Looking at the causes of, and possible treatments for, psychiatric diseases: gene–environment interactions, circadian rhythms and neuronal dysfunction

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The press conference sessions at the 23rd European College of Neuropsychopharmacology (ECNP) Congress held in Amsterdam, The Netherlands covered an interesting array of research into the causes of psychiatric diseases. The presenters covered research work looking at a possible gene–environment interaction as the basis for schizophrenia, how circadian rhythm disruption appears to have an impact on all psychiatric disorders, and the latest imaging techniques showing a neuronal basis for depression. The aim behind their research is to elucidate the mechanisms involved in each disease so that future treatments might be better targeted and more successful.

How gene–environment interactions may provide a model for psychosis

At the first press conference, Professor Jim van Os (Maastricht University Medical Centre, The Netherlands) gave an overview of a research collaboration that aims to unravel the causes of schizophrenia and related psychotic disorders: the European Union Gene Environment Interaction (EU-GEI) project.

Professor van Os stated that schizophrenia and related disorders have a lifetime prevalence of 3.5%. Schizophrenia is associated with a reduced life expectancy of 10–15 years less than the general population. The aetiology of schizophrenia is complex. In twin and family studies, a genetic basis for vulnerability to schizophrenia has been clearly demonstrated; however, the genes that relate directly to psychotic disorders have been hard to elucidate, mainly because of the interplay

between gene and environment. Research is now focused on comprehending the complex interactions between genetic factors and the environment that lead to psychosis. Thus, the ‘gene – environment’ interaction model proposes that genes influencing risk for schizophrenia may make people more sensitive to the effects of causal environmental risk factors. This approach suggests that synergy is the cause of psychosis: when the effect of one is conditional on the other. Evidence seems to suggest that approximately 75–90% of developmental psychotic experiences are transitory and disappear over time; however, in some people prone to psychosis, these experiences may become persistent and lead to impairment.

High rates of schizophrenia occur in large cities, and among immigrants, people who use cannabis and people who are traumatized, which shows sensitivity to causal environmental risk factors. The chronic experience of marginalization, subordination or exclusion leads to social defeat and produces psychosis among people whose genotype makes them vulnerable to this environmental burden.

The EU-GEI project

The EU-GEI project is a research collaboration that aims to reveal the causes of schizophrenia and related psychotic disorders. It involves more than 7500 participants and their families from 15 countries and has the following aims:

1. to find gene – environment interactions underlying schizophrenia risk;

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2. to establish how gene – environment interactions affect brain pathways and create psychological vulnerability;
3. to elucidate how behavioural expressions of psychological vulnerability are mediated by cerebral and psychological pathways.

Further research within the project will aim to answer why the expression of vulnerability never progresses to overt illness in some people while schizophrenia manifests itself in others.

Because there were no tools available to adequately monitor changes in the participants, the project developed a prototypic device (PSYMATE) to be carried by participants so that they can input information about their mental state, context and activities. This device allows the steady stream of daily life to be captured: in effect a film rather than a snapshot of participants' daily life. The main study results will begin to appear in 3 years and are eagerly awaited.

Restoring circadian rhythms: light therapy or agomelatine?

Professor Anna Wirz-Justice (Centre for Chronobiology, Psychiatric University Clinics Basel, Switzerland) explained how our circadian rhythms drive our regular work and rest routine and how their disruption can have drastic consequences on brain functions. She presented evidence that several psychiatric disorders, including depression, bipolar disorder, seasonal affective disorder (SAD), schizophrenia and borderline-related disorders, are commonly associated with abnormalities in circadian rhythms.

The main internal biological clock (or 'zeitgeber') is in the suprachiasmatic nucleus (SCN) of the brain. Photoreceptors in the retinal ganglion cells contain melanopsin, which is sensitive to blue light. Daylight stimulates these receptors and signals are relayed to the SCN, which governs body functions according to the 24-h light-dark cycle. These functions include the release of melatonin (another zeitgeber) from the pineal gland. Other lesser zeitgebers are social contacts, mealtimes and exercise. Adhering to a regular temporal routine can optimize performance at the right time of the day.

Specific circadian genes (e.g. CLOCK, BMAL1, PER) are responsible for the main SCN

clockworking machinery as well as subsidiary clocks in other parts of the body (e.g. the liver). Animal studies suggest that such 'clock genes' direct circadian rhythms in all physiological processes. Physiological and biochemical processes such as body temperature, cortisol, melatonin, thyroid-stimulating hormone, nor-adrenaline and serotonin levels exhibit a circadian rhythm.

Of course, modern society has had a significant impact on a regular work–rest scheme governed by daylight. People stay up late and others have to do shift work or cross timezones, all of which disrupt their internal biological clocks and can lead to an enhanced risk of errors and accidents, loss of productivity, and predispose them to ill health, both physical and mental.

Circadian disturbances: affective disorders and chronotherapeutics

Circadian rhythm disruption and sleep disturbance are key elements of bipolar disorder and major depressive disorder. Insomnia may precede depression; in fact, insomnia often appears before the onset of mood disorder symptoms and may persist into clinical remission. Importantly, sleep disturbance may have as great an impact on health-related quality of life as the mental illness itself.

