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The association among smoking, HSV-1 exposure, and cognitive functioning in schizophrenia, bipolar disorder, and non-psychiatric controls

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ABSTRACT

Previous investigations have found that smokers with schizophrenia demonstrate reduced performance on cognitive tasks compared to non-smokers. However previous studies have not taken into account other environmental factors associated with cognitive functioning such as exposure to Herpes Simplex Virus type 1 (HSV-1). We examined these factors in a sample consisting of individuals with schizophrenia ($n = 773$), bipolar disorder ($n = 493$), or controls without a psychiatric disorders ($n = 548$). Participants were assessed on a cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and had a blood sample drawn to measure seropositivity to HSV-1. Within each group linear regression models were constructed to determine whether cigarette smoking and HSV-1 seropositivity were jointly associated with cognitive functioning after adjusting for relevant covariates. Within the schizophrenia group, the effect size of lower total cognitive score was −0.279 ($p < 0.0001$) for individuals who were both smokers and HSV-1 seropositive and a significant effect was found in all cognitive domains. The odds of being in the highest quartile of RBANS Total score were significantly lower for smokers (OR = 0.58, 95% CI 0.41, 0.82, $p = 0.002$). Smoking was not as consistently associated with levels of cognitive functioning in the bipolar disorder or the non-psychiatric control group. While experimental studies show that nicotine transiently improves functioning on sensory gating and attention tasks known to be deficient in schizophrenia, long-term nicotine exposure via smoking appears to have an adverse effect on cognitive functioning.

1. Introduction

Cognitive deficits contribute to the social disability and long-term functional impairments of persons with schizophrenia and bipolar disorder (Dickerson et al., 1996; Green, 1996). In individuals with schizophrenia, cognitive functioning is generally reduced compared to persons in the general population across a wide range of domains including attention, verbal memory, executive functioning, and processing speed (Blanchard and Neale, 1994; Heinrichs and Zakzanis, 1998). Similar effects are found in individuals with bipolar disorder although the cognitive deficits are not as marked as those found in schizophrenia (Bortolato et al., 2015; Dickerson et al., 2010; Schretlen et al., 2007). The determinants of cognitive deficits in persons with serious mental illness are not known with certainty but are likely to involve both genetic and environmental factors.

In terms of environmental factors, exposure to neurotropic infectious agents such as Herpes Simplex Virus type 1 (HSV-1) has been found to be associated with reduced cognitive functioning in several populations of individuals with schizophrenia or bipolar disorder (Dickerson et al., 2004; Gerber et al., 2012; Thomas et al., 2013; Yolken et al., 2011). Additional studies have found that the cognitive impairments related to HSV-1 exposure can be associated with structural and functional changes as measured by brain imaging (Prasad et al., 2011; Schretlen et al., 2010). The mechanism by which HSV-1 modulates neurocognitive functioning in individuals with schizophrenia and other populations has not been totally elucidated. In light of the biological properties of HSV-1 and the neuroimaging studies, it is likely that the effect of HSV-1 on neurocognitive functioning is related to its ability to establish latency within the central nervous system and to undergo periodic reactivation. Individuals with schizophrenia may be at

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particular risk of the effects of HSV-1 infection due to underlying neuroanatomical deficits, immune suppression or other environmental exposures and the effects of medications.

The association between cigarette smoking and cognitive functioning in serious mental illness has also been studied. It has been observed that the administration of nicotine, the active ingredient in cigarettes, transiently improves functioning on some sensory gating and attention tasks known to be deficient in schizophrenia. This observation has contributed to the idea that smoking may serve as a form of "self medication" for schizophrenia-related cognitive deficits (Featherstone and Siegel, 2015; Gehricke et al., 2007). On the other hand, most, but not all, investigations have found that smokers with mental illness as a group demonstrate reduced performance on cognitive tasks compared to non-smokers (Caldirola et al., 2013; Depp et al., 2015; Iasevoli et al., 2013; Morisano et al., 2013; Wing et al., 2011; Zhang et al., 2012).

The issue of smoking's effect on cognition in schizophrenia is important because individuals with schizophrenia have reduced cognitive functioning and also because they are three times more likely to smoke cigarettes than those in the general population (Dickerson et al., 2013b). The prevalence of smoking is also relatively high in other psychiatric disorders such as bipolar disorder (de Leon and Diaz, 2005; Dickerson et al., 2013b) where smoking has been found to have an adverse effect on quality of life and illness course (Thomson et al., 2015). The reasons for the higher prevalence of smoking in persons with mental illness are not known with certainty; social and psychological explanations have been offered as well as biological ones (Dome et al., 2010; Featherstone and Siegel, 2015). It is of note that previous studies examining the association between smoking and cognitive functioning have not taken into account other biomarkers associated with cognitive functioning such as exposure to HSV-1, nor have studies examined the association between smoking and cognition in relatively large samples of individuals with schizophrenia, bipolar disorder, and controls employing the same methods of cognitive assessment.

