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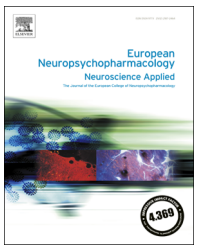

Sleep duration, depression, and oxytocinergic genotype influence prepulse inhibition of the startle reflex in postpartum women

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Abstract
The postpartum period is characterized by a post-withdrawal hormonal status, sleep deprivation, and susceptibility to affective disorders. Postpartum mothering involves automatic and attentional processes to screen out new external as well as internal stimuli. The present study investigated sensorimotor gating in relation to sleep duration, depression, as well as catecholaminergic and oxytocinergic genotypes in postpartum women.
Prepulse inhibition (PPI) of the startle reflex and startle reactivity were assessed two months postpartum in 141 healthy and 29 depressed women. The catechol-O-methyltransferase (*COMT*) Val158Met, and oxytocin receptor (*OXTR*) rs237885 and rs53576 polymorphisms were genotyped, and data on sleep duration were collected.
Short sleep duration (less than four hours in the preceding night) and postpartum depression were independently associated with lower PPI. Also, women with postpartum depression had higher startle reactivity in comparison with controls. The *OXTR* rs237885 genotype was related to PPI in an allele dose-dependent mode, with T/T healthy postpartum women carriers displaying the lowest PPI.
Reduced sensorimotor gating was associated with sleep deprivation and depressive symptoms during the postpartum period. Individual neurophysiological vulnerability might be mediated by oxytocinergic genotype which relates to bonding and stress response. These findings implicate the putative relevance of lower PPI of the startle response as an objective physiological correlate of liability to postpartum depression.
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1. Introduction

Postpartum depression, one of the most common complications in the peripartum period, has a major impact on women's lives in the critical first year after childbirth (Skalkidou et al., 2012). Many factors play a role in the aetiology of postpartum depression. Among these is the withdrawal of gonadal and stress hormones, which may influence cognitive and emotion processing, as well as the development of psychiatric symptoms (Mueller et al., 2014; Toffoletto et al., 2014). However, although the neurophysiological mechanisms of postpartum depression have not been well studied, emerging findings suggest that neurobiological factors may play a role. For example, mothers with postpartum depression are more likely to identify negative emotions and less accurate at identifying positive emotions in infant faces (Webb and Ayers, 2014), and display diminished infant stimuli-related neural reactivity and brain resting-state activity (Moses-Kolko et al., 2014). One putative tool to dissect the psychobiology of postpartum mental illness is the use of intermediate phenotypes. Basic, objective, biologically grounded, and reasonably heritable correlates (e.g. neurophysiological parameters) can quantifiably assess neurophysiological or behavioural processes and give insights into mechanistic and research domain-related signatures of mental health (Meyer-Lindenberg and Weinberger, 2006).

Postpartum mothering involves automatic and attentional processes to screen many new external as well as internal stimuli. Sensorimotor gating is a neural process which encompasses filtering and processing of information during sensory integration and is a major component of all action selection and inhibition and higher order function (Cromwell and Atchley, 2015; Grillon and Baas, 2003). A weakened sensory gating likely leads to altered attention, information misperceptions, and disordered thinking (Schell et al., 2000). Sensorimotor gating can be measured by means of prepulse inhibition (PPI) of the startle reflex eye blink (Braff et al., 1992). PPI is a semi-automatic process consisting of the reduction of response to a second auditory stimulus when the first stimulus is presented milliseconds prior to the target stimulus (Filion et al., 1993; Schell et al., 2000). Besides being a correlate of schizophrenia (Swerdlow et al., 2014), reduced PPI has been associated discordantly with post-traumatic stress disorder (Acheson et al., 2014), uncertainly with panic disorder in one study (Ludewig et al., 2002), whereas no association with depressive disorders has been previously observed (Ludewig and Ludewig, 2003; Perry et al., 2004; Quednow et al., 2006b). Sex and hormone dependent differences in PPI have been demonstrated (Kumari, 2011; Swerdlow et al., 1993; Swerdlow et al., 1997). Women display lower PPI during the luteal phase of the menstrual cycle (Bannbers et al., 2010) and pregnancy (Kask et al., 2008a), and similar findings have been noted in patients with premenstrual dysphoric disorder (PMDD) during the luteal phase (Kask et al., 2008b) and in women with anxiety disorders during pregnancy (Comasco et al., 2015). These time-points in women's lives are associated with affective disorders such as PMDD and antenatal depression, both of which occur in concomitance with gonadal hormone changes. Though a handful of studies seems to point to normal PPI in the presence of depression and anxiety symptoms (Kohl et al., 2013; Takahashi et al., 2011), the relationship between PPI and affective disorders during the postpartum period remains to be investigated.

Additionally, postpartum women commonly experience sleep deprivation, which may affect depression and PPI (Bhati and Richards, 2015; Tomfohr et al., 2015; Wesstrom et al., 2014). It was recently proposed that one single night of sleep deprivation may reduce PPI in healthy subjects (Petrovsky et al., 2014), thus suggesting that the lack of sleep experienced by many postpartum women likely influences PPI.

The startle response is an reflexive, and protective response to stimuli which exists across species. It is used as a neurophysiological tool to measure emotional or motivational psychological states or as a reflection of brain activity in limbic areas (Grillon and Baas, 2003; Lee et al., 1996). Higher baseline startle response is often associated with negative psychiatric outcomes and emotional traits (Grillon and Baas, 2003). On the other hand, no difference in startle reactivity has been found after sleep deprivation (Petrovsky et al., 2014).

Finally, the individual response to the postpartum hormonal changes, and sleep loss, is presumably determined by the combination of genetic vulnerability as well as sensitivity to environmental factors. The neurochemical regulation of PPI involves, among others, the catecholaminergic corticolimbic circuitry (Swerdlow et al., 2001), which is impaired in affective disorders and regulated by sex hormones. The neurotransmitters dopamine, adrenaline, and noradrenaline as well as catechol oestrogens and exogenous catechols are ubiquitously degraded in the brain by the catechol-O-methyltransferase (COMT). The functional rs4680 polymorphism on the *COMT* gene (rs4680) (Chen et al., 2004) has been associated with differential PPI (Takahashi et al., 2011) and affective correlates, although in a somewhat complex interaction with sex and gonadal hormones (Tunbridge and Harrison, 2011). The G (Valine (Val)) allele, leading to a three- to four-fold higher enzyme activity compared to the A (Methionine (Met) allele), has been associated with lower PPI (Comasco et al., 2015), and higher startle response in pregnant women (Comasco et al., 2013), but remains to be investigated in postpartum women.

Moreover, oxytocin, through its receptor (OXTR), regulates not only emotional and cognitive processing, but also social behaviour and stress responses, all key functions in the postpartum period (Ebstein et al., 2009). Oxytocin influences PPI in rodents (Feifel et al., 2012), and polymorphisms of the *OXTR* (e.g. rs53576 and rs237885) have been related to peripartum mood and emotional reactivity (Mileva-Seitz et al., 2013; Tost et al., 2010). Hence, cathecolaminergic and oxytocinergic genotypes presumably influence PPI in postpartum women.

In the present study we aimed to investigate sensorimotor gating in postpartum women by measuring PPI and the acoustic startle response. In order to replicate a previously demonstrated deteriorating effect of sleep deprivation on PPI (Petrovsky et al., 2014), postpartum women reporting short relative to normal sleep duration were compared. To test the hypothesis that postpartum depression is associated with decreased PPI and higher startle response, women with or without depression were compared. As no previous

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