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Testing the estrogen hypothesis of schizophrenia: Associations between cumulative estrogen exposure and cerebral structural measures

C. van der Leeuw [a], P. Habets [a], E. Gronenschild [a], P. Domen [a], S. Michielse [a], M. van Kroonenburgh [b], J. van Os [a,c], M. Marcelis [a,*], for G.R.O.U.P.

[a] Department of Psychiatry & Psychology, School for Mental Health and Neuroscience, EURON, Maastricht University Medical Centre, PO Box 616, 6200 MD Maastricht, The Netherlands
[b] Department of Nuclear Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands
[c] Psychiatric Epidemiology, King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK

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ABSTRACT

Background: Bone mineral density (BMD), as an indicator of cumulative estrogen exposure, may be reduced in female patients with psychotic disorder (van der Leeuw et al., 2013), possibly reflecting reduced cerebral exposure to estrogen and alterations in neuroprotective effects. To the degree that BMD is a marker of cumulative (endogenous) estrogen exposure, we hypothesized that BMD would be positively associated with cerebral gray and white matter indices.
Methods: Dual X-ray absorptiometry (DEXA) and magnetic resonance (MRI) scans were acquired in fourteen female patients diagnosed with a psychotic disorder. BMD was expressed in total BMD (g/cm^2), Z- and T-scores. Cerebral cortical thickness (CT) (as indicator of gray matter status) and fractional anisotropy (FA) (as indicator of white matter integrity) were measured and served as the dependent variables in multilevel random regression models. BMD measures were the independent variables.
Results: Femoral BMD measures were positively associated with CT at trend significance (total BMD: $B = 0.266$, 95% CI: −0.019–0.552, $p = 0.067$; Z-score: $B = 0.034$, 95% CI: 0.001–0.067, $p = 0.046$; T-score: $B = 0.034$, 95% CI: 0.000–0.068, $p = 0.052$). There were no significant associations between femoral BMD measures and FA.
Conclusions: The data suggest that in women with psychotic disorder, alterations in the neuroprotective effect of estrogen (as measured by BMD) impact cortical gray matter, but not white matter integrity. These findings merit further investigation and, if replicated, would lend support to the estrogen hypothesis of schizophrenia.
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1. Introduction

Gender differences in the incidence and course of schizophrenia have been ascribed to neuroprotective effects of endogenous estrogen in females. In early adulthood, incidence rates of schizophrenia are lower in women than in men, and the age at onset of schizophrenia occurs three to four years later in women (Riecher-Rossler and Hafner, 1993, 2000; Hafner et al., 1998; Halbreich and Kahn, 2003; Markham, 2011). However, when estrogen levels decline around menopause, women display a second peak in the incidence of schizophrenia, which is absent in men (Riecher-Rossler and Hafner, 1993; Hafner et al., 1998; Abel et al., 2010). In the premenopausal period, female patients generally tend to fare better than their male counterparts, displaying a less severe course of symptoms, with a superior response to antipsychotic (AP) treatment and better social outcome (Seeman, 1983, 1996; Hafner et al., 1998; Salem and Kring, 1998; Hafner, 2003; Abel et al., 2010; Markham, 2011). Also, symptom variability during the menstrual cycle has been reported. Amelioration of symptoms is associated with a rise in estrogen and more clinical admissions take place during low estrogen phases (Riecher-Rossler et al., 1994; Seeman, 1996; Huber et al., 2004).

There are two (related) estrogen hypotheses of schizophrenia: 1) the hypoestrogenism or deficiency hypothesis which describes (chronic) gonadal dysfunction in women with schizophrenia, and 2) the protection hypothesis which states that estrogen exerts a relative protection against schizophrenia in premenopausal women (Riecher-Rossler and Hafner, 1993; Riecher-Rossler, 2002). The neuroprotective mechanism of estrogen in the human brain is complex. It includes structural effects such as the conservation of neurons, stimulation of growth and synaptogenesis, as well as effects at the receptor level, i.e. preservation of neurotransmitter receptors and modulation of neurotransmission (Brann et al., 2007; Boerma et al., 2010; Liu et al., 2010; Azcoitia et al., 2011; Kulkarni et al., 2012; McEwen et al., 2012).

The dysconnectivity hypothesis of schizophrenia proposes that altered structural connectivity may represent a key pathological mechanism in schizophrenia (Friston, 1998; Konrad and Winterer, 2008). The estrogen and dysconnectivity theories are possibly linked. Recently,

* Corresponding author at: Dept of Psychiatry & Psychology, Maastricht University Medical Centre, PO Box 616, 6200 MD Maastricht, the Netherlands. Tel.: +31 43 3883928; fax: +31 43 3884122.
E-mail address: m.marcelis@maastrichtuniversity.nl (M. Marcelis).

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Peper et al. (2011b) reviewed the available literature reporting on the potential association between sex steroid hormones, white matter (WM) indices and functional connectivity in the human brain, and concluded that gonadal hormones appear to organize and activate structural connections within the brain. Animal studies have shown that sex steroid hormones play an essential role in myelination (Peper et al., 2011b). In humans, sex steroids have been associated with structural brain development during puberty, exerting effects on both white (Asato et al., 2010; Herting et al., 2011; Peper et al., 2011a) and gray matter (Neufang et al., 2009; Peper et al., 2009, 2011a).

