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Second-to-fourth digit length ratio is associated with negative and affective symptoms in schizophrenia patients

Nataly Paipa [a,b,1], Christian Stephan-Otto [a,b,c,1], Jorge Cuevas-Esteban [d], Araceli Núñez-Navarro [a,b], Judith Usall [a,b,c], Gildas Brébion [a,b,c,*]

[a] Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain
[b] Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
[d] Servei de Psiquiatria, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

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ABSTRACT

Background: Higher levels of circulating oestrogens in women and testosterone in men have been shown to have a protective effect against the clinical manifestations of schizophrenia, mostly with respect to negative symptomatology. Certain studies suggest that they also have a protective effect against the neuropsychological impairment observed in the disease. We investigated whether greater prenatal exposure to estrogens in women and to testosterone in men, reflected by the 2D:4D ratio, was similarly associated with decreased negative symptomatology and improved neuropsychological functioning in patients.
Method: 51 schizophrenia patients and 50 healthy participants were administered a neuropsychological battery. The 2D:4D ratio was measured in all participants. Positive, negative, and affective symptoms were assessed in patients. Regression analyses were conducted separately in male and female subgroups.
Results: No associations with positive symptoms were revealed. In male patients, the 2D:4D ratio was positively associated with avolition and inversely associated with anxiety. In female patients, it was inversely associated with alogia, and tended to be positively associated with depression. No association between higher prenatal concentration of the relevant sex hormone and improved neuropsychological performance emerged in patients.
Conclusions: Higher concentrations of prenatal testosterone in male patients, and prenatal oestrogens in female patients, are associated with a decrement in certain aspects of negative symptomatology. In addition, prenatal sex hormone concentration seems to be associated with predisposition to anxiety in male patients, and to depression in female patients.

1. Introduction

1.1. Sex hormones and clinical symptoms of schizophrenia

1.1.1. Circulating sex hormones

Differences between men and women have been observed in several of the clinical aspects of schizophrenia, and the disease involves alterations in sex hormone levels (da Silva and Ravindran, 2015; Markham, 2012; Mendrek and Stip, 2011). Men have been found to demonstrate greater probability than women of developing schizophrenia (McGrath et al., 2004). Indeed, studies of circulating oestrogen levels in female patients provide arguments in favour of a protective role for oestrogens in the clinical manifestations of the disease. Hoff et al. (2001) reported a trend level inverse association between plasmatic oestrogen concentration and a global negative symptom score. Ko et al. (2006b) demonstrated that higher levels of plasmatic oestrogens were associated with decreased negative symptomatology, notably alogia and attention deficit. Psychotic symptoms have also been found to vary across the menstrual cycle (Bergemann et al., 2007), which argues in favour of a modulatory role of sex hormones in female patients. Further, adjunctive oestrogen treatment in women with schizophrenia was demonstrated to have beneficial effects on negative and other psychotic symptoms (Heringa et al., 2015; Ko et al., 2006a; Kulkarni et al., 2002, 2015, 2016; Markham, 2012; Usall et al., 2011, 2016).

Nonetheless, testosterone too might demonstrate some protective effect against the symptoms of schizophrenia. Indeed, several studies have reported an inverse association between plasmatic concentration of testosterone and negative symptoms in male patients (Akhondzadeh et al., 2006; Goyal et al., 2004; Hashim and Negm, 2012; Ko et al., 2007; Markham, 2012; Shirayama et al., 2002; Sisek-

* Corresponding author at: Unit of Research and Development, PSSJD, c\ Doctor Antoni Pujadas 42, 08830 Sant Boi de Llobregat, Barcelona, Spain.
E-mail address: g.brebion@pssjd.org (G. Brébion).
[1] Both authors contributed equally to this study and share first authorship. Their names have been entered in alphabetical order.

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Šprem et al., 2015). Further, an adjunctive testosterone treatment in a sample of men with schizophrenia was found to lead to significant improvement of negative symptoms (Ko et al., 2008).

1.1.2. Prenatal sex hormones

Prenatal sex hormone concentration might be approximated by measuring the length of the second and fourth fingers in the adult. The length of the second finger is assumed to reflect prenatal exposure to oestrogens, and therefore the ratio of these two finger lengths (2D:4D) is a putative biomarker of the prenatal concentration of sex hormones (Hudson and Hodgson, 2016; Manning et al., 1998; McIntyre, 2006; Muller, 2013; Procopio et al., 2006). A low ratio reflects high concentration of prenatal testosterone relative to oestrogens whereas a high ratio reflects high exposure to oestrogens (de Bruin et al., 2006; Hudson and Hodgson, 2016).

Several studies have investigated prenatal sex hormone concentrations in relation to non-clinical symptoms in the general population. Williams et al. (2003) reported that, in preschool girls, low ratios were related with poor social functioning, whereas in preschool boys, high ratios were related with high rates of emotional symptoms. Further, higher ratios in healthy men were found to be associated with stronger paranormal beliefs and superstition scores (Voracek, 2009), and with increased anxiety (Evardone and Alexander, 2009). These findings suggest that prenatal testosterone acts as a protective factor against various types of non-clinical symptoms in the general male population. However, Rogers et al. (2017) observed that higher digit ratios were associated with stronger paranormal beliefs only in women. Other studies did not reveal any association of the 2D:4D ratio with either positive or negative schizotypy (Daly et al., 2008; Gooding et al., 2010). In the only relevant schizophrenia study that we are aware of, higher 2D:4D ratios were found to be associated with lower global negative symptom scores in a sizeable male Turkish sample (Bolu et al., 2015), which is in contradiction with the alleged protective role of prenatal testosterone.

