Journal of Psychiatric Research 56 (2014) 144–149

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Cortical thickness correlates of psychotic experiences: Examining the effect of season of birth using a genetically informative design

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ARTICLE INFO

Article history:
Received 4 December 2013
Received in revised form
13 May 2014
Accepted 14 May 2014

Keywords:
Cortical thickness
Psychotic experiences
Season of birth
Winter/Spring
MRI
Monozygotic twins

ABSTRACT

Season of birth has been shown to influence risk for several neuropsychiatric diseases. Furthermore, it has been suggested that season of birth modifies a number of brain morphological traits. Since cortical thickness alterations have been reported across some levels of the psychosis-spectrum, this study was aimed at i) assessing the scarcely explored relationship between cortical thickness and severity of subclinical psychotic experiences (PEs) in healthy subjects, and ii) evaluating the potential impact of season of birth in the preceding thickness–PEs relationship. As both PEs and brain cortical features are heritable, the current work used monozygotic twins to separately evaluate familial and unique environmental factors.

High-resolution structural MRI scans of 48 twins (24 monozygotic pairs) were analyzed to estimate cortical thickness using FreeSurfer. They were then examined in relation to PEs, accounting for the effects of birth season; putative differential relationships between PEs and cortical thickness depending on season of birth were also tested.

Current results support previous findings indicative of cortical thickening in healthy individuals with high psychometrically assessed psychosis scores, probably in line with theories of compensatory aspects of brain features in non-clinical populations. Additionally, they suggest distinct patterns of cortical thickness–PEs relationships depending on birth seasonality. Familial factors underlying the presence of PEs may drive these effects.

1. Introduction

Consistent epidemiological evidence demonstrates that genetic background and neurodevelopmental disruptions play a role in the etiology of schizophrenia (SZ) (Gejman et al., 2011; Matheson et al., 2011). Likewise, subclinical phenotypes such as psychotic experiences (PEs) share some genetic and early risk factors with SZ, and may also have similar neuroanatomical correlates with this psychotic disorder (Kelleher and Cannon, 2011). Consequently, clinicopathological significance of obstetric complications on PEs could be studied in relation to SZ.

Among the most broadly studied obstetric risk factors for SZ is being born during Winter or Spring in the Northern Hemisphere (Davies et al., 2003). Nevertheless, currently available studies evaluating its association with subclinical psychotic phenotypes offer inconclusive results (Cohen and Najolia, 2011; Tochigi et al., 2013; Zammit et al., 2009). A number of mediating processes

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http://dx.doi.org/10.1016/j.jpsychires.2014.05.014
0022-3956/

have been suggested for the association between birth seasonality and SZ risk, such as maternal infections, vitamin D deficits and maternal chronobiology alterations due to temperature changes (Schwartz, 2011).

Accordingly, these three risk factors have independently been linked to fetal brain development disturbances (Boksa, 2010; Eyles et al., 2013; Garbett et al., 2012; Schwartz, 2011). Similarly, maternal prenatal infections and vitamin D deficits have formerly been examined in relation to brain cortical thickness, especially in animal studies. Cortical thickness is a measure of the average distance between the pial and white matter cortical surfaces. It is linked to the number of neurons within a cortical column (Rakic, 2008), and it is relevant in this context due to its high sensitivity to brain development across stages (Sowell et al., 2003). While some have proposed that the aforesaid exposures correlate with cortical thinning (Carpentier et al., 2013; Eyles et al., 2003; Fatemi et al., 1999; Hatfield et al., 2011), others have found that they may lead to increases in cortical thickness (Smith et al., 2012; Willette et al., 2011). Though conflicting results may be caused by design heterogeneity, all these reports agreed in suggesting that cortical thickness is influenced by immune responses in-utero.

Neuroimaging evidence indicates that several brain features may be different depending on season of birth, in both healthy adults (Pantazatos, 2013) and within groups of individuals suffering neuropsychiatric disorders (d'Amato et al., 1994; Giezendanner et al., 2013; Kaasinen et al., 2012; Moore et al., 2001; Sacchetti et al., 1992). Nevertheless, research on seasonal effects on cortical thickness of subjects manifesting SZ and related phenotypes is still scarce. This is an important issue since several studies using novel neuroimaging techniques have consistently shown widespread decreases of cortical thickness in SZ patients (Goldman et al., 2009; Nesvag et al., 2008; Rimol et al., 2012; Schultz et al., 2010). Besides, although the relationship between cortical thickness and subclinical psychosis in the general population has been less studied, a recent report found increased cortical thickness in subjects from a healthy population exhibiting high scores on a schizotypy assessment (Kuhn et al., 2012), consistent with the theory that some brain volumetric and functional features of individuals with psychotic traits may act as protective/compensating factors (Hazlett et al., 2008; Suzuki et al., 2005) thus avoiding transitions to more severe psychotic conditions.

