All in the mind?

New molecular insights might bridge the gap between the effects of psychiatric therapy and drugs

After the death of Sigmund Freud (1856–1939), the father of psychoanalysis, psychiatry underwent a schism and has remained divided ever since. Broadly, one camp has promoted the use of drugs as crucial to the treatment of behavioural problems such as addiction and depression, whereas the other has regarded drugs as a last resort, only to be used after cognitive therapies have been tried and have failed. This dichotomy has also influenced our understanding of behaviour and behavioural disorders: some argue that psychological problems are rooted in molecular neurobiology—and are thus amenable to drug intervention—whereas others contend that events at the molecular level alone cannot explain the complex psychotic conditions from which humans can suffer.

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This rift could be about to be healed in the light of growing evidence that both cognitive therapies and the drugs used to treat psychiatric disorders act through the same pathways and cause similar changes in behaviour and neurochemistry. As a result, there is increasing optimism among neurobiologists that the whole foundation of psychiatry—and our understanding of behaviour—could be transformed into a more exact science. However, this would not be at the expense of traditional therapy; although it is likely that biomarkers and imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) will be used increasingly to diagnose neurobiological changes and to assess

treatments of all types, the only true measure of success for behavioural therapies or psychoactive drugs will remain an increase in the quality of life for individual patients. Clinical practice will therefore continue to focus on the dialogue between patient and psychoanalyst in the Freudian tradition—at least for the foreseeable future—albeit with increasing assistance from neurobiological techniques. “We can’t write off Freud just yet, with his view that life should be just love and work,” cautioned Markus Heilig, Clinical Director of the US National Institute on Alcohol Abuse and Alcoholism (NIAAA; Bethesda, MD, USA). “The fact remains that the appropriate level of psychological health is functionality in the workplace, family and emotional life.”

Heilig believes that recent neurobiological research will help to treat victims of stress, addiction and other disorders more effectively, in order to return them to a functional level of psychological health. This would be in addition to psychoactive drugs that have shown measured success against a range of disorders such as Prozac® (fluoxetine; Ely Lilly, Indianapolis, IN, USA), which is used for treating depression, or methadone, which is prescribed to treat heroin addiction. “But these have all been serendipitous discoveries so far,” Heilig commented. “Now, the new body of neurobiological work is ready for translation into therapies and new medications much more quickly.” At the same time, the increasing use of functional imaging using PET and fMRI to monitor the progress of patients, whether treated by medications, psychoanalysis or a combination of both, is helping physicians and psychiatrists to treat their patients more effectively.

This convergence of behavioural conditioning and drug treatment is a logical development given that a growing body of research indicates that

both operate through the same neuronal pathways. As Rosario Leopardi, head of the molecular psychiatry research group at the Karolinska Institute in Stockholm, Sweden, put it, “a symbol or a word are as good as a chemical. In practice, voice, sound and vision all act through a neuromediator.” By way of example, Leopardi pointed out that anything that causes us to feel fear, or that alleviates it, must operate through the amygdala—an almond-sized region of the brain that regulates emotional state and is implicated in a range of mental disorders. “Based on available data, anything that scares you does it through activation of the amygdala,” he said. Similarly, any successful treatment, whether using drugs or cognitive therapies, would have to affect the amygdala.

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Clearly, behavioural conditioning and drugs must begin by activating different molecular pathways and, presumably, converge later at common regulators of brain activity such as the amygdala. In fact, recent work by Nobel Prize winning neurobiologist Eric Kandel at Columbia University (New York, NY, USA) provided some of the first compelling evidence that behavioural and drug therapies are both mediated through the same target sites, but that they each approach these sites by different pathways (Pollak *et al*, 2008).

By using mice, Kandel showed that conditioning against fear had an effect similar to the commonly prescribed antidepressant Prozac. The mice were split into two groups,

one of which was conditioned to associate an audible tone with an electric shock, whereas the other group heard the tone but did not receive a shock. As a result, the mice in the second group became safety conditioned. The mice from both groups were then placed in a pool of water from which there was no escape; the swim test is widely used for the animal testing of antidepressant drugs, which tend to reduce panic in mice forced to stay in the water. Kandel and his co-workers found that the safety conditioning, similar to the antidepressants, alleviated fear as well as symptoms of depression.

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This result was expected; however, the intriguing discovery was that the safety conditioning altered levels of dopamine and neuropeptide transmitters in the mouse amygdala, in a similar manner to Prozac. But, unlike Prozac, conditioning had no

effect on serotonin levels, which led Kandel to conclude that behavioural treatment of fear works through at least some of the same neuronal systems as pharmacological antidepressants, but reaches the targets through different molecular pathways.

