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Smoking status as a potential confounder in the study of brain structure in schizophrenia

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ABSTRACT

Several but not all MRI studies have reported volume reductions in the hippocampus and dorsolateral prefrontal cortex (DLPFC) in patients with schizophrenia. Given the high prevalence of smoking among schizophrenia patients and the fact that smoking has also been associated with alterations in brain morphology, this study evaluated whether a proportion of the known gray matter reductions in key brain regions may be attributed to smoking rather than to schizophrenia alone.

We examined structural MRI data of 112 schizophrenia patients (53 smokers and 59 non-smokers) and 77 healthy non-smoker controls collected by the MCIC study of schizophrenia. An automated atlas based probabilistic method was used to generate volumetric measures of the hippocampus and DLPFC. The two patient groups were matched with respect to demographic and clinical variables.

Smoker schizophrenia patients showed significantly lower hippocampal and DLPFC volumes than non-smoker schizophrenia patients. Gray matter volume reductions associated with smoking status ranged between 2.2% and 2.8%. Furthermore, we found significant volume differences between smoker patients and healthy controls in the hippocampus and DLPFC, but not between non-smoker patients and healthy controls.

Our data suggest that a proportion of the volume reduction seen in the hippocampus and DLPFC in schizophrenia is associated with smoking rather than with the diagnosis of schizophrenia. These results may have important implications for brain imaging studies comparing schizophrenia patients and other groups with a lower smoking prevalence.

1. Introduction

Among the variety of brain regions which have been implicated in schizophrenia, the hippocampus and the lateral prefrontal cortex, in particular the dorsolateral prefrontal cortex (DLPFC), have shown some of the most consistent, replicated abnormalities (Heckers, 2001; Crespo-Facorro et al., 2007). The hippocampus is part of the medial temporal lobe memory system and is responsible for the consolidation of short-term into long-term memory (Squire and Zola-Morgan, 1991). Abnormalities in the hippocampus are thought to play an important role in memory dysfunction in schizophrenia (Weiss and Heckers, 2001; Saykin et al., 1991, 1994; Beatty et al., 1993). Furthermore, changes in the hippocampal formation have been linked to the sensory gating deficits in schizophrenia, leading to a diminished capacity to filter out unimportant features of the environment and to misperception (Adler et al., 1998).

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The DLPFC is involved in cognitive control, working memory and in the integration of sensory and mnemonic information (Crespo-Facorro et al., 2007; Zilles et al., 2009; Potkin et al., 2009b; Barbey et al., 2013). It has also been implicated in the regulation of mental flexibility specific to the capacity of using context and organized information for information retrieval (Maher et al., 1995). Most importantly, DLPFC dysfunction is associated with the genetic risk for schizophrenia (Becker et al., 2008; Potkin et al., 2009a).

Several magnetic resonance imaging (MRI) studies have demonstrated significant reductions in gray matter (GM) density and volumes in patients with schizophrenia (SCZ), relative to healthy controls (HC) (for review see Wright et al., 2000; Shenton et al., 2001; Haijma et al., 2013; Shepherd et al., 2012). The two regions most consistently reported to show GM reductions are the hippocampus and prefrontal cortex (Seidman et al., 2003; Adriano et al., 2012; Shepherd et al., 2012). Overall, hippocampal volumes are reduced approximately 4% in each hemisphere in SCZ patients compared to healthy subjects, and slightly smaller reductions have been found in medication-naïve, first episode patients and in individuals at high risk for schizophrenia (Heckers, 2001; Nelson et al., 1998; Watson et al., 2012; Adriano et al., 2012; Shepherd et al., 2012). In the DLPFC, studies have shown GM volume reductions of approximately 9–11% (Gur et al., 2000; Lopez-Garcia et al., 2006; Kikinis et al., 2010). Volumetric abnormalities of the DLPFC have been related to impairments in executive functions such as cognitive control and working memory (Crespo-Facorro et al., 2007). In addition to GM volume, reduced cortical thickness has been found in schizophrenia, including thinning in frontal and temporal regions (Voineskos et al., 2013; Ehrlich et al., 2012b; Takayanagi et al., 2011; Goldman et al., 2009; Narr et al., 2005). Cortical thickness is assumed to reflect the arrangement and density of neurons in the cortex; the decrease of regional GM volumes in schizophrenia is likely caused by a combination of changes of the GM surface area and cortical thinning (Parent and Carpenter, 1995).

