

The chemical brain

WITH so much contemporary psychology preoccupied by a purely phrenological mission to map out which neural areas are active during which tasks, it's easy to forget all those chemicals washing through our brains, each exerting its own profound influence on our feelings and behaviour. Worse still, to some, mention of neurochemicals may imply unwelcome connotations relating to Pharma companies and the 'chemical imbalance' model of mental illness. But these prejudices should be cast aside – there's a generation of psychologists and psychiatrists working at the interface of neuropharmacology and psychology whose research is providing valuable new insights into mental health.

Salience everywhere

Professor Shitij Kapur, the Canada Research Chair for Schizophrenia and Therapeutic Neuroscience at the University of Toronto, has used what we know about the neurochemistry of schizophrenia to formulate a psychological explanation for the illness. Schizophrenia is associated with an excess of the brain chemical dopamine, and antipsychotic drugs work by blocking this substance. Dopamine is known to be involved in motivation and reward – this is key to Kapur's proposal that the positive symptoms of

*Our journalist **CHRISTIAN JARRETT** talks to people working at the forefront of neurochemical research.*

schizophrenia, particularly delusions, are caused by people finding inappropriate salience in the world around them.

According to Kapur, dopamine inflames the cognitive tendencies that people with schizophrenia exhibit even before they become ill. He says: 'If you could test patients before they were psychotic, you'd probably find they tend to jump to conclusions or choose extreme explanations. When you add to this a biochemical fuel – excess dopamine – you inflame this way of thinking. That's what dopamine does. The antipsychotic drugs douse the flames and take away the fuel – they don't fundamentally change the patients' tendencies, and that's why relapse usually occurs when medication is stopped.'

Kapur has taken the obvious, but surprisingly rare, approach of asking patients if, and how, they think taking antipsychotic drugs have changed the way they feel. 'Take a delusion such as believing the police are out to get them,'

says Kapur. 'Using a traditional rating scale and saying to a patient "Two weeks ago you thought the police were out to get you, how do you feel now?" – you might recognise the delusion had improved from a score of five to three, but you wouldn't know exactly what about the delusion had changed. We asked patients how their delusion had changed, and they tended to say they hadn't abandoned their belief that the police were after them, rather it just didn't bother them as much any more, it was on the back-burner.'

Consistent with this, a study by Kapur and colleagues published in 2005 compared patients' expectations about the way medication would help them, with how they subsequently described the drugs' effects. Whereas the patients had said they expected the drugs to take their symptoms away, their subsequent description of the drugs' actual effect was consistent with the drugs having helped them deal with or detach themselves from the symptoms, rather than eradicating them altogether.

Kapur's aberrant salience framework allows us to get away from an either/or approach to drug and psychological treatments for schizophrenia. Kapur explains that we all have self-correcting mechanisms and that most psychological therapy is not about the therapist casting a healing spell; rather it involves the therapist helping patients use their own coping mechanisms. In the case of schizophrenia, the antipsychotics can reduce the aberrant salience while cognitive behaviour therapy can be used to examine how the patient has come to hold their beliefs, and to help them gradually undergo a reality check. The 'drugs provide a neurochemical milieu for a psychological resolution', says Kapur.

Everyday stresses

One psychologist who has been inspired by Professor Kapur's framework is Dr Inez Myin-Germeys of Maastricht University. 'Dopamine has been around a long time in psychosis research, but little attention has been focused on mechanisms – the actual psychological effect of having an excess of

THE PRACTICALITIES

How easy is it for psychologists to measure levels of neurochemicals? One of the reasons Dr Myin-Germeys and colleagues measured dopamine reactivity in the lab, before participants went away and recorded their daily experiences, is because dopamine is so difficult to measure. In fact they actually measured a dopamine metabolite called plasma homovanillic acid, which can be used as an indicator of central dopamine activity. 'In the future I want to use better measures of dopamine reactivity, for example using PET (positron emission tomography) brain scanning, and compare this with participants' daily life experiences,' says Myin-Germeys.

Professor Kapur says he plans to give healthy participants pro-dopamine drugs like amphetamine or anti-dopamine drugs like haloperidol and see how participants' motivation and learning changes, and how this relates to changes in the brain using neuroimaging.