Considering these elements, the current study was aimed at: *i*) testing whether factors involved in the expression of PEs are associated with brain cortical thickness, and *ii*) assessing the impact of birth seasonality on this potential relationship.

As the role of gene-environment interactions in early neurodevelopment has been previously underscored due to its potential to shed light on psychiatric research (Demjaha et al., 2012; Rapoport et al., 2012), and since both genes and environment influence cortical thickness (Panizzon et al., 2009) and PEs (Lataster et al., 2009), a genetically informative design was implemented here to test for associations. Insofar as members of a monozygotic (MZ) twin pair have identical DNA sequences, this work studied their phenotypic similarities and differences in order to obtain insights on familial and environmental influences.

2. Methods

2.1. Sample description

The present sample was gathered from a set of 115 Spanish Caucasian adult twin pairs (230 individuals) from the general population, who gave permission to be contacted for research purposes. All twins were contacted by telephone and invited to participate in a general study of early risk factors and adult cognitive and psychopathological traits. A battery of psychological and neurocognitive tests was administered to the twins by trained psychologists (S.A. and X.G.). Similarly, they were interviewed for medical records (S.A. and X.G.). Exclusion criteria applied were age under 17 and over 65 years, current substance misuse or dependence, a medical history of neurological disturbance and presence of sensory or motor alterations. Written informed consent was obtained from all participants after a detailed description of the study aims and design, approved by the local Ethics Committee. All procedures were carried out in accordance with the Declaration of Helsinki.

Zygosity of all pairs was assessed by genotyping 16 highly polymorphic microsatellite loci from DNA samples (SSRs; PowerPlex® 16 System Promega Corporation). Identity on all the markers can be used to assign monozygosity with greater than 99% accuracy (Guilherme et al., 2009). In the whole sample (115 twin pairs), 86 duos were MZ.

From that group of participants, using the previously collected data, a subset of 54 individuals (27 MZ twin pairs) was selected, as they were informative for obstetric and psychopathological traits and gave consent to participate in the MRI part of the present study.

Twins included in this subset of 54 participants met the following criteria: a) age at scan between 20 and 56 years, b) both twins right-handed, and c) none of the twins manifested liability for DSM-IV-R psychiatric diagnoses other than depression and/or anxiety. Pairs where one or both twins manifested either neurological or major medical illnesses were excluded as well (see Measures).

After this point, due to image artifacts or lack of data about six participants, the final sample (i.e., the subset included in all statistical analyses) consisted of 48 individuals (20 males).

2.2. Measures

To evaluate liability for psychopathology in this general population sample, a clinical psychologist (X.G.) applied the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, 1997) in a face-to-face interview to screen for presence of any lifetime psychiatric disorder.

Then, dimension-specific (positive, negative and depressive) PEs were assessed by means of the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002), a 42-item self-report questionnaire measuring subclinical manifestations of psychosis in the general population. This dimensional representation of PEs somehow parallels the fact that psychotic patients manifest symptom clusters, and supports the view of psychosis as a quantitative trait in which symptoms may co-occur together. The CAPE evaluates lifetime prevalence of PEs using a frequency scale ranging from "never" to "nearly always", and provides a distress score for each item ranging from "not distressful" to "very distressful". Examples of items assessing positive, negative and depressive PEs in this questionnaire are, respectively, "do you ever feel as if there is a conspiracy against you?", "do you ever feel that you are spending all your days doing nothing?", and "do you ever feel pessimistic about everything?".

Participants were asked to report if they had received pharmacological or psychological treatment or had consulted a psychiatrist or psychologist since they first participated in the study. Only three individuals had life-time exposure to drug treatment for anxiety or depression.

Information about obstetric complications was collected by direct interviews with the participants' mothers (Walshe et al., 2011) by means of the Lewis–Murray Obstetric Complications Scale (Lewis et al., 1989). Using birth data included herein, birth season of each twin pair was classified as either Winter/Spring (risk factor) or Summer/Autumn.