Other evidence for associations between estrogen and gray matter comes from the work of Goldstein et al. (2001, 2002) showing disruption of the normal sexual dimorphism in schizophrenia, particularly in the cortex. In addition, hormonal fluctuations during the menstrual cycle (Protopopescu et al., 2008; Pletzer et al., 2010) and hormonal contraceptive use (Pletzer et al., 2010) have been associated with gray matter changes in women of childbearing age. In the context of estrogen therapy (ET) and its effect on the aging brain in postmenopausal women, both higher and lower gray matter concentrations in specific cortical areas have been suggested (Boccardi et al., 2006; Robertson et al., 2009; Lord et al., 2010). Animal models of multiple sclerosis have demonstrated prophylactic effects of estrogen with regard to gray matter atrophy (Mackenzie-Graham et al., 2012). Thus, disparate research fields have provided clues as to the relationship between estrogen and cerebral structure at different life stages. However, studies investigating cumulative estrogen exposure and brain structure in patients with psychotic disorder have, to the best of our knowledge, not been conducted.

Previously, we used dual X-ray absorptiometry (DEXA) to assess bone mineral density (BMD) as a marker of cumulative estrogen exposure (Clemons and Goss, 2001), and found that reduced femoral BMD was associated with being female and having a psychotic disorder, but not with familial risk for psychotic disorder. This suggests that unique environmental factors, contributing to primary low estrogen levels in women, may impact the risk of developing a psychotic disorder, in support of the estrogen (deficiency) hypothesis of schizophrenia (van der Leeuw et al., 2013).

The aim of the current study was to investigate the potential association between endogenous estrogen exposure (as indexed by BMD, corrected for exogenous estrogen exposure such as contraceptives) and gray and white matter indices in this female patient group. Using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), cortical thickness (CT) and white matter integrity (represented by fractional anisotropy (FA)) were assessed respectively. We hypothesized that both CT and FA would be positively associated with BMD, reflecting the neuroprotective effects of estrogen in schizophrenia.

2. Methods and materials

2.1. Subjects

Data was collected in the context of an ongoing multicenter longitudinal study (Genetic Risk and Outcome of Psychosis, G.R.O.U.P.) in the Netherlands. In selected representative geographic areas in the Netherlands and Belgium, patients presenting consecutively at mental health services either as outpatients or inpatients were recruited for the study. Patients between the ages of 16 and 50 years, with a diagnosis of non-organic, non-affective psychosis according to DSM-IV criteria, were included (Korver et al., 2012). Sufficient command of the Dutch language was mandatory. A complete description of the recruiting protocol of the MRI sub-study is provided by Habets et al. (2011).

As mentioned in the introduction, the aim of the current study was to investigate associations between BMD and brain measures in female patients with a psychotic disorder, as a reduction in BMD (possibly reflecting low endogenous estrogen levels) was previously found in female ($n = 16$), but not in male ($n = 46$) patients (van der Leeuw et al., 2013). A T1-weighted structural MRI scan was obtained in 14, and an additional DTI scan in 13 of the original 16 female patients. Thus, the present study sample comprised 14 female patients.

The sample included eight patients who were diagnosed with schizophrenia, one patient with schizoaffective disorder, four patients with a diagnosis of psychotic disorder not otherwise specified and one patient with a diagnosis of brief psychotic disorder. Patients were genetically unrelated. The mean illness duration was 6.6 years.

Prior to DEXA acquisition, participants were screened for the following exclusion criteria: 1) metabolic or endocrinologic disease, 2) dietary deficiency or eating disorder, 3) medication: corticosteroids, thyroxin, anti-epileptics, heparin, lithium, cytostatic agents, 4) (semi-) professional athletes, 5) polydipsia (>3 l/day), 6) pregnancy, and 7) hormonal (infertility) treatment. Exclusion criteria for MRI constituted: 1) head injury with loss of consciousness for a duration of more than 1 h, 2) meningitis of other neurological diseases that might affect brain structure or function, 3) cardiac arrhythmia requiring medical treatment, 4) severe claustrophobia, 5) (suspected) pregnancy, and 6) any metal foreign object in the body, including the presence of an intrauterine device.

2.2. Measures

2.2.1. Age at menarche and dysmenorrhea

Age at menarche and the occurrence of menstrual irregularity were assessed. Dysmenorrhea was specified as altered duration and/or frequency of menses or the absence of two or more menses during the previous three months. Amenorrhea was defined as the absence of menses for at least three months.

2.2.2. Use of contraceptive drugs (exogenous estrogen exposure)

Cumulative (lifetime) exogenous estrogen exposure in women was expressed in micrograms, as the product of daily dose and total days of use.

2.2.3. Substance use

Substance use was assessed using the composite international diagnostic interview (CIDI). Cannabis use was assessed as the reported lifetime frequency of use. Other drug use, such as stimulants, sedatives, opiates, cocaine, PCP, psychedelics, inhalants or other (e.g. ecstasy, poppers) was assessed in the same way. Alcohol use was defined as the average number of weekly consumptions during the previous 12 months. Tobacco use was defined as the number of cigarettes per day, in the past year.

2.2.4. Antipsychotic medication (AP) exposure

Current AP use was classified by type: "prolactin-raising" APs, in this study comprising first-generation APs, risperidone and amisulpride; or "prolactin-sparing" APs, comprising second or third-generation APs with the exception of risperidone and amisulpride. Subjects who were AP-free at the time of the investigations were placed in the prolactin-sparing group.

Previous AP use was assessed retrospectively by self-report. Best estimate lifetime (cumulative) AP exposure was determined by multiplying the number of days of AP use with the daily AP dose converted to haloperidol equivalents (in milligrams), and summing all periods of use. Lifetime exposure was calculated for all APs and separately for prolactin-raising APs.

2.3. DEXA acquisition and processing

DEXA scans were acquired at Maastricht University Medical Centre with a Hologic Discovery A (Tromp Medical, Castricum, the Netherlands) (NHANES and Ethnic Reference Data). DEXA scans were performed in two anatomical areas: the lumbar spine, vertebrae L2 through L4; and the proximal left femur, specifically the collum, trochanter major, intertrochanteric area and Ward's triangle. BMD measures

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