Cortisol levels can be measured in small samples of saliva, so this is obviously much easier than working with dopamine. However, there are other difficulties. Emma Adam explains: 'The biggest concern in relation to cortisol research is its strong diurnal rhythm – time of sampling has a huge impact on the level of cortisol that you see.' In fact, 60 to 70 per cent of the variation in cortisol is due to the time of day, and how cortisol changes across the day is of interest in research, so it's crucial researchers take time of day into account in their analysis. Because the measure 30 minutes after waking is so important, it's also vital that participants collect their saliva at the time they are asked. 'We use an electronic monitor, also used in pill trials, which registers the exact time that participants open a small bottle to retrieve the supplies they need for sampling,' says Adam.



Dr Inez Myin-Germeys

Dopamine – little research had looked at the psychological effects of an excess

this neurotransmitter. Then Kapur's theory on salience came along,' she says.

It's been established for some time that stress, sometimes in response to small, everyday events, can play a key role in the onset of many people's psychotic experiences. But why stress should be linked to psychosis in some people but not others has, until recently, remained unknown.

Kapur's framework suggested to Myin-Germeys that dopamine could underlie the physiological mechanism by which stress is linked to psychosis in some people but not others. However, the trouble with investigating this idea is that most patients with schizophrenia are on antipsychotic medication that would interfere with any dopamine measures. To get around this, Myin-Germeys has studied the first-degree relatives of people with psychosis. These relatives are medication free but are known to have a higher than usual incidence of subtle psychosis-like experiences.

Myin-Germeys and her colleagues invited 50 first-degree relatives of people with psychosis and 50 controls to the lab to measure their dopamine reactivity. The researchers gave the participants an intravenous infusion of a glucose-like substance that made them feel sweaty and shaky (a physical stressor), and they measured

what effect this had on their dopamine levels. The plan was to see whether this characteristic – participants' dopamine reactivity – would be related to whether everyday stresses appeared to trigger psychotic-like experiences in them. So 10 times a day for six days, whenever a special wrist-watch they were wearing beeped, the participants recorded any stresses and psychotic-like experiences they had (for example, seeing things that others couldn't see, or feeling afraid of losing control) and these records were then compared with their dopamine reactivity.

The researchers found that in the relatives, but not the controls, those participants with higher dopamine reactivity showed a greater psychotic

reaction to everyday stresses. 'It's a test of Kapur's theory' says Myin-Germeys. 'It shows that an increase in dopamine reactivity is involved in how people psychologically react to stressors in normal daily life, so it fits perfectly with his theory that if you have a hyperactive dopamine system, your salience attribution is



Professor Shitij Kapur

OXYTOCIN AND TRUST

In another example of research at the interface between psychology and neuropharmacology, a team of Swiss researchers, including psychologist Markus Heinrichs, presented compelling evidence in 2005 that the neurochemical oxytocin underlies trust. In an economic game, investors chose how much of an initial budget of 12 monetary units to pass to a trustee. Any money they passed was tripled by the bank, but there was no guarantee the receiving trustee would share these proceeds with the investor. The researchers found that 45 per cent of investors who had inhaled oxytocin chose to invest the full amount, compared with 21 per cent of investors who inhaled a placebo. The same effect was not observed when investors gambled with a random mechanism rather than another player, suggesting oxytocin specifically affects perceived social risk (i.e. trust), not risk perception in general. Moreover, there were no changes in participants' mood and calmness after inhaling oxytocin, suggesting the apparent effect on trust was not caused by non-specific psychological effects. The researchers concluded: 'Our findings may have positive clinical implications for patients with mental disorders that are associated with social dysfunctions, for example social phobia or autism.'

Oxytocin might also be involved in mind-reading. In a study published just this year, Heinrichs and colleagues found oxytocin helped improve the ability of 30 men to read emotions conveyed in other people's eyes.

different or increased and seems to be triggered by environmental factors, including stress.'

However, the story isn't entirely straightforward because the relatives of people with psychosis didn't have greater overall dopamine reactivity than controls. It's just that it was only in the relatives that dopamine reactivity predicted a psychotic reaction to stress. Myin-Germeys explains: 'So in people who are vulnerable to psychosis, then dopamine reactivity is involved. But the fact dopamine reactivity was no higher in relatives shows other systems must also be involved... that's something I want to look at next.'