The purpose of our study was to investigate the association between smoking, exposure to HSV-1, and cognitive functioning in a large cohort of individuals with schizophrenia, bipolar disorder, and non-psychiatric controls.

2. Methods

Participants were individuals with schizophrenia, bipolar disorder, or non-psychiatric controls who were enrolled during the period January 1999–October 2015 in the Stanley Research Program at Sheppard Pratt, Baltimore, Maryland, USA for a study of the association between infection, immunity, and psychiatric disorders.

The inclusion criterion for individuals with schizophrenia was a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. The inclusion criterion for individuals with bipolar disorder included a diagnosis of bipolar disorder including bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified. The psychiatric participants were recruited from inpatient and day hospital programs of Sheppard Pratt and from affiliated psychiatric rehabilitation programs. The diagnosis of each psychiatric participant was established by the research team including a board-certified psychiatrist and based on the Structured Clinical Interview for DSM-IV Axis 1 Disorders (First et al., 1996) and available medical records.

The inclusion criterion for the non-psychiatric control individuals was the absence of a current or past psychiatric disorder as determined by screening with the DSM-IV Axis I Disorders, Non-patient Edition (First et al., 1998). As previously described, these individuals were recruited from posted announcements at local health care facilities and universities in the same geographic area as the settings where the psychiatric participants were recruited (Dickerson et al., 2014).

Participants in all groups met the following additional criteria: age 18–65 (except the control participants who were aged 20–60); proficient in English; absence of any history of intravenous substance abuse; absence of mental retardation; absence of HIV infection; absence of serious medical disorder that would affect cognitive functioning; absence of a primary diagnosis of alcohol or substance use disorder. Participants were not selected based on their smoking status.

All participants were assessed with a cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) which was individually administered by research staff. The RBANS is comprised of 12 subtests that are used to calculate 5 Index scores and a Total score. Test indices are Immediate Memory (comprised of List Learning and Story Memory tasks); Visuospatial/Constructional (comprised of Figure Copy and Line Orientation tasks); Language (comprised of Picture Naming and Semantic Fluency tasks); attention (comprised of Digit Span and Coding tasks); and Delayed Memory (comprised of List Recall, Story Recall, Figure Recall, and List Recognition tasks). Each Index score is expressed as an age-adjusted standard score with a mean of approximately 100 and a standard deviation of approximately 15 based on a normative study group of 540 healthy subjects, ranging in age from 20 to 89, matched to the U.S. Census on gender, ethnicity, and years of education. The Index scores are combined to yield a Total score, which is a summary score of the performance on the RBANS. The RBANS takes about 30 min to administer. Previous studies indicate that the RBANS is highly correlated with more extensive assessment including the Wechsler Adult Intelligence Scale III and the Wechsler Memory Scale III (Hobart et al., 1999) and that it has adequate test-retest stability (Wilk et al., 2004).

Psychiatric participants were also assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to evaluate their psychiatric symptom severity. Medications received at the time of study enrollment were recorded from the medical chart and self-report.

All participants had a blood sample drawn using standard venipuncture methods. Plasma was separated from the blood by centrifugation and was stored at −70 °C until testing from which were measured antibodies to Herpes Simplex Virus type 1 (HSV-1) using previously described methods (Dickerson et al., 2003).

At time of the study visit participants were asked if they were a current cigarette smoker and, if yes, the amount of cigarettes smoked per day which was quantified in number of packs per day.

A series of linear regression models were constructed to determine whether cigarette smoking and HSV-1 seropositivity were jointly associated with each measure of cognitive function after adjusting for relevant covariates. Demographic variables that were significantly associated with smoking in each group were included as covariates in that model; in the schizophrenia group, gender and age were included as covariates; in the bipolar disorder group, gender was included; no covariates were included in the model for the non-psychiatric controls. Standardized regression coefficients were calculated to serve as unitless effect size indices in order to facilitate comparison between diagnostic groups. The level of statistical significance used for all hypothesis tests was alpha = 0.05.

Within each group, the odds of being in the highest quartile of RBANS Total score and in the lowest quartile of total cognitive score were calculated. These odds ratios were adjusted for the same covariates used in the regression analyses.

3. Results

3.1. Schizophrenia

Characteristics of the 773 individuals in the schizophrenia sample by smoking status are shown in Table 1. The majority (62.0%) were smokers; 20.4% smoked no more than half a pack of cigarettes per day, 25.6% smoked more than half a pack but no more than a pack of cigarettes per day, and the remaining 15.9% smoked more than one pack of cigarettes per day.

Within the schizophrenia group, a total of 647/773 (83.7%) were receiving an atypical antipsychotic medication; 187 (24.2%) received