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RETHINKING REHAB

Alcoholics Anonymous and its spin-off programmes have been helping people with addictions for decades. **Jim Schnabel** talks to the neuroscientists who are looking deeper into the approach.

In the depths of the Depression, in a Manhattan alcoholism clinic, a ruined Wall Street speculator named Bill Wilson had a vision. His room suddenly blazed "with an indescribably white light" and he experienced euphoria and a godlike "presence", followed by a "great peace"[1]. Like St Paul after his experience on the road to Damascus, Wilson soon turned away from his old, inebriated life and became an evangelist — preaching a radical, spiritual cure for alcoholism.

That cure grew into the modern addiction rehabilitation industry, which even today is dominated by Wilson's Alcoholics Anonymous (AA) paradigm and its 'twelve-step' approach to recovery. Perhaps unsurprisingly, given its spiritual origins, this approach has had an uneasy relationship with the evidence-based culture of medical research. Both perceive addiction as a chronic disease; but whereas scientists seek rationally targeted interventions to blunt drug cravings, AA and related programmes tend to feature group therapy, tearful confessions and the call to "surrender to a higher power".

In the past few years, however, these two cultures have been finding common ground. Neuroscientists have begun to recognize that some of the most important brain systems impaired in addiction are those in the prefrontal cortex that regulate social cognition, self-monitoring, moral behaviour and other processes that the AA-type approach seems to target. "A lot of the treatment programmes out there are targeting these systems without necessarily knowing that they are doing it," says Nora Volkow, director of the National Institute on Drug Abuse in Bethesda, Maryland.

Researchers are now searching for ways to boost these prefrontal systems even further — not to remove the need for twelve-step and other behaviourally oriented treatment programmes, but to enable people with addictions to get more out of them. "It completely changes the way that we look at medications," Volkow says.

Until recently, addiction researchers focused almost entirely on 'limbic' circuits in the brain that mediate fear and desire. These dopamine-fuelled networks are effectively hijacked by addictive drugs and behaviours so that the person ends up wanting, and compulsively seeking, little else but the next fix. Drugs such as methadone and naltrexone can blunt the activity of these circuits, but they are not a cure.

Impulse management

While doing neuroimaging studies at the Brookhaven National Laboratory in Upton, New York, in the 1990s, Volkow was one of the first researchers to suggest that abnormalities in the prefrontal cortices of drug users might weaken the systems that normally counteract drug cravings[2]. Since then, the prefrontal regions and their links to the limbic system have garnered more and more attention, and researchers are now attempting "a very extensive evaluation of how the different areas in the prefrontal cortex participate in the process of drug addiction", Volkow says.

The prefrontal cortex — the most recently

evolved set of structures in the brain and the one that most clearly differentiates humans from other species — is the headquarters for the circuits that help shape feelings and behaviour according to long-term goals, moral strictures and social cues. These systems are extensively wired into limbic regions, and are often portrayed as a 'braking' system to resist impulsive behaviour. The slow development of prefrontal structures after birth tracks the maturation of children into adults, and people whose prefrontal areas are damaged by trauma or stroke, for example, seem to have lost some control of the brakes and are apt to be childishly impulsive and uninhibited in their behaviour.

> "The inverse association between religion and addiction is one of the most unsung findings in the entire literature on drug and alcohol abuse."
> — Michael McCullough

With tools such as psychological tests and brain imaging, researchers have been finding similar braking problems associated with drug use and are starting to tease apart the mechanisms involved. Some have shown that people with drug addictions are poor at monitoring their own behaviour[3], making appropriate decisions and inhibiting impulses — and these behavioural findings have been matched to functional magnetic resonance imaging (fMRI) data that show reduced activity in the corresponding prefrontal areas. Animal studies have supported the human ones by showing, for example, that monkeys given cocaine swiftly develop prefrontal impairments[4]. And other researchers have found that stress, which frequently triggers drug use and relapse in people with addiction, seems to do so at least in part by shutting down prefrontal functions[5]. "We're really starting to understand the molecular basis of why this cortex falls apart with drugs of abuse, and during stress, and how those two interact," says Amy Arnsten at Yale University School of Medicine in New Haven, Connecticut.