A helpful/harmful hormone

Another chemical that researchers are putting under the psychological magnifying glass is the stress hormone cortisol. In response to perceived stressors in the environment, a series of chemical signals

originating in the brain causes the release of cortisol from the adrenal gland into the bloodstream. Once released, cortisol has a wide range of effects on the body and circulates back to influence the brain. Studies in the past have tended to average cortisol readings over several days, but last year Dr Emma Adam at Northwestern University and colleagues looked closely at how older people's daily experiences affected their cortisol levels on a day-by-day basis, and how in turn these cortisol fluctuations affected the way they felt. By linking people's feelings and daily experiences with their biology, the research has clear echoes of Kapur's and Myin-Germeys' work with dopamine.

For three days, 156 participants completed diaries each night detailing experiences they'd had that day, as well as choosing a description for how they were feeling, such as lonely or energetic. To measure cortisol levels, the participants took their own saliva samples before going to sleep, upon waking, and 30 minutes after waking. This latter measure was particularly important. 'When you wake up, your cortisol levels are high and then there's an extra cortisol boost called the "cortisol response to awakening" that occurs between wake up and 30 minutes after waking,' explains Adam. 'We're making the argument that this is functional, that this happens because it's responding to and preparing you for the anticipated demands of the day.'

Supporting this idea, Adam and colleagues found that participants who felt more sad, lonely or overwhelmed at the

end of one day had a larger 'cortisol response to awakening' the next morning. 'We're arguing that the function of this is to give you an additional burst of energy that gets you out of the door to engage with others and have a better day the next day', says Adam. The day-by-day design of the study meant the researchers were able to show that this high-cortisol response in the morning was linked to the person's feelings the previous evening, rather than it being a pervasive, genetically-determined characteristic of the individual. Indeed, if the day after feeling lonely was a better day, the researchers found participants' early morning cortisol boost dropped back to a lower level the following morning. Adam's explanation for the functional role of the early morning cortisol boost was further supported by the finding that participants who had low cortisol levels in the morning reported having lower energy/greater fatigue throughout that same day.

Given that cortisol has been linked with stress-related ill health by many studies, some people might be surprised by the interpretation that higher morning cortisol can serve a beneficial purpose. 'It's a confusing hormone, in that it can be both helpful and harmful,' says Adam. 'It needs to be in the moderate range. If cortisol is either too high or too low over a long period of time, this can contribute to negative health outcomes. It is supposed to help mobilise your body and brain to deal with the occasional stressful demands of daily life. If you fail to increase this hormone when needed, or elevate it too frequently in response to frequent or chronic stress, it can become problematic.'

Adam believes that her findings carry a positive message for therapists and their clients. After all, she didn't find that lonely people have higher cortisol all the time, rather that its level changed in response to how they were feeling. She says: 'This gives an indication that this system is malleable, that there is the possibility that if you improve your experience, you're going to have a reduction of this hormone.' In other words, if we take steps to improve our experiences and reduce our negative emotions, our bodies will respond. 'I think it helps to give people a message that it's important to take care of themselves, that loneliness is not just unpleasant to you, it's something that has potential biological and health implications – but it turns out if you do something about this, you can reverse

those potential pathways to negative outcomes.'

Intricately intertwined

Research of the kind conducted by Shitij Kapur, Inez Myin-Germeys and Emma Adam demonstrates why it is important for psychologists to appreciate the two-way relationship between biological and psychological factors. It's right that people are wary of reductionist accounts of mental illness, but this new research is showing that how people respond to their daily experiences can affect their biology, and this in turn can have a profound effect on their mental well-being. As Emma Adam says: 'Sometimes it's biology influencing emotion, in other cases it's emotions affecting biology, so they're intricately intertwined; to focus solely on one or the other is not helpful. That's not to say every therapist needs to go out there and start measuring brain chemistry and stress hormones in their patients as some sort of clinical indicator, but knowing about the interplay between biology and psychological experience can be a vital tool in talking with patients.'

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