Journal of Affective Disorders 143 (2012) 75–83

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

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

Research report

Star-crossed? The association of the 5-HTTLPR s allele with season of birth in a healthy female population, and possible consequences for temperament, depression and suicide

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ARTICLE INFO

Article history:
Received 10 April 2012
Received in revised form
29 May 2012
Accepted 29 May 2012
Available online 25 July 2012

Keywords:
Serotonin transporter gene
Allele frequency
Birth seasonality
Affective temperaments
Procreational habits hypothesis

ABSTRACT

Background: Birth season has well-known effects on neuropsychiatric disorders, and may also influence genotype distribution by possibly influencing chance of conception via parental idiosyncratic conception patterns or survival of foetuses or infants. The 5-HTTLPR is associated with phenomena including affective temperaments or suicide which are also associated with birth season. Our aim was to investigate the association of 5-HTTLPR genotype and birth season in a healthy female population.

Methods: Birth date and 5-HTTLPR genotype was determined for 327 psychiatrically healthy women. The association between presence of s allele and time of birth was analysed using generalized linear models.

Results: A significant association between s allele frequency and time of birth was detected. S allele carrier frequency was marginally significantly higher in July borns and significantly lower in autumn borns.

Limitations: We investigated an adult sample so genotype frequency data do not reflect birth frequencies. Our sample consisted exclusively of females.

Conclusions: There is no clear explanation for the observed association, although idiosyncratic parental conception patterns, the association of 5-HTTLPR with sudden infant/intrauterine death, or other s allele-mediated behaviours may play a role. Our results are strikingly parallel with earlier data reporting a higher risk of completed suicide in July borns, and higher scores of July borns and lower scores of autumn borns on certain affective temperament scales, both of which are also associated with the s allele of 5-HTTLPR. Thus our results may add to the growing body of evidence regarding the etiological background of affective disorders.

1. Introduction

One extensively investigated question in contemporary psychiatric genetics is the relative role of genetic and environmental factors and their interaction in the emergence of personality traits, endophenotypes and psychiatric disorders. Several studies, however, deal with the effect of the environment on genetic factors, not only with respect to epistatic effects on gene expression, but also with the possible impact of environmental factors in effect during conception, gestation, perinatally or in the early postnatal period influencing genotype selection or frequency in a given population.

The investigation of birth season effect is an expanding field in psychiatry. Birth season in non-equatorial countries is a good indicator of the complex constellation of environmental factors

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http://dx.doi.org/10.1016/j.jad.2012.05.031

present in the time of conception, gestation, and pre- or perinatally, as well as during the early postnatal period which may exert a significant influence on development (Torrey et al., 2000). Phenomena associated with birth season include neuropsychiatric disorders as schizophrenia, bipolar depression or epilepsy (Torrey et al., 1997), psychological traits and characteristics including the Novelty Seeking trait measured by TCI (Chotai et al., 2001; Chotai et al., 2003a; Chotai et al., 2009) or affective temperaments (Rihmer et al., 2011), as well as suicidal behaviour (Courtet et al., 2006) also independently of psychiatric disorders (Chotai and Salander Renberg, 2002; Dome et al., 2010). In spite of these well-replicated associations, there is no exhaustive explanation for this phenomenon and we do not understand which factors mediate the effect of season of birth. There has been a consistent association reported between season of birth and white matter lesions in bipolar patients (Moore et al., 2001) as well as monoamine transmitter functions (Chotai and Asberg, 1999; Chotai and Adolfsson, 2002; Chotai et al., 2006) observable in healthy adults as well. These neurochemical and neuroanatomical characteristics may mediate the environmental effects associated with birth season in the development of the above mentioned characteristics and disorders. It is also possible, however, that birth season exerts these effects though genetic factors, by influencing selection of genotypes associated with illnesses or other endophenotypes (Chotai et al., 2003b), via mediating pathways we do not yet understand. Season-related conditions in interaction with parental genetically-determined behaviours may lead to the emergence of idiosyncratic conception patterns, which in turn contribute to uneven year-round conception rates in parents with a certain genotype, thus leading to an uneven distribution of genotype in monthly birth cohorts. Also, a certain gene may be associated with the survival success of foetuses or infants in general or under certain environmental conditions active in certain seasons, causing an uneven genotype distribution in the adult population.

