Psychiatry Research: Neuroimaging 224 (2014) 296–302

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Adding insult to injury: Childhood and adolescent risk factors for psychosis predict lower fractional anisotropy in the superior longitudinal fasciculus in healthy adults

Pamela DeRosse [a,b,*], Toshikazu Ikuta [c], Bart D. Peters [a,b], Katherine H. Karlsgodt [a,b], Philip R. Szeszko [a,b,d], Anil K. Malhotra [a,b,d,e]

[a] Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset, NY, USA
[b] Division of Psychiatry Research, The Zucker Hillside Hospital, Division of the North Shore-Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004, USA
[c] Department of Communication Sciences and Disorders, School of Applied Sciences, University of Mississippi, University, MS, USA
[d] Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA
[e] Hofstra North Shore – LIJ School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, NY, USA

ARTICLE INFO

Article history:
Received 12 March 2014
Received in revised form
3 July 2014
Accepted 1 September 2014
Available online 16 September 2014

Keywords:
Psychosis
Risk factors
Diffusion tensor imaging (DTI)
Superior longitudinal fasciculus

ABSTRACT

Although epidemiological studies provide strong support for demographic and environmental risk factors in psychotic disorders, few data examine how these risk factors relate to the putative aberrant neurodevelopment associated with illness. The present study examined how the accumulation of risk factors including low IQ, low parental socioeconomic status (SES), history of adolescent cannabis use and childhood trauma, and high levels of subclinical psychotic-like experiences (PLEs) contributed to aberrant neurodevelopmental outcomes in 112 otherwise healthy adults recruited from the community. Participants were studied with diffusion tensor imaging (DTI), and voxel-wise statistical analysis of fractional anisotropy (FA) using tract-based spatial statistics (TBSS) was used to examine the relation between cumulative risk (CR) for psychosis and white matter (WM) integrity across the whole brain. Analyses revealed that higher CR was significantly associated with lower FA in a cluster in the left superior longitudinal fasciculus (SLF). These results suggest that risk factors previously associated with psychotic disorders are associated with WM integrity even in otherwise healthy adults and may provide insight into how previously identified risk factors contribute to the structural brain abnormalities associated with psychotic illness. Prospective longitudinal studies examining the effect of risk factors on the developmental trajectory of brain WM are warranted.

1. Introduction

Psychotic disorders such as schizophrenia (SZ) are complex illnesses with typical onset in late adolescence or early adulthood (Cannon et al., 2003). Although several lines of evidence suggest that SZ represents an end state of abnormal neurodevelopment that begins many years before the onset of the illness, the pathophysiology of the disease is not well understood (Rapoport et al., 2012). A range of epidemiological studies, however, provide strong support for myriad antecedent demographic and environmental risk factors in the development of SZ (Matheson et al., 2011). To date few studies have examined how these risk factors relate to the putative aberrant neurodevelopment associated with illness.

Among the most comprehensively studied antecedents to the development of SZ are deficits in intellectual function (Aylward et al., 1984;; Heinrichs and Zakzanis, 1998; Matheson et al., 2011). Data from several birth cohorts (Jones et al., 1994; Kremen et al., 1998; Cannon et al., 2002; Zammit et al., 2004) suggest that low IQ scores are associated with an increased risk for the later development of SZ. Given the complex, and somewhat controversial, association between IQ and socioeconomic status (SES) (Turkheimer et al., 2003), it is not surprising that low SES has also been found to increase risk for SZ (Saha et al., 2005; Saha et al., 2006). Perhaps due to the illness itself, patients with SZ are overrepresented in the lowest social strata (Hollingshead and Redlich 1958; Eaton, 1985; Dohrenwend et al., 1992). However, recent data suggest that low parental SES (PSES) at the time of birth is also associated with an increased risk for the later development of SZ (Werner et al., 2007).

* Corresponding author at: Division of Psychiatry Research, The Zucker Hillside Hospital, Division of the North-Shore-Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004, USA. Tel.: +1 718 470 8601; fax: +1 718 343 1659.
E-mail address: pderosse@lij.edu (P. DeRosse).

http://dx.doi.org/10.1016/j.pscychresns.2014.09.001
0925-4927/

Recently, attention has been focused on the role of cannabis in increasing risk for SZ. Initial data from 40,000 Swedish conscripts followed up for 15 years indicated that individuals who had smoked cannabis by the age of conscription had a two-fold increase in risk of later developing SZ (Andreasson et al., 1987; Zammit et al., 2002). These findings have been replicated in several prospective studies (van Os et al., 2002; Fergusson et al., 2003; Arseneault et al., 2002), and the pooled odds ratios from recent meta-analyses have yielded effect sizes ranging from 1.4 to 2.1 (Henquet et al., 2005; Moore et al., 2007).

Several recent studies have also provided robust evidence for an association between childhood maltreatment and risk for the development of SZ. In a recent meta-analysis (Varese et al., 2012), childhood adversity was substantially related to an increased risk for psychosis with a population attributable risk of ~33%. Moreover, several prospective studies have shown that reverse causation is unlikely to account for this association (Read et al., 2005; Arseneault et al., 2011; Husted et al., 2012; Alemany et al., 2013).

Finally, longitudinal studies have suggested that high levels of psychosis-related symptoms may also predate illness. For example, Chapman et al. (1994) initially demonstrated that adolescents who rated high on scales of magical ideation and perceptual aberration had high rates of psychotic outcomes 10 years later. These results have been further replicated in several distinct cohorts (Poulton et al., 2000; Cannon et al., 2002; Hanssen et al., 2005; Welham et al., 2009).

