Cognitive impairment is a sine qua non of schizophrenia – even patients with apparently intact neuropsychological function are likely to have declined from a higher premorbid level. The evidence indicates that this is generalised in nature and can affect many abilities important for effective negotiation of the world, including learning, remembering, planning and strategy formation. These higher-order cognitive functions are underpinned by more specific processes such as working memory, inhibition, memory consolidation and information-processing speed, all of which are impaired in schizophrenia. Cognitive impairment is present at psychosis onset and is a strong predictor of later social and occupational dysfunction. Thus there is a recognised and urgent need for interventions targeting this disability and, with this in mind, all potentially treatable sources of cognitive impairment deserve examination.
new strategies for cognitive remediation of this disorder. The authors assessed the 24-hour activity of well-characterised patients with schizophrenia by asking them to wear ‘actigraphs’, which resemble wrist watches, over a 3-week period. They also measured melatonin secretion before and after sleep on several occasions during this time to provide a biological marker of circadian master clock activity. Although the patient group was relatively small ($n = 14$), the effort involved in producing such valuable longitudinal data should not be underestimated and, further, the results are clear. The 24-hour activity of all patients was appropriately entrained to light–dark phases. Thus these patients slept at night and were awake during the day and therefore did not exhibit the gross disruptions of circadian activity sometimes seen in people with mental health problems whereby normal day–night activity is persistently irregular. Instead, circadian activity was disrupted in a more subtle way. Half of the patients had increased night-time activity, shorter and more fragmented time spent asleep and more daytime sleepiness. In addition, whereas the patients with normal day–night activity showed synchronised melatonin rhythms, in the others melatonin release was out of phase, beginning after their usual bedtime (rather than before) and extending beyond their waking time.

Cognition was measured before and after the actigraphy study and was essentially stable. The group with normal circadian rhythms performed within the normal range according to published population data for the tests employed. These focused on executive functions, examined by the ability to call up from memory semantically related words (verbal fluency), inhibit a pre-potent response (the Stroop Test) and rapidly switch attention from one category to another (the Trail Making Test). Compared with the normal group, patients with disrupted circadian rhythms were worse on all but one of these cognitive functions.

One explanation of these findings is that the impaired group was simply more ill. Importantly, however, across all patients there were large associations between the ratio of day–night activity and the cognitive measures, with effect sizes ranging from 0.66 to 0.83, but no such associations with symptom severity or length of illness. This suggests that there is a specific relationship between abnormalities of circadian rhythm and impaired cognition in schizophrenia and that this is significant for a subgroup of patients.

All patients were receiving antipsychotic medication and some adjunctive medications, but this did not seem to explain the group differences; nor did illness duration or other variables such as age and body mass index. One possibility is that the patients with abnormal sleep–wake activity were not being exposed to strong enough zeitgebers because of social withdrawal or lack of daytime structure. There is a hint from the study that this might apply as more of the patients with disrupted circadian rhythms were out-patients and therefore less likely to have a daily routine of the kind imposed on in-patients. Another explanation is neurobiological; that is, people with schizophrenia may have intrinsically unstable circadian oscillators. For example, there may be impaired circadian synchronisation between cellular networks of local brain areas participating in sleep–wake regulation and cognition which might arise from natural genetic variation, as seen in animal models of neuronal PAS-domain protein-2 (NPAS2) deficiency. Abnormalities of local oscillators residing in the hippocampus and frontal cortex are candidate mechanisms as both are structurally abnormal in schizophrenia and highly implicated in mediating the cognitive impairment associated with the disorder.

In addition, there is some, albeit modest, evidence for an association between schizophrenia and a common polymorphism of the NPAS2 gene. Conflicting zeitgeber signals (e.g. light exposure at night) would further hamper abnormal neuro-biological temporal adaptation processes, while daily clinical routines would strengthen temporal synchronisation. Thus, whether the primary mechanism is environmental or neuro-biological, patients with schizophrenia with disrupted circadian activity are at a disadvantage because of its effect on already compromised cognitive function, which may lead to a vicious cycle of failure in the performance of everyday functions, further social withdrawal and reduced zeitgeber exposure. Recognising sleep–wake disturbances and establishing their underlying causes is therefore of great importance.

There is already evidence to suggest that exogenous melatonin can help with the type of sleep–wake abnormalities described in the study by Bromundt and colleagues. Procedures comparing melatonin onset (measured in saliva or urine) and sleep–wake timing (measured with actigraphy) are straightforward to conduct and could provide useful information at an individual level by assessing circadian phase relationships and separating out internal desynchronisation and misalignment between internal phase and environmental light–dark phase. The results could then be used to inform rehabilitation strategies and, if indicated, introduce personalised chronotherapy, which might include individually timed melatonin administration and/or exposure to bright light. The ability to regulate circadian activity to encourage consolidated sleep patterns may thus prove a valuable intervention that targets one source of cognitive difficulties in patients with schizophrenia.

What is the origin of disrupted circadian rhythms in schizophrenia?

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References


Before the Meeting

Sarvenaz Keyhani

Sarvenaz Keyhani is a staff grade psychiatrist working in general adult psychiatry in London. She has been painting from a young age and had an exhibition in Tehran in 2000. She continues to paint alongside practising psychiatry and believes there is a strong relationship between painting and psychiatry, art therapy being just one example.

The painting Before the Meeting was done in 2008, after the artist attended a psychiatry meeting in Wessex, where she was having her psychiatry training. It is chalk pastel on coloured paper of a group of people gathering in a waiting area. It is a realistic painting; the large areas of warm colour, especially the brown, intensify the warm atmosphere of the place, as well as the aroma of the coffee the guests are drinking. The three paintings on the walls are copies of Lautrec’s, added here to increase the effect of colour in the painting as well as being a homage to the great painter for his intense realistic vision and impressive use of colour.
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