Antidepressant drug treatment can eventually improve sleep disturbance; however, initially these drugs often exacerbate sleep problems, necessitating the prescription of additional hypnotic drugs. While psychotherapy and cognitive behavioural therapy are well-accepted adjunctive treatments, chronotherapeutics do not appear to fit into any conventional category.

Chronotherapeutics provide controlled exposure to light or other zeitgebers in an attempt to reset impaired circadian rhythms. Light therapy is well recognized as the treatment of choice for SAD; however, Professor Wirz-Justice argued that it is also effective across all groups of major depression. Light therapy may be used in addition to antidepressant drugs in unipolar depression, or lithium in bipolar disorder. Light therapy hastens and potentiates the antidepressant response and can provide benefit even for people who have had chronic depression for at least 2 years. Light therapy is of course an alternative for people in whom medication is not suitable. Other forms of chronotherapy include 'dark therapy', which has

been used to control symptoms in people with acute mania and to calm people with 'rapid-cycling' bipolar disorder in the manic phase; this treatment is being refined with the use of blue-blocking sunglasses to induce a 'circadian darkness'.

While light therapy may help to reset the SCN, it is also possible to do this directly with melatonin (and, as argued in other sessions, with agomelatine, as described below). Orally administered melatonin can synchronize circadian rhythm and induce a rapid onset of sleep. Both light therapy and oral melatonin are not mainstream treatments for depression despite increasing evidence for their efficacy. Professor Wirz-Justice commented that this may be because they are nonpatentable treatments and thus are not marketable by commercial organizations. She encourages enterprising doctors to try them out and for the techniques to be taught in medical school and during residency. The Center for Environmental Therapeutics (CET) has set up a nonprofit, multilingual website for patients (www.cet.org) and one for clinicians (www.chronotherapeutics.org), which provide support and further information.

Agomelatine

Agomelatine is a melatonin agonist and a 5-HT_{2c} antagonist. Both melatonin (M₁ and M₂) and 5-HT_{2c} receptors are expressed in the SCN. Agomelatine's dual action may lead to resynchronization of the circadian rhythms that are disturbed in people with depression.

New data presented at the ECNP Congress by Kasper and colleagues (abstract S348) shows that agomelatine is more efficacious than selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, a serotonin noradrenaline reuptake inhibitor. These data were taken from a pooled analysis of four multicentre trials in people with major depressive disorder. Both improvements in the Hamilton Rating Scale for Depression (HAM-D) and the percentage of people who responded were greater with agomelatine compared with SSRIs or venlafaxine over a treatment period of 6–8 weeks. A subpopulation of people with severe depression also fared significantly better with agomelatine than the other drugs. A sponsored satellite at the ECNP Congress highlighted other key features, including a faster clinical response (within 1–2 weeks) than other antidepressants, rapid sleep restoration and

improved adherence. (The editors note that as such claims have been made for many other antidepressants over the years, these findings will need to be confirmed by independent researchers.) The agomelatine studies have also demonstrated that this drug has anxiolytic properties among people with depression and has shown long-term efficacy with relapse rates that are half that of placebo over a 6-month period. The main findings of this satellite symposium have been published in a supplement [*J Psychopharmacol* 2010; 24(8 Suppl): 1–30].

Defining the neural basis of depression

In the final press conference of the symposium, Professor Philippe Fossati (University Pierre & Marie Curie, Paris, France) sought to explain how depression is a true brain disease associated with dysfunction of specific brain regions that leads to mood changes, motor deficits, cognitive impairment and vegetative symptoms. Positron emission tomography scans have shown that abnormalities of metabolism occur in various parts of the brain in people with major depressive disorder.

Current research efforts are using brain imaging techniques such as functional magnetic resonance imaging (fMRI). In one study by Lemogne and colleagues, participants performed a self-referential task: they were asked to judge whether certain personality traits described them or described a generally desirable trait. The fMRI showed that people with depression had an abnormal activation of the medial prefrontal cortex. It was postulated that this dysfunction may explain the particular emotional processing in people with depression in that they tend to prioritize the processing of negative stimuli, have a negative view of themselves and an abnormal self focus (i.e. rumination, self blame, feeling of guilt). The activation pattern was present during the course of depression and also after 8 weeks of antidepressant treatment. Similar results have also been reported recently by Yoshimura and colleagues.

The findings are preliminary, but appear to suggest that medial prefrontal cortex activity may be a trait measure for depression. Further research is required to determine whether such activity is always present in people prone to depression or whether it occurs at certain times, and also whether the activity may be reduced by certain antidepressant drugs or cognitive behavioural

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therapy. It is hoped that brain imaging studies such as this may be used to define biomarkers of diagnosis and predict response to treatment, thus allowing antidepressant treatment to be tailored to the biological needs of the person.

Conflict of interest statement

The authors declare they have no conflict of interest to declare in preparing this manuscript.