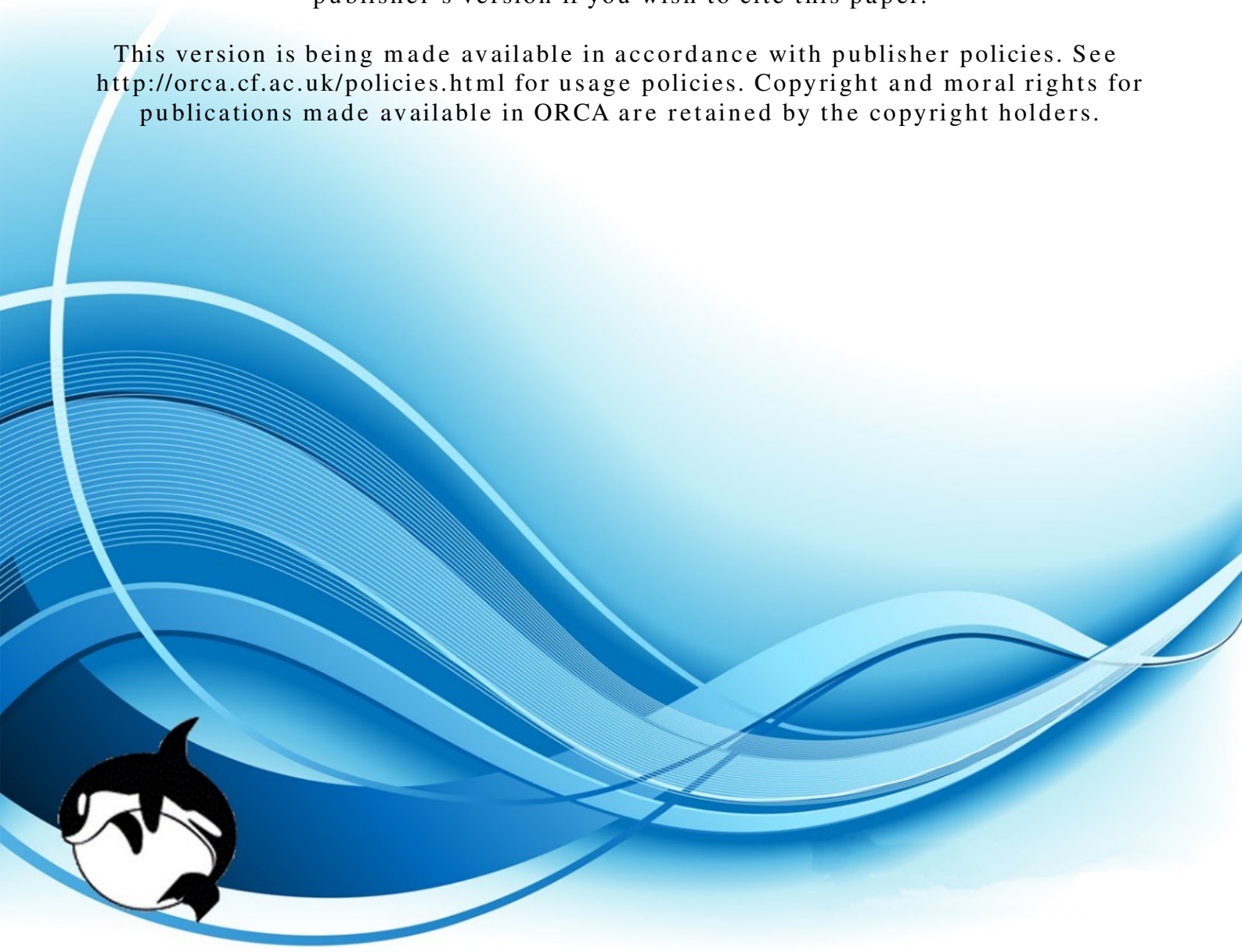

Is Sleep Disruption a Trigger for Postpartum Psychosis?

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Summary

An episode of postpartum psychosis (PP) can be devastating for a woman and her family, and it is vital we understand the factors involved in the aetiology of this condition. Sleep and circadian rhythm disruption (SCRD) is a plausible candidate but further research is needed that builds on the latest advances in chronobiology and neuroscience.

