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Menstrual cycle irregularity and menopause status influence cognition in women with schizophrenia

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ABSTRACT

Cognitive impairments are a core feature of schizophrenia and contribute significantly to functional complications. Current pharmacological treatments do not ameliorate cognitive dysfunction and the aetiology of cognitive impairments are poorly understood. Hormones of the hypothalamic-pituitary-gonadal (HPG) axis that regulate reproductive function have multiple effects on the development, maintenance and function of the brain and have been suggested to also influence cognition. The aim of the current study was to investigate how HPG axis hormones effect cognition, specifically exploring the influence of menopause status and menstrual cycle irregularity on cognitive performance in women with schizophrenia. The data for the present study represents pooled baseline data from three clinical trials. Two hundred and forty female participants with a diagnosis of schizophrenia or schizoaffective disorder were included in the analysis. Cognition was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status. Hormone assays for serum sex steroids and pituitary hormones (including estradiol, progesterone, luteinising hormone and follicle-stimulating hormone) were conducted and women were classified as postmenopausal; perimenopausal; premenopausal/reproductive, further classified into regular and irregular menstrual cycles. To model a comparison of cognitive performance for i) perimenopausal; ii) post-menopausal women and iii) reproductive aged women with irregular cycles to reproductive aged women with regular cycles a semiparametric regression model (generalised additive mode) was fitted. The results revealed that in females with schizophrenia, menstrual cycle irregularity predicted significantly poorer cognitive performance in the areas of psychomotor speed, verbal fluency and verbal memory. Perimenopause was not associated with cognitive changes and the post-menopausal period was associated with poorer visuospatial performance. This study provides evidence to associate reproductive hormones with cognitive dysfunction in schizophrenia.

1. Introduction

Cognitive symptoms in schizophrenia, such as impaired memory, poor attention and information processing, and difficulties with executive functions, are a core feature of schizophrenia, strongly related to quality of life and functional outcomes (Green, 1996) (Nuechterlein et al., 2012). The aetiology and capacity to treat cognitive symptoms is understudied (Nuechterlein et al., 2012). Hormones of the hypothalamic-pituitary-gonadal (HPG) axis that regulate reproductive function have multiple effects on the development, maintenance and function of the brain (Vadakkadath Meethal and Atwood, 2005) and have been previously implicated in the aetiology of schizophrenia (Markham, 2012). HPG axis dysregulation may be a potential contributor to cognitive dysfunction in schizophrenia.

Cognitive changes and dysfunction linked to HPG axis dysregulation is typically ascribed to the influence of sex hormones, predominantly estrogen. There is a relatively large knowledge base, primarily derived from animal studies, demonstrating that estrogens can influence spine density in the hippocampus and prefrontal brain regions (Tuscher et al., 2016; Woolley et al., 1990) promote neurotrophin synthesis (Milne et al., 2015), influence cholinergic (Mennenga et al., 2015) and dopaminergic neurotransmitter (Sinclair et al., 2014) systems and protect the brain against stress and inflammation (Luine, 2016). Animal studies additionally provide evidence that exogenous administration of estrogen has the capacity to enhance cognition, particularly in the areas of learning and memory (Engler-Chiurazzi et al., 2016; Luine, 2014). Progesterone receptors have also been identified in cognitively relevant brain regions, including the frontal cortex, hypothalamus, thalamus, hippocampus, amygdala, and cerebellum (Brinton et al., 2008). Like estrogens, progestogens have been described as an enhancer of neuronal function through similar mechanisms to estrogens, including reducing inflammation and apoptosis, increasing neurogenesis and

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neuronal regeneration as well as enhancing synaptic transmission (Brinton et al., 2008; Singh and Su, 2013; Rossetti et al., 2016).

Gonadotropin levels, particularly in the context of aging and neurodegenerative processes, have also been implicated as a potential regulators of cognitive functioning (Blair et al., 2015; Koebele and Bimonte-Nelson, 2017). Luteinising hormone (LH) may regulate learning and memory directly through actions of endogenous LH on LH receptors, which have been identified in cognitive relevant brain regions, such as the hippocampus (Lei et al., 1993), or indirectly via estrogens capacity to regulate LH activity (as proposed by (Blair et al., 2015)). Less research has been conducted exploring the link between follicle stimulating hormone (FSH) and cognition. Preliminary studies suggest a positive relationship exists between FSH and cognition (Rodrigues et al., 2008).

In addition to studies investigating correlations between endogenous hormone levels and cognitive functioning, are cross-sectional and longitudinal studies exploring cognition in the context of menopause transition. The menopause transition is associated with fluctuating and eventually decreasing levels of ovarian estrogens (estradiol and estrone) and progesterone and an increase in serum FSH. A recent meta-analysis concluded that the menopause transition, in non-clinical populations, is associated with decreases in verbal memory and verbal fluency (Weber et al., 2014).