Despite the routine observation that a subset of children who experience multiple risk factors are much more likely to experience adverse psychological outcomes than those with single risk factors (Rutter, 1979; Rutter, 1981), to date there are a paucity of data on the cumulative effects of psychosis-related risk factors. Examination of the effects of multiple risk factors generally relies upon a metric constructed by dichotomizing each risk factor (i.e., 0=no risk, 1=risk) and then summing the total number of risk factors to obtain a measure of cumulative risk (CR). Although alternative metrics, for example, a summary score representing the sum of *Z* scores for each risk factor, may be more theoretically compelling, several lines of evidence suggest that such methods are problematic due to low statistical power, extreme higher order interaction terms, low robustness, and collinearity among risk factors. In contrast, the CR metric is "more parsimonious and more statistically sensitive and makes no assumptions about the relative strength of the risk factors, or their collinearity" (Evans et al., 2013).

Although there are few data documenting how CR contributes to psychotic illness, at least one study has produced some intriguing results. Zammit et al. (2010) recently studied a sample of over 50,000 Swedish conscripts characterized at age 18 for risk factors including low IQ, cannabis use, psychiatric diagnoses, AND disturbed behavior and social relations. This study found that over a 27-year follow-up period, the risk of developing any non-affective psychosis was greater in the presence of two risk factors than in the presence of a single risk factor. Thus, it seems plausible that the accumulation of risk factors contributes to the underlying pathophysiology of psychotic illness.

In recent years, SZ has increasingly been viewed as a disorder of dysconnectivity, in which decreased connection between brain areas is associated with psychotic symptoms. The primary measure derived from diffusion tensor imaging (DTI), fractional anisotropy (FA), is thought to index white matter (WM) integrity and potentially reflects both myelination and organization of fiber tracts that form the basis of inter-regional brain connections. Generally, FA is lower in SZ patients relative to controls (Ellison-Wright and Bullmore, 2009; Patel et al., 2011; Yao et al., 2013). In our recent meta-analysis of WM development in healthy adolescents (Peters et al., 2012), we found significant correlations between age and FA in several predefined WM tracts. A number of studies have demonstrated a disruption in the trajectory of WM development in psychotic and clinical high risk samples (Karlsgodt et al., 2009; Bloemen et al., 2010; Carletti et al., 2012), suggesting that FA might be an ideal target for assessing the effects of risk factors, which are present during childhood and adolescence, on WM development.

The present study sought to examine how the accumulation of risk factors for psychotic disorders might contribute to aberrant neurodevelopmental outcomes in otherwise healthy adults. We used a whole brain DTI method, a powerful tool for examining WM microstructure in vivo (Beaulieu, 2002). Specifically, we used tract-based spatial statistics (TBSS) (Smith et al., 2006) to examine the relation between previously identified risk factors and WM integrity across the whole brain in a large sample of adult controls recruited from the community.

2. Methods

2.1. Participants

The present sample consists of 112 healthy adult volunteers (60 males, 52 females, mean age=36.07 ± 13.23; age range=18.47–68.04 years) who were recruited from the general population for a study of subclinical psychosis funded by the National Institute of Mental Health (MH086756). Details regarding the full sample are provided in DeRosse et al. (2014). A total of 38 additional participants were screened for participation in the present study but were not included because they failed to meet all of the inclusion criteria or met some of the exclusion criteria. Exclusion criteria included first-degree family member with a psychotic illness, present or past psychotic or affective disorder diagnosis, active or recent substance abuse (as assessed by urine toxicology testing), contraindications to magnetic resonance imaging, prior psychosurgery, or pregnancy. All participants provided written informed consent to a protocol approved by the Institutional Review Board of the North Shore-Long Island Jewish Health System.

2.2. Diagnostic rule-out

Participants were initially administered the Structured Clinical Interview for DSM-IV, Non-Patient edition (SCID-I/NP) (First et al., 2002) by trained graduate-level research assistants, and absence of past or present affective or psychotic disorder was then determined by consensus with two senior clinicians on the Zucker Hillside Hospital faculty.

2.3. Assessment of risk factors associated with psychotic illness

2.3.1. Estimated IQ

We used the Wide Range Achievement Test-Third Edition-Reading Subtest (WRAT-3) as an estimate of IQ (Kremen et al., 2006). Although the WRAT-3 may underestimate full-scale IQ, it tends to be very accurate when used to classify individuals with below average intelligence (Griffin et al., 2002).

2.3.2. Parental socioeconomic status (PSES)

PSES was determined using the Hollingshead and Redlich Two-Factor Social Position Index (Hollingshead, 1975), which is based on measures of educational attainment and occupational prestige. PSES is rated on the social position index (SPI) and classifies individuals into one of five potential classes ranging from the highest (Class I) to the lowest (Class V) socioeconomic classes. In the present study, we used the rating for the parent that produced the highest class as the primary measure of PSES.

2.3.3. History of cannabis use

History of cannabis use was defined as using cannabis more than once before the age of 18 as assessed with the substance abuse module of the SCID-I/NP (First et al., 2002). None of the participants in the present study met diagnostic criteria for a cannabis use disorder (although that was not an exclusion criterion for the study).

2.3.4. Childhood trauma

To assess the history of childhood trauma, we used the 28-item Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a 5-point Likert-type self-report questionnaire that measures several dimensions of trauma during childhood, including physical, emotional and sexual abuse as well as emotional and physical neglect. Summing across all of these dimensions provides a total score that represents the severity of overall trauma experienced by an individual during childhood. The present study used the total score derived from the CTQ.