Declaration of Interest

None.

1 Postpartum Psychosis and Sleep/Circadian Rhythm Disruption

Postpartum psychosis (PP), a severe episode of mania or psychosis following childbirth, occurs following around 1 in every 1000 births and requires prompt identification and treatment. Despite investigation of hormonal, immunological, and genetic factors[1], the precise aetiology of PP and the nature of the childbirth-related trigger remain unclear. However, episodes of PP are frequently characterised by symptoms of mania, and women with a history of bipolar disorder (BD) have a particularly high risk of PP (around 20%[2]), suggesting that many episodes of PP are a manifestation of BD triggered by childbirth. One possibility is that PP is triggered by similar factors to non-puerperal mania, one of the most common being sleep and circadian rhythm disruption (SCRD)[3]. The greatest sleep disruption occurs in the immediate perinatal period[4] , which closely coincides with the onset of PP symptoms[5]. Therefore it is possible that SCRD incurred in the perinatal period increases the risk of PP in vulnerable women.

A relationship between sleep disruption and PP is often assumed but the evidence base is surprisingly lacking. A frequently-cited study by Sharma and colleagues reported that women with PP were more likely to give birth at night and have a longer duration of labour, suggesting that increased sleep disruption played a role in the onset of their illness[6]. In contrast, a prospective study of "high risk" pregnant women (i.e. those with a history of BD or PP) found no significant differences between their sleep during pregnancy compared to healthy pregnant controls[7]. However, as only 3 of the women in this

study relapsed upon giving birth, this study was not able to compare the sleep of women who developed PP compared to those who remained well. Both studies also relied solely on subjective or indirect measures of sleep. Therefore, despite being a plausible hypothesis, more work is clearly needed on the association between SCRD and PP before we are able to draw firm conclusions.

Previously, researchers have highlighted the need to conduct prospective studies of SCRD that include both objective and subjective measures of sleep throughout the perinatal period[8]. In addition, we suggest that future studies are informed by recent findings in neuroscience and chronobiology. In the last decade, there has been a heightened awareness of the physiological and psychological consequences of SCRD within both healthy and psychiatric populations. It is prudent, therefore, that our current understanding of the mechanisms underlying sleep and circadian rhythm regulation inform future research on the aetiology of PP.

2 The Neuroscience of Sleep and Circadian Rhythms

2.1 Neuroscience of Sleep & Circadian Rhythms

We can only provide a brief overview of the mechanisms governing sleep and circadian rhythms here, but for more detail see[9]. At the heart of the circadian timing system is a small structure located within the ventral hypothalamus called the suprachiasmatic nuclei (SCN). Individual SCN neurons generate a ~24-hour oscillation in cellular activity, and the coupling of these individual oscillators allows the SCN to act as the "master" clock within the body. Such circadian rhythms are driven by a transcriptional-translational feedback loop that modulates the expression of clock genes and clock-controlled genes. Originally it was assumed that the SCN alone drives 24-hour rhythms in physiology and behaviour, but we now appreciate that most cells in the body also have the capacity to generate ~24-hour rhythms, and the role of the SCN is to sustain and coordinate the activity of the circadian network across the tissues and organ systems of the body. The daily adjustment of our physiology by the circadian system has no adaptive value unless the "internal day" and external day are appropriately aligned. Jet lag represents the classic miss-match between internal and external time. The circadian system is synchronised to the dawn/dusk cycle by specialised photoreceptors within the eye that project to the SCN[10,11] . The SCN then in-turn entrains the peripheral oscillators throughout the body.

But sleep-wake timing involves more than just the circadian system. Homeostatic processes within the brain drive sleep propensity such that the longer we are awake the greater the need for sleep. A key element of the sleep drive is adenosine, which builds up in the brain as a result of the breakdown of ATP. Caffeine antagonises adenosine receptors, which is why we feel less tired after a cup of strong coffee!