The next question is therefore whether behavioural therapy can emulate the effect of antidepressants and, if so, what are the implications for physical and mental health. After all, it is well known that some neurotransmitters—such as serotonin and dopamine—perform other functions throughout the body, including the mediation of inflammation. Successful behavioural treatments for depression might therefore have positive side effects for various inflammatory conditions.

Indeed, evidence that behavioural conditioning can have a direct impact on health comes from a recent Swedish study of more than 200 women suffering from coronary heart disease (Orth-Gomér *et al*, 2009). One group received normal care measures—such as the administration of aspirin—whereas the other group received additional cognitive therapy to alleviate stress, which included advice on self-help and coping with family and work

while recovering. The results after one year of treatment were significant: cognitive therapy led to improvements in various inflammatory-related measurements and to a threefold reduction in mortality. After an average of just over seven years, 25 women among the group who had received only normal care had died, compared with only eight of those who had also been given cognitive therapy.

The mechanisms involved were not clear; however, the results suggest that the reduction in stress caused changes in the levels of neurotransmitters and probably other molecules that also have a role in the immune system and in reducing inflammation. Elucidating these mechanisms will be an important research goal for the next few years, according to Heilig: “I do think that inflammation will enter the equation in the next few years, because it turns out that many molecules we thought were confined to the immunology domain, such as pro-inflammatory cytokines, are also hormones and affect neurons.”

This suggests that, just as cognitive therapy might improve general health, as it did among the Swedish women, it might also work the other way around. In

other words, a treatment for an inflammatory disorder might alleviate depression in some cases. This turned out to be the case among sufferers of the skin disease psoriasis, who were treated with an inhibitor of the pro-inflammatory cytokine TNF (tumour necrosis factor). Not only did the treatment reduce psoriasis, but it also alleviated depression, as measured by factors including mood, insomnia and anxiety (Tyring *et al*, 2006). Of course, the improved condition of the skin itself could have reduced depression, but the authors of the study pointed out that several patients whose psoriasis did not improve still enjoyed significant reductions in depression. However, the authors conceded that to study the effect on depression alone, it would have to be evaluated on patients without psoriasis or other inflammatory conditions whose improvement by itself might have an impact on mental well-being.

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In studies such as these, it is difficult or high impossible to observe in detail any molecular effects of either drugs or behavioural therapies. However, improved imaging techniques are making it possible to locate regions of the brain that respond to treatment, and to compare human brain responses with animal models by tracking electrical activity and blood flow. One study at Uppsala University in Sweden (Furmark *et al*, 2002) used PET to monitor the effect of treatment with the anti-depressant drug citalopram (Celexa, Citrol; Lundbeck, Copenhagen, Denmark) on blood flow in the amygdala, hippocampus and some other regions of the cerebral cortex among patients suffering from fear of public speaking.

All of the people in the study experienced panic just before and during speaking in public, which was accompanied by an increase in regional cerebral blood flow (rCBF) to the amygdala and other areas of the brain implicated in the fear response. Patients treated with citalopram were able to speak in public with little or no fear, and PET scans revealed a decreased rCBF response in those fear-related areas. The study provides more direct evidence that the same regions are involved in fear in the human brain as in mice and rats—the animals most extensively used for research in molecular psychiatry.

In fact, animals are still required for many experiments, given that human brains cannot be dissected after experiments to observe directly the effect of drugs or therapy in whole brain regions, as in Kandel's fear-conditioning study using mice. Yet, this raises the question of how reliable animals are for studying systems as complex as the brain. According to Heilig, the answer is that it depends on which mental condition is being investigated: “[i]f you look at the fear circuits, they are highly conserved—at least between mammalian species—and the predictive power of animal models is probably decent. So when it comes to anxiety and perhaps depression, we should be able to extrapolate from mice to humans. But, when it comes to psychotic disorders involving the cortex, such as schizophrenia, it becomes much harder. It is difficult to conceive of a psychotic rat.” Indeed, Heilig speculated that schizophrenia might be a uniquely human disease.