Although GM density, volume or thickness reductions in schizophrenia have been reported in a large number of studies, many structural MRI studies have not confirmed these findings (i.e. Niemann et al., 2000; Sanfilipo et al., 2000; Honea et al., 2005; Shenton et al., 2001; Adriano et al., 2012); surprisingly, evidence for morphometric abnormalities in the hippocampus and prefrontal cortex in schizophrenia is only moderately consistent. It remains unclear whether the observed structural abnormalities are closely tied to the pathophysiology of schizophrenia or whether they are due to confounding variables, such as those associated with schizophrenia, but not a direct consequence of the illness.

One important confounding variable may be smoking behavior, since the prevalence of smoking is approximately 75%, three- to four-fold higher in patients with schizophrenia compared to the general population (de Leon and Diaz, 2005; Ziedonis et al., 2008). Studies in healthy controls have found associations between cigarette smoking and a variety of adverse central nervous system effects, such as global brain atrophy, and structural abnormalities in prefrontal regions as well as reduced GM volumes in the anterior cingulate, occipital and temporal cortices including the parahippocampal structures and hippocampal substructures (Brody et al., 2004; Gallinat et al., 2006; Durazzo et al., 2013, 2010). Moreover, smoking has been related to cerebrovascular changes such as increased cerebral blood flow velocity and reduced vasomotor reactivity (Boyajian and Otis, 2000), to biochemical abnormalities such as reduced N-acetylaspartate concentration in hippocampus (Gallinat et al., 2007) and to alteration of DNA methylation of specific genes (Ehrlich et al., 2012a).

Despite the high prevalence of smoking in SCZ patients and the well-known adverse effects of smoking on brain structure in healthy subjects, diagnosis-related differences in smoking status have as yet rarely been taken into consideration (Tregellas et al., 2007; Van Haren et al., 2010). In this study, we aimed to determine the percentage of GM volume reduction of the hippocampus and the DLPFC in patients with schizophrenia that can be attributed to smoking rather than to the diagnosis. Based on prior findings in healthy subjects, we hypothesized that patients with schizophrenia who smoke will show greater volume reduction in the hippocampus and DLPFC compared to non-smoker patients. We also performed secondary data-driven analyses to test for similar effects of smoking in alternative brain regions using both a region-of-interest volumetric and a surface-wide cortical thickness approach. Lastly, we examined the effect of additional confounding variables such as premorbid cognitive functioning and antipsychotic medication.

2. Methods and materials

2.1. Participants

The Mind Clinical Imaging Consortium (MCIC) study of schizophrenia (Ehrlich et al., 2010) obtained baseline structural MRI scans on a total of 328 subjects from four participating sites: Massachusetts General Hospital in Boston (MGH) and the Universities of Iowa (UI), Minnesota (UMN) and New Mexico (UNM). All subjects provided written informed consent prior to study enrollment. The human subjects research committees at each of the four sites approved the study protocol. The patient group (SCZ) consists of subjects with a DSM-IV diagnosis of schizophrenia established using structured clinical interviews and review of case files by trained clinicians. Healthy controls (HC) were included if they had no history of a medical or Axis I psychiatric diagnosis. All participants were required to be at least 18 years of age and no older than 60 and to be fluent in English. Participants were excluded if they had a history of neurologic disease, psychiatric disease other than schizophrenia, history of a head injury with loss of consciousness, history of substance abuse or dependence within the past month, severe or disabling medical conditions, contraindication to MR scanning, or a premorbid cognitive achievement score less than 70 based on the reading subtest from the WRAT-IIIRT (Wilkinson, 1993). The final sample with complete and high-quality structural MRI, demographic, clinical and smoking data comprised 112 SCZ (53 smokers and 59 non-smokers) and 77 non-smoker HC.

2.2. Instruments

All study participants underwent an extensive clinical diagnostic assessment that included either the Structured Clinical Interview for DSM-IV (SCID) (First et al. 2002) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). To further characterize our sample, the severity of positive and negative symptoms was assessed using the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984, 1983) and the Calgary Depression Scale for Schizophrenia (Addington et al., 1993). Extrapyramidal symptoms were assessed using the Barnes Akathisia Scale (Barnes, 2003) and the Abnormal Involuntary Movement Scale (1988). Premorbid cognitive achievement was estimated by the Reading Subtest of the Wide Range Achievement Test (WRAT-IIIRT) (Wilkinson, 1993); parental socioeconomic status (SES) was determined using the Hollingshead index (Hollingshead, 1965) and handedness was determined using the Annett Scale of Hand Preference (Annett, 1970).

Life-time exposure to smoking was recorded for all participants using site-dependent sources MGH and UMN: Clinical records and MRI debriefing form, UI: CASH, UNM: smoking-related variables