The circadian system allows the expression of this sleep drive at night and sustains wakefulness during the day. Multiple brain structures and neurotransmitter systems give rise to the different states of sleep and consciousness, indeed our increasing understanding of how the brain generates sleep is one of the recent success stories of neuroscience research. It is also the complexity of sleep generation and regulation that makes sleep vulnerable to disruption. An abnormality in any one of the key neurotransmitter systems of the brain (e.g. serotonin or dopamine) will ultimately have an impact upon sleep[9].

2.2 SCRD and Bipolar Disorder

Recent evidence suggests that the neural mechanisms underlying sleep and circadian systems overlap with those implicated in bipolar disorder (see [12] for a review). First, the neurotransmitters implicated in mood regulation and BD such as serotonin and dopamine have also been found to influence sleep and circadian rhythms. Second, some genetic studies have found associations between polymorphisms in clock genes and BD (although results are not consistent). Third, there is evidence that lithium exerts its therapeutic action via GSK-3β, a regulator of the circadian clock. Finally, therapies that aim to stabilise sleep and biological rhythms have been associated with reduced rates of relapse[13].

2.3 Individual variation in response to SCRD

As discussed above, studies of clock genes in BD have produced inconsistent results, leading some researchers to propose that there may be variation ***between*** bipolar individuals in the extent that SCRD is a trigger for episodes of illness. Findings in healthy populations suggest that sleep deprivation may affect neurobehavioural functions to a greater degree in some individuals[14]. In addition, there is evidence that vulnerability to SCRD is under genetic influence, with one twin study reporting a heritability estimate of 83.4%[15] and studies in healthy populations finding associations between vulnerability to sleep loss and variation in sleep and circadian rhythm genes such as PER3[16]. Sleep characteristics such as circadian instability could therefore be very promising candidate endophenotypes to explore in BD[12].

3 Implications for research on PP and clinical practice

It has been over a decade since the initial call for research on sleep disruption as a risk factor for PP[8], yet there continues to be a dearth of research in this area. More work is clearly needed, particularly research which is informed by recent findings within the field of sleep and circadian neuroscience. Based on the literature outlined above, we propose three avenues. First, given that the majority of episodes of PP are bipolar in nature, research on PP should be informed by knowledge of how SCRD influences the course of

BD including the neurotransmitters and genetic factors that may be involved. Second, research should account for individual variation in response to SCRD, which may increase risk of relapse following sleep-depriving events such as protracted labour. Finally, future research should incorporate more objective measures of sleep, such as actigraphy. Refining research questions in light of such information will bring us closer to identifying women who are most vulnerable to the effects of perinatal SCRD and PP.

The ultimate aim of research in this area is to procure findings translatable to clinical practice. Identifying those who are most vulnerable to the effects of SCRD can help to focus specific interventions on women for whom they are most beneficial. Combined with other measures of high risk, such as a history of bipolar disorder, individual differences in response to SCRD could be used to give more accurate and individualised assessment of risk of severe postpartum episodes. This could potentially help women and their clinicians make the very difficult decisions about the use of medications in the perinatal period. For those women in whom SCRD is likely to be a triggering factor, provisions may then be taken to (a) prevent the woman from suffering extensive sleep loss, (b) monitor sleep in the perinatal period and (c) plan interventions to administer if a critical level of sleep loss is detected.

However, as the majority of clinicians will not have access to sophisticated measures of SCRD, it is imperative that research utilises behavioural correlates of sleep disturbance. Possible measures of SCRD in a clinical setting include brief questionnaires and sleep diaries completed by patients and/or clinicians, as well as actigraphy. Thus, future protocols should incorporate a variety of subjective and objective measures of sleep in order to determine which indices are reliable at detecting incipient postpartum mood episodes.

To conclude, awareness of current research on SCRD should guide future research on PP. Measures of SCRD may be used to identify (and monitor) individuals who are at high risk of PP in addition to being useful in treatment and prevention strategies. It should be noted that risk for PP is most likely influenced by a myriad of factors, thus the physiological effects of perinatal SCRD may interact with other risk factors (e.g. immunological, genetic, hormonal) to increase risk. However, the first step is to understand and quantify the increase in risk (if any) that is conferred by perinatal SCRD. Hopefully, such efforts will bring us closer to understanding the aetiology of this severe postpartum disorder and therefore improve our ability to help women at high risk.

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