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Evidence that reduced gray matter volume in psychotic disorder is associated with exposure to environmental risk factors

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ABSTRACT

The aim of this study was to examine whether cannabis use, childhood trauma and urban upbringing are associated with total gray matter volume (GMV) in individuals with (risk for) psychotic disorder and whether this is sex-specific. T1-weighted MRI scans were acquired from 89 patients with a psychotic disorder, 95 healthy siblings of patients with psychotic disorder and 87 controls. Multilevel random regression analyses were used to examine main effects and interactions between group, sex and environmental factors in models of GMV. The three-way interaction between group, sex and cannabis (χ^2 =12.43, p < 0.01), as well as developmental urbanicity (χ^2 = 6.29, p = 0.01) were significant, indicating that cannabis use and developmental urbanicity were associated with lower GMV in the male patient group (cannabis: B= −32.54, p < 0.01; developmental urbanicity: B= −10.23, p=0.03). For childhood trauma, the two-way interaction with group was significant (χ^2 = 5.74, p = 0.02), indicating that childhood trauma was associated with reduced GMV in the patient group (B= −9.79, p=0.01). The findings suggest that reduction of GMV in psychotic disorder may be the outcome of differential sensitivity to environmental risks, particularly in male patients.

1. Introduction

Changes in brain volumes, changes in white matter integrity, and cortical thinning have been associated with psychotic disorder (Sommer and Kahn, 2015). Meta-analyses have confirmed reductions of gray matter volume (GMV) in patients with psychotic disorder (Haijma et al., 2013; Vita et al., 2015). It remains to be discovered whether these structural alterations are the result of a disease-related processes or factors, altered neurodevelopment due to genetic liability and/or differential sensitivity to environmental risks. Studies that report gray matter alterations in individuals at high familial risk for psychotic disorder and in persons at clinical high risk for psychotic disorder support the hypothesis of altered neurodevelopment associated with genetic predisposition (Sprooten et al., 2013; van Lutterveld et al., 2014), though not all studies are consistent (Boos et al., 2012; Goldman et al., 2009). Reports of progressive loss of gray matter over time in patients (Cannon et al., 2015; van Haren et al., 2011; Vita et al., 2012) support the hypothesis that this is the result of a disease-specific process or disease-related factors such as medication (Vita et al., 2015), either or not in combination with altered neurodevelopment.

Although gene × environment interactions (G×E) in psychotic disorder have been studied (European Network of National Networks studying Gene-Environment Interactions et al., 2014; Iyegbe et al., 2014) the number of G×E studies using structural brain phenotypes as the outcome variables is limited (French et al., 2015; Geoffroy et al., 2013). One of the first studies focused on fetal hypoxia, which was associated with reduced GMV and increased cerebrospinal fluid in individuals who had later developed schizophrenia, and in their healthy relatives (Cannon et al., 2002).

Cannabis, a recognized environmental risk factor for psychotic disorder (Moore et al., 2007), has been associated with reduction of GMV (Rais et al., 2008) in patients with a psychotic disorder and with loss of cortical thickness in patient with schizophrenia and in cannabis users without schizophrenia (Epstein and Kumra, 2015). Further, cannabis has also been related to changes in white matter of the brain in patients with psychotic disorder (Rigucci et al., 2016) and in the general population (Rigucci et al., 2016; Zalesky et al., 2012).

Childhood trauma, another risk factor for psychotic disorder (Varese et al., 2012), has been associated with reduced GMV in psychotic disorder (Sheffield et al., 2013). In addition, cortico-limbic GMV

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differences between patients with schizophrenia, patients with bipolar disorder and healthy controls have been reported in individuals with high, but not low, levels of adverse childhood experiences (Poletti et al., 2016). In non-psychotic populations, associations between childhood trauma and brain development (Andersen et al., 2008), structure (Bremner, 2005; Tomoda et al., 2012) and function (Bremner, 2005) have been described.

Lastly, developmental urbanicity, as a proxy environmental risk factor for psychotic disorder (Vassos et al., 2012), has not yet been examined in relation to structural gray matter alterations in this population. The risk-increasing mechanisms underlying the proxy variable developmental urbanicity remain unknown. One of the mechanisms that can be envisaged is altered stress processing (Lederbogen et al., 2011) due to higher levels of social isolation (van Os et al., 2000) and social defeat (Selten and Cantor-Graae, 2007) in urban areas. Indeed, early life stress has been associated with cerebral alterations in humans (Tomoda et al., 2009) and in animals (Spinelli et al., 2009), through altered levels of neurohormones, neurotransmitters, and neurotrophic factors (De Bellis, 2005).