Despite many studies implicating HPG hormones in the aetiology of schizophrenia (mostly ascribing to the hypothesis that estrogen provides a protective role in the development and expression of psychotic symptoms (Kulkarni et al., 2012)), few studies have specifically investigated how endogenous hormones levels relate to cognition in schizophrenia. One small cross-sectional study in 22 female schizophrenia patients who spanned a broad age range (27–63years) and included 10 taking estrogen containing hormone therapy or oral contraceptives and five nonovulatory participants, revealed significant associations between hormone levels and cognitive performance (Hoff et al., 2001). Specifically estrogen levels (average of four blood samples taken weekly across four weeks) were positively related to almost all cognitive domains assessed, including language, executive functioning, verbal memory, spatial memory and concentration/speed. Average progesterone levels were associated with better performance on measures of perceptual-motor processing speed. Similar positive associations were reported in a separate cross-sectional study involving 35 women with chronic schizophrenia (mean age = 34 years) who were all tested during the follicular phase (Ko et al., 2006). Specifically, significant positive correlations were found between serum estradiol and list acquisition; oral fluency; digit symbol and a significant inverse relationship was found between Trails B and estradiol (Ko et al., 2006). In contrast, cognitive performance was reported as unrelated to sex steroid levels across the menstrual cycle in a small study of naturally cycling women (n = 23) and men (n = 27) with schizophrenia (Rubin et al., 2015). Hence, although limited, evidence thus far appears to indicate a relationship between endogenous hormone levels and cognitive functioning. Cognitive changes associated with the menopause transition have not been previously explored in women with schizophrenia.

Menstrual cycle irregularity is considered an indicator of women's reproductive health (Rostami Dovom et al., 2016), and commonly reported in schizophrenia (although partially related to antipsychotic induced hyperprolactinaemia (Grigg et al., 2017)). We have previously suggested that global cognitive functioning is superior in women with schizophrenia who have a regular cycle, when compared to women with schizophrenia who have an irregular cycle (Gleeson et al., 2016); however, a detailed exploration of which cognitive domains may be influenced by menstrual cycle irregularity has not been conducted. The aim of the current study was to investigate how menopause status and menstrual cycle irregularity are associated with cognitive functioning in women with schizophrenia. Specifically, this cross sectional study compared the cognitive performance of women with schizophrenia who were i) post-menopausal, ii) perimenopausal and iii) of a reproductive age with irregular menstrual cycles to women with schizophrenia with regular menstrual cycles (after controlling for covariates including age, endogenous hormone levels and mood/psychopathology). It was hypothesised the menopause transition as well as menstrual cycle irregularity would adversely impact cognition.

2. Materials and methods

2.1. Study design

The data for the present study represents pooled baseline data from three clinical trials where the primary aim of these studies was to determine the effects of adjunctive estradiol and adjunctive raloxifene treatment on symptoms of psychosis in women (Kulkarni et al., 2016). Women underwent assessment for eligibility in inpatient and outpatient settings in 2 treatment centres, Alfred Health and Barwon Health, in Melbourne, Australia, from January 1, 2006, to December 31, 2015. All three trials were conducted according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Moher et al., 2010) and conducted as parallel-design, 12-week, double-blind RCT. Further details on study design can be found at (Kulkarni et al., 2016) and (Kulkarni et al., 2015). The Alfred Human Research Ethics Committee approved all study protocols, and all participants gave written, informed consent before entering the study. The three original studies are registered at ClinicalTrials.gov Identifier: NCT00361543 and NCT02354001 and NCT00357006

2.2. Participants

For the larger studies, women were eligible for the studies if they met criteria for schizophrenia or schizoaffective disorder and were receiving a stable dose of antipsychotics for at least 4 weeks before enrolment. They were required to be physically well, have normal findings on a mammogram within the last 12 months, and normal results of a Papanicolaou smear examination, breast and pelvic examination within the last 24 months. For the purpose of the present study, 240 participants from the larger trials completed cognitive assessment at baseline and were included in the current analyses.

2.3. Measures and procedure

As part of the larger trials, participants' psychiatric and medical histories were recorded at screening, together with a physical examination and the Mini-International Neuropsychiatric Interview to confirm psychiatric diagnosis.

Cognitive function was assessed at baseline using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). The RBANS is a brief, individually administered test designed to assess attention, language, visuospatial/constructional abilities, and immediate and delayed memory. It consists of 12 subtests with demonstrated reliability in schizophrenia (Wilk et al., 2002, 2004).

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS is a semi-structured interview that

consists of 30 items across three subscales – positive, negative and general psychopathology. The subscales are added to create a total PANSS score, with a range of 30–210. Depression was assessed using the Montgomery–Asberg Depression Rating Scale (MADRS), a 10-item researcher rated scale of depression (Montgomery and Asberg, 1979).

Relevant clinical factors for the current study were age, and menopause status. For the present study, women were classified as premenopausal/reproductive; perimenopausal or postmenopausal according to the Stages of Reproductive Aging Workshop classification system (Harlow et al., 2012). Premenopausal/reproductive age women were further classified into regular and irregular cycles based on their