)	54.4(12.9)	*N.S.*
Spatial Span				
Mean (SD)	56.6(8.1)	55.1(12.0)	55.9(10.2)	*N.S.*
Letter Number Sequencing				
Mean (SD)	52.7(6.5)	49.2(6.7)	151.0(6.8)	$p \leq 0.05$
Nicotine Frequency				
Mean Rank[1]	29.3	38.3	--	$p \leq 0.05$
Mean	0.3(0.75)	0.6(0.73)	0.5(0.75)	

Note: Not significant (N.S.); Wide Range Achievement Test (WRAT); A chi-square test was employed to compare gender composition between groups, independent t-tests were utilized to compare group differences in age, parental education and cognitive function, and a Mann-Whitney *U* test was used to compare nicotine frequency between the groups; scores from the cognitive tests are reported as uncorrected t-scores from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery.

[1]Mean rank is reported because the analyses for nicotine frequency used non-parametric statistics.