When examining structural brain phenotypes as a function of environmental and genetic risk, potential sex differences should be taken into account. First, with respect to the incidence, age of onset and course of disease in psychotic disorder, sex differences have been extensively described (Aleman et al., 2003; Cascio et al., 2012; Eranti et al., 2013; Zhang et al., 2012). Second, sex differences have been reported in the association between psychotic disorder and respectively childhood trauma (Fisher et al., 2009) and cannabis (Decoster et al., 2011). Third, there is evidence for sex differences in brain morphology in psychotic disorders (Abel et al., 2010), i.e., gray matter alterations may be more prominent in male patients with a psychotic disorder (Bora et al., 2011; Suzuki et al., 2002).

In the present study, we hypothesized that the sensitivity to environmental risk factors (cannabis, trauma, urbanicity), as expressed by GMV alterations, is dependent on the genetic predisposition for psychotic disorder, as well as on sex. This was tested in three groups with differential proxy genetic risk for psychotic disorder: patients with a psychotic disorder (highest risk), non-psychotic siblings of patients with psychotic disorder (higher than average risk) and healthy controls (average risk).

2. Materials and methods

2.1. Participants

Data pertain to baseline measures of a longitudinal magnetic resonance imaging (MRI) study in Maastricht, the Netherlands. In selected geographic areas in the Netherlands and Belgium, patients presenting consecutively at metal health services either as outpatients or inpatients were recruited for the study. The sample consisted of 89 patients with a diagnosis of a non-affective psychotic disorder, 95 siblings, and 87 control subjects. The sample included 60 families, of which 37 families contributed one patient and one sibling, 3 families contributed one patient and two siblings, and one family contributed one patient and three siblings. One family contributed two patients, 7 families contributed two relatives, 1 family contributed three relatives, and ten families contributed two controls. In addition, 44 independent patients, 32 independent siblings, and 67 independent controls were included.

Inclusion criteria for the patient group were the following: (1) age 16–50 years; (2) diagnosis of non-affective psychotic disorder; and (3) sufficient command of the Dutch language. Sibling non-patient status was defined as the absence of any lifetime psychotic disorder. Controls had no first-degree relative with a psychotic disorder as established by the Family Interview for Genetic Studies (Maxwell, 1992) with the control as informant. Before MRI acquisition, participants were screened for the following exclusion criteria: (1) brain injury with loss of consciousness of more than 1 h; (2) meningitis or other neurological diseases that might have affected brain structure or function; (3) cardiac arrhythmia requiring medical treatment; and (4) severe claustrophobia. In addition, subjects with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy.

The study was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht. Written informed consent was obtained from all. The selection procedure and the in- and exclusion criteria are described in full detail in a previous paper (Habets et al., 2011).

2.2. Measures

The level of symptoms in all groups was assessed with the Positive and Negative Syndrome Scale (PANSS)(Kay et al., 1987). The Five Factor Model by van der Gaag (2006) was used, dividing the PANSS in Positive symptoms, Negative symptoms, Disorganization symptoms, Excitement, and Emotional Distress (van der Gaag et al., 2006).

Educational level was defined as highest accomplished level of education.

2.2.1. AP medication

Antipsychotic (AP) medication use was determined by patient report and verified with the treating consultant psychiatrist. Best estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (including the exposure period between baseline assessment for the G.R.O.U.P. study and the moment of baseline MRI scanning), using the recently published conversion formulas for AP dose equivalents described in Andreasen and colleagues (Andreasen et al., 2010).

2.2.2. Substance use

Substance use was measured with the Composite International Diagnostic Interview (CIDI) sections B–J–L (WHO, 1990). Use of cannabis and other drugs was assessed as the reported frequency of use during the last 12 months, as well as lifetime use. CIDI frequency data on lifetime cannabis use were available for 263 participants (3.0% missing data). In addition, cannabis was tested in urine available for 247 participants (8.9% missing data). The two measurers were combined into one variable, which was coded as follows: never used cannabis = 0, ever used cannabis = 1 (no missing data). CIDI frequency data on lifetime other (non-cannabis) drug use were available for 267 participants (1.5% missing data). Alcohol use was defined as the reported number of weekly consumptions during the last 12 months available for 235 participants (13.3% missing data).

2.2.3. Childhood trauma

Childhood trauma was assessed with the Dutch version of the Childhood Trauma Questionnaire Short Form (CTQ)(Bernstein et al., 1997). The short CTQ consists of 25 items rated on a 5-point Likert scale (1 = never true to 5 = very often true) inquiring about traumatic experiences in childhood. Five types of childhood maltreatment were assessed: emotional, physical and sexual abuse, and emotional and physical neglect, with five questions covering each type of trauma. As a general measure of childhood trauma a summary score was created by adding the mean scores of each trauma type. The CTQ data were missing for two persons (0.7% missing data).

2.2.4. Developmental urbanicity

A historical population density record was generated for each municipality from 1930 onwards using the Dutch Central Bureau of Statistics (CBS)(Statistics Netherlands, 1993) and equivalent Belgium database (Vanhaute and Vrielinck, 2013). When data were not available, linear extrapolations were computed. When historical names of