Previous studies mostly investigate the association between birth season and genotype frequencies in case of patient groups and only to study the interaction between birth season and genotype in the development of illness symptoms or endophenotypes. One such study reported a significant date of birth effect also in the healthy control group on the distribution frequency of the A218C polymorphism of the TPH gene (Chotai et al., 2003b), which has already been shown to be associated with unipolar and bipolar depression (Bellivier et al., 1998a; Souery et al., 2001; Barnett and Smoller, 2009; Shen et al., 2011), disorders also showing an association with birth season (Rihmer, 1980; Torrey et al., 1996; Torrey et al., 1997). Another polymorphism widely associated with affective illness in most (Bellivier et al., 1997; Bellivier et al., 1998b; Furlong et al., 1998; Hauser et al., 2003; Cervilla et al., 2006; Karg et al., 2011) but not all studies (Hoehe et al., 1998; Frisch et al., 1999; Mendlewicz et al., 2004) is the 5-HTTLPR polymorphism of the serotonin transporter gene, also associated with neuroticism- (Gonda et al., 2009) or anxiety-related traits (Lesch et al., 1996; Lesch et al., 2003), affective temperaments (Gonda et al., 2006), and suicide (Bellivier et al., 2000; Gonda et al., 2011a), the latter two of which also having been reported to be influenced by birth season (Chotai et al., 1999; Chotai and Salander Renberg, 2002; Courtet et al., 2006; Dome et al., 2010; Rihmer et al., 2011). Season-of-birth association of the frequency of certain genotypes associated with important personality traits and temperaments and other possible endophenotypes in the general population may be one possible contributing factor to the season-of-birth association of these traits and temperaments, as well as psychiatric illnesses. In the present study our aim was to investigate the possible association between season of birth and frequency of 5-HTTLPR genotypes in a female adult psychiatrically healthy population.

2. Materials and methods

Three hundred and twenty seven psychiatrically healthy unrelated women participated in our study. Mean age of participants was 37.58 years (SD=13.14, range 18.00–79.00). The present sample was part of a related study investigating the mood effects of the reproductive cycle in psychiatrically healthy women, therefore only females were enrolled. Including only females also ensures homogeneity of our findings as there are significant differences between serotonergic function in males and females (Nishizawa et al., 1997; Williams et al., 2003; Costes et al., 2005) and it was also hypothesized that the 5-HTTLPR may have opposite consequences in women and men (Brummett et al., 2008). We included a psychiatrically healthy sample to allow for a broader scope for 5-HTTLPR related phenomena. Participants were recruited as volunteers not suffering from current or past psychiatric illnesses, and were screened by the M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998) administered by a clinical psychologist in the National Institute for Psychiatry and Neurology. In all cases exact date of birth was registered. All participants were Caucasian and born and residing Hungary. Date of birth was investigated by month, season and half year. Season was defined according to the meteorological division of seasons (spring: March–May, summer: June–August, autumn: September–November, winter: December–February). DNA samples were obtained in the National Institute for Psychiatry and Neurology after the screening interview by non-invasive buccal swabs, and all participants were genotyped for 5-HTTLPR (Heils et al., 1996). All participants were given thorough explanation of the study and provided informed consent before participation in the study. All research procedures were carried out in compliance with the Code of Ethics of the World Medical Association and the Helsinki Declaration. The study procedure was approved by the Ethical Committee of the Scientific Health Council, in charge of ethical approval of human genetic studies.

For detecting an eventual cyclic trend over the year with respect to the month of birth in the mean frequency of allele s, we performed a non-linear regression analysis. Given the well-known recessive characteristics of the 5-HTTLPR s allele (Heils et al., 1996; Lesch et al., 1996), the presence of s allele (s allele carriers vs non-carriers, i.e., ss+sl vs ll genotypes) served as dependent variables in the analyses. The independent variable was the cosine function of the month of birth (Jan=1, Feb=2, …, Dec=12), given by the regression equation as follows (for one cycle per year): allele $s = M + A^{*}\cos(2\pi/12^{*}(t+F))$, where M is the mean of the curve, cos denotes the cosine function, A is the amplitude (regression coefficient) of the cosine curve, 2π is one cycle per year in radians, t is the month of birth, and F is the phase angle that enables us to determine the birth months $t_{\max}=F$ and $t_{\min}=t_{\max}+6$, which give the maximum and the minimum of the cosine curve. The regression analysis was performed by non-linear ordinary least squares modeling by the MODEL procedure of the Statistical Analysis System (SAS 9.2). This yields estimates of the parameters M, A and F from the data, as well as their 95% confidence intervals. Association between dependent and independent variables in the model was tested by t statistic.

Association between allele frequencies and date of birth was also analysed by Generalized Linear Model (GENMOD) analysis to detect specific differences. Association between dependent and independent variables was tested by the likelihood ratio Chi-square statistic. Dependent variables in the analyses were determined according to presence of s allele. Date of birth was included in the analysis in 3 separate ways: as month, season, and half-year of birth. The year was divided into 2 half-years after visual inspection of relative frequencies of s allele carriers according to birth months (Fig. 1). First half-year was defined as the time