If the cortex falls apart with drug abuse, then it may be impossible to recover from an addiction without putting it back together. In unpublished studies, Hugh Garavan and his colleagues at Trinity College, Dublin, have found that cocaine users and tobacco smokers who go through treatment and are able to stay abstinent for more than a year "seem to show hyperactivity in these prefrontal control centres" in fMRI images. Garavan says that this extra activity seems to be especially prominent during the first few weeks of abstinence, hinting at "a heavy reliance on these prefrontal centres to avoid falling off the wagon".

The recognition that prefrontal systems might need boosting in people with addictions has helped fuel a new interest in whether AA and similar behavioural treatments are already having these kinds of effects. "It behooves us to try to understand how [twelve-step approaches] link to what we're addressing in terms of intervention," Volkow told the annual meeting of the Society for Neuroscience in Washington DC last November. So far, these treatment programmes have been difficult to study formally, says Martin Paulus, a psychiatrist who is researching addiction at the University of California, San Diego. "It's very much a voluntary-based programme, with little standardization, and the whole programme thrives on anonymity."

But much of what is known about the AA approach suggests that it aims to protect or enhance prefrontal circuits. In the protected environment of a rehab centre, drugs and other cues associated with drug taking are gone and stressful situations that suppress prefrontal activity are minimized. Volkow notes that the feeling of ceding control to a higher power is also likely to "enhance your sense of security, decreasing stress and anxiety". Similarly, says Garavan, the confessions of bad behaviour and other "strategies that push users to become more aware of their drug-related actions presumably aim to boost their capacity for self-monitoring, which is largely a prefrontal function".

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Bill Wilson (left) set up Alcoholics Anonymous in 1935. Its twelve-step paradigm is widely used to treat addiction.

The social environment in rehab is another factor that works in part through prefrontal systems. "Our brains have evolved to be very sensitive to social cognition and social reinforcers," says Volkow. By putting people with drug addictions into a group with anti-drug values, "you are providing them with a very powerful reinforcer", she says.

Spiritual control

And then there is religion, which has been shown to have a strong inverse association with drug addiction. Psychologist Michael McCullough, who studies religion and behaviour at the University of Miami in Florida, calls this inverse association "one of the most unsung findings in the entire literature on drug and alcohol abuse". Both adults and children deemed religious by various measures "drink, smoke and do drugs less often", McCullough says. "If they get into trouble with drinking and drugs and smoking, they're more likely to be able to get away from those problems."

McCullough suggests that when a person commits to any cultural system that regulates behaviour, the psychological effort to conform strengthens the brain systems that mediate self-monitoring and self-control. "What makes religion unique, I think, is that the code of conduct isn't just laid down by your parents or your friends or your principal at school, but ostensibly by the individual who is superintending the Universe, so it has an extra moral force." Some religious rituals, he says, have been shown to provoke enhanced activity in prefrontal regions[6]. "It's as if certain forms of prayer and meditation are pinpointing precisely those [prefrontal] areas of the brain that people rely on to control attention, to control negative emotion and resolve mental conflict."

However the twelve-step strategies actually work on the brain, "there is now excellent documentation that those who attend AA-type programmes regularly do very well by anyone's standard", says Thomas McLellan, director of the Treatment Research Institute in Philadelphia, Pennsylvania. The problem, McLellan says, is that the vast majority of people who enter such programmes do not go regularly — they drop out after a few days or weeks — and are more than likely to relapse.

Anna Rose Childress, a psychiatrist at the University of Pennsylvania School of

Medicine in Philadelphia, has encountered a similar resistance to treatment in the crack cocaine users she has studied. In her lab she uses a cognitive behavioural training technique — like "prefrontal pushups", she says — that tries to make these users more aware of their drug-related actions and the consequences. But her studies indicate that "most of our cocaine patients are not great at it".