There is certainly little if any understanding of the evolutionary origin of psychotic disorders such as schizophrenia. Conversely, many of these disorders have genetic risk factors, which tend to be much more prevalent in some families than others. This finding allowed geneticists and neurobiologists to map specific alleles to abnormalities in the brain in sufferers of schizophrenia. For example, at the Camden and Islington Mental Health and Social Care National Health Service Trust (London, UK), Hugh Gurling and colleagues examined the relationship between the volume of select brain areas and the gene *PCMT1*, which is known to have a crucial role in schizophrenia (Gurling *et al*, 2006); people who have inherited a particular mutation of *PCMT1* have a 68% chance of developing schizophrenia (Datta *et al*, 2008). Gurling applied a technique called vortex-based morphometry to measure the volume of the orbitofrontal cortex grey matter in schizophrenia patients and found that patients with the *PCMT1* mutation had less orbitofrontal grey matter than those without. Some clues are also emerging about how *PCMT1* reduces grey matter; a recent study at the Johns Hopkins University School of Medicine (Baltimore, MD, USA) found that the *PCMT1* protein is a crucial component in the centrosome (Kamiya *et al*, 2008), an organelle that has an important role in DNA replication during cell division. In schizophrenic patients with the *PCMT1* mutation, this role is disrupted, which leads to abnormal cortical development.

Although the *PCMT1* mutation has an important role in schizophrenia, the disease clearly has several causes and seems to be largely, if not entirely, genetically determined. Even so, it might not be that the genetic abnormalities that cause it are unique to *Homo sapiens*; the complexities of the human brain may simply translate these flaws into distinctive psychotic conditions. As such, it might be that it is impossible to observe behaviour that could be recognized as psychotic in, for example, mice with similar mutations.

At any rate, there is plenty of scope left for the use of animal models in elucidating the role of structural proteins involved in psychotic disorders. But animal studies also remain important for another reason: although psychotic disorders might be largely genetically predetermined, conditions such as fear and anxiety are often acquired. As mentioned above, cognitive therapies to alleviate these types of acquired disorder seem to act on the same areas in the brain as drugs, albeit through different pathways. Fundamentally, epigenetic mechanisms must be involved and must cause changes in gene expression. According to Isabelle Mansuy at the University of Zurich's Brain Research Institute (Zurich, Switzerland), events such as stress are mediated by epigenetic changes and can be reversed through therapy, but can also be inherited by offspring in some cases. Mansuy and colleagues have shown that offspring of mice can inherit behavioural disorders induced by stress in their mothers.

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“This data is not published yet, so I prefer not to talk about it for the time being,” Mansuy commented. “But what I can say though is that, yes, the mechanisms involved are epigenetic and operate in germ cells. The genes implicated are multiple, we've identified a few which are known to be involved in the regulation of emotional processes. We suspect that similar mechanisms occur in Man and are currently checking this possibility in collaboration with psychiatrists at the University Hospital Zurich.”

It would be an important step forward for psychiatry if it were possible to target specific genes with drugs that could reverse deleterious epigenetic changes. At the same time, this and other work is reaffirming the value of cognitive therapies by showing that they have a genuine physiological effect. More detailed knowledge of how psychoactive drugs and cognitive therapies work will hopefully give psychiatrists a new and improved tool set to treat behavioural disorders. Ultimately, however, the value of any psychiatric therapy is still best measured qualitatively, as Heilig suggested: whether it restores mental health, even if that measure can be rather subjective.

REFERENCES

- Datta SR *et al* (2008) A threonine to isoleucine missense mutation in the pericentriolar material 1 gene is strongly associated with schizophrenia. *Mol Psychiatry* [doi: 10.1038/mp.2008.128]
- Furmark T, Tillfors M, Marteinsdottir I, Fischer H, Pissiota A, Långström B, Fredrikson M (2002) Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry* **59**: 425–433
- Gurling HMD *et al* (2006) Genetic association and brain morphology studies and the chromosome 8p22 pericentriolar material 1 (PCM1) gene in susceptibility to schizophrenia. *Arch Gen Psychiatry* **63**: 844–854
- Kamiya A *et al* (2008) Recruitment of PCM1 to the centrosome by the cooperative action of DISC1 and BBS4: a candidate for psychiatric illnesses. *Arch Gen Psychiatry* **65**: 996–1006
- Orth-Gomér K, Schneiderman N, Wang H, Walldin C, Blom M, Jernberg T (2009) Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease. *Circ Cardiovasc Qual Outcomes* **2**: 25–32
- Pollak DD, Monje FJ, Zuckerman L, Denny CA, Drew MR, Kandel ER (2008) An animal model of a behavioral intervention for depression. *Neuron* **60**: 149–161
- Tyring S *et al* (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind, placebo-controlled randomized trial. *Lancet* **367**: 29–35

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