1.2. Sex hormones and neuropsychological performance

1.2.1. Circulating sex hormones

Oestrogens might also exert their protective effect on cognition, limiting the neuropsychological impairment observed in patients with schizophrenia (Pompili et al., 2012). Indeed, certain studies of female schizophrenia patients have revealed positive associations between high levels of circulating oestrogens and performance in various neuropsychological functions including verbal and spatial memory, verbal fluency, and processing speed (Hoff et al., 2001; Ko et al., 2006b). Other studies, however, have failed to reveal such associations (Halari et al., 2004; Rubin et al., 2015). Notably, menstrual cycle studies have yielded conflicting results (Ko et al., 2006b; Rubin et al., 2015; Thompson et al., 2000). Adjunctive oestrogen therapy in women with schizophrenia has demonstrated cognitive improvement in verbal functions and processing speed (Bergemann et al., 2008; Huerta-Ramos et al., 2014, 2015; Ko et al., 2006a; Weickert et al., 2015) although negative results have been reported as well (Kulkarni et al., 2015, 2016; Weiser et al., 2017).

Very few studies have investigated the potential beneficial effects of testosterone on cognition in schizophrenia. No association between plasmatic testosterone level and neuropsychological performance was observed in male patients in Halari et al.'s (2004) study, but in female patients, higher testosterone predicted better performance in spatial working memory. More recently, Moore et al. (2013) reported that high levels of circulating testosterone were associated with better performance in various neuropsychological tasks – including verbal memory, working memory, and processing speed – in men with schizophrenia.

1.2.2. Prenatal sex hormones

The relationship between the 2D:4D ratio and neuropsychological functioning in the general population does not provide a clear pattern. Lower ratios – reflecting higher prenatal exposure to testosterone – were found to be associated with better numerical or spatial performance in male or female healthy samples in certain studies (Bosch-Domènech et al., 2014; Bull et al., 2010; Fink et al., 2006; Kalmady et al., 2013; Kempel et al., 2005), but not in others (Coolican and Peters, 2003; van Anders and Hampson, 2005). In healthy women, higher ratios were found to be associated with better visual memory performance (Poulin et al., 2004), suggesting the role of oestrogens in this function. As far as we know, no study has used the 2D:4D ratio in relation to neuropsychological impairment in a schizophrenia sample.

1.3. Aims of the study

We investigated the associations of prenatal sex hormone concentrations, as indexed by the 2D:4D ratio, with positive and negative symptomatology as well as with neuropsychological performance in a schizophrenia sample. Results were studied separately in male and female patients. 1) Following previous findings of the impact of circulating oestrogens and testosterone concentrations on negative symptoms, we tested the hypothesis that prenatal oestrogen and testosterone concentrations too have a protective effect against negative symptoms. More specifically, we hypothesized that decreased negative symptomatology was associated with higher ratios – reflecting higher prenatal exposure to oestrogens – in women, and with lower ratios – reflecting higher prenatal exposure to testosterone – in men. 2) Given the overlap that negative symptoms present with affective symptoms and illness duration, we investigated whether these factors influenced the alleged associations between digit ratio and negative symptoms. 3) Potential beneficial effects of prenatal oestrogen and testosterone concentrations on neuropsychological performance were examined in both the patients and the healthy sample.

2. Method

2.1. Participants

Fifty-one in-patients with schizophrenia (18 women, including 6 in the follicular phase of the menstrual cycle [day 1–14] and 8 postmenopausal) were recruited from our network of mental health services in Spain. The diagnosis was made by consensus on the basis of DSM-IV criteria by two experienced psychiatrists who used patient histories and chart reviews. The patients suffered from chronic schizophrenia, with illness duration of over two years for most of the patients. The inclusion criteria were age between 18 and 65 years, fluency in Spanish, and the ability to provide informed consent. The exclusion criteria were current or recent alcohol or drug abuse (DSM-IV criteria), organic mental disease, intellectual disability, history of brain injury, dementia, and current severe physical disease. All the patients were receiving antipsychotic medication and were at a stabilized dose at the time of testing. Socio-demographic and substance use information for each sex group is presented in Table 1. *t*-tests showed that male and female patients were not significantly different in age, education level, verbal IQ as assessed by a vocabulary test (Test de Acentuación de Palabras), tobacco intake, or caffeine intake.

Fifty healthy control participants (19 women, including 5 in the follicular phase and 9 postmenopausal) were recruited from the community (see Table 1). They were screened by telephone interview to rule out current or recent alcohol abuse, drug abuse, and psychiatric disease, as well as severe current non-psychiatric disease. Men and women were not significantly different in age, education level, or caffeine intake. However, men presented significantly higher verbal IQ ($t(48) = 2.19$, $p < .05$) and tobacco intake ($t(48) = 2.26$, $p < .05$) than did women.

t-test comparisons between schizophrenia patients and healthy controls revealed that the level of education was significantly higher in the healthy control group ($t(99) = 5.45$, $p < .0001$), as was the verbal

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