Results such as these raise what Childress and others call the "chicken or egg question" — is drug use the cause of users' prefrontal problems, or do they have pre-existing defects that make them susceptible to addiction? As Garavan puts it: "A lot of people might be able to enjoy drugs but there's only a certain percentage who actually go on to become addicted. And maybe part of that is because these people lack that prefrontal-mediated control over behaviour."

Some research already links prefrontal-related conditions such as impulsivity and attention deficit hyperactivity disorder (ADHD) to a heightened risk of later drug use. But to really start answering the chicken or egg question, says Childress, "you would need some good large-scale developmental studies for one thing; you would like to look at adolescents before they've ever touched drugs". Garavan and several dozen other European researchers are now participating in a project that aims, in part, to do just that. Known as IMAGEN and begun in late 2007, the five-year, €10-million (US$14-million) project funded by the European Commission will ultimately enrol 2,000 14-year-olds and follow them through their late teens. Principal investigator Gunter Schumann, a psychiatrist at Kings College, London, says that the testing will include fMRI and structural MRI, as well as a full genome scan. He expects to start publishing findings in the next few years.

Quenching the flame

In the meantime, researchers are pursuing other ways to boost prefrontal systems — and medicines for ADHD seem an obvious place to start. Attention-enhancing drugs such as methylphenidate and atomoxetine boost the activity of key receptor systems in the prefrontal cortex, in particular those for noradrenaline and dopamine. Some evidence already suggests that patients with ADHD are less likely to go on to abuse drugs if they are receiving medication for their condition[7]. And earlier this year, a team led by Daina Economidou at the University of Cambridge, UK, reported that atomoxetine helped rats with an ADHD-like impulsivity to resist a relapse to cocaine-seeking[8].

The National Institute on Drug Abuse has also been supporting studies of cognitive and behavioural strategies, and Volkow says that she is particularly enthusiastic about an approach that involves "real-time fMRI feedback". Developed by researcher and entrepreneur Christopher deCharms earlier this decade, the technique involves placing drug users in an fMRI machine and showing them a symbolic representation — a flame — of the fMRI-measured brain activity that corresponds to their cravings. The users are then asked to apply their own cognitive exercises, such as imagining their child is with them, to quench their cravings and douse the flame. After half a dozen sessions with this feedback the user will, in principle, develop cognitive circuitry that is more efficient at suppressing craving and that can then be used in ordinary life. A version of the technique, used for pain relief, has already shown some efficacy in a small clinical trial[9], and deCharms and his Silicon Valley start-up, Omneuron, are currently running a small trial in smokers — with plans for a follow up with some of Childress's cocaine users.

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AA-type group behavioural therapy may tap into brain regions neuroscientists think are crucial in overcoming addiction.

For some people, even the most sophisticated therapies may not be enough to rescue a prefrontal cortex that has been damaged by genetics, development and perhaps decades of drug use. "It's like somebody who has had a stroke and is paralysed," says psychologist Antoine Bechara at the University of Southern California, "and you tell them, well, you should walk, you should exercise. But the part of the brain that allows them to do that is not there and they just cannot do it."

To Bechara, a more efficient approach would be to protect and strengthen these critical brain regions as they are developing. As an example, he cites preliminary data from a study in China. "There are children who grow up whose parents make all the decisions for them, and others who are encouraged to make decisions and are rewarded or punished for their bad decisions," he says. "The latter children grow up to show better performance on measures of decision making, and there is even a hint of evidence from fMRI that the kids with that latter kind of parenting style have better prefrontal cortex function."

Even for those beyond the influence of parenting style, researchers hope that a little lift in prefrontal efficiency could go a long way. Such a boost, says Paulus, could be "the critical piece that helps prevent the person from getting onto a very destructive pathway".

The question now is how best to give that boost. As researchers come to understand the neural mechanisms of addiction better, the twelve-step approach may give way to more secular strategies. But it seems unlikely that all behavioural approaches will soon be replaced by a pill. "I think most researchers would say, and I know I would say, that medicines should be used in the context of a good behavioural programme," says Childress, "because a person is essentially trying to restructure a lot of behaviour, and the more support that you can provide for that, the better." ■

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