

The malign misuse of neuroscience

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In discussing the possible hostile misuse of the ongoing revolution in the life sciences, George Poste famously suggested that we need to think “beyond bugs” and to consider what he called “the brain bomb”. He explained, “as we begin to understand the exquisite molecular mechanisms that regulate this remarkable structure called the human body ... the ability to understand those circuits means that simultaneously we gain the capacity to scramble them”.¹

Certainly there is a strong opinion in the commercial world that there will be rapid developments in applicable neuroscience in coming decades,² and it is also well known that there is keen military interest in the development of new “non-lethal” weapons based on such discoveries.³

Many scientists and other observers of the revolution in the life sciences may, however, think that little has changed since the days of the middle of the twentieth century when the first crude incapacitants (such as the fentanyl derivative⁴ used to break the Moscow theatre hostage siege) were developed on the back of the initial detailed discoveries of chemical means to help people with mental illnesses. Poste clearly does not agree. He believes an understanding of brain circuits, which allows us to scramble them, means that “you can engineer ... a complete spectrum of activity from transient immobilization ... to catastrophic effects which can be acute or chronic”.⁵

This article aims to demonstrate that point by reference to two specific examples of our increasing knowledge of the brain. There are many such examples that could be described so it must be understood that these are merely illustrative of the general problem of the increasing extent of our dual-use science and technology. We must begin, however, with a brief review of the basis of our knowledge of the nervous system.

Structure and function in the nervous system

Only in the last few centuries has the link between the brain and behaviour become clear, and only at the end of the nineteenth century was it demonstrated that the nervous system was made up of billions of separate nerve cells or neurons. We now know that during evolution complex networks of such neurons have developed in order to effect certain behaviours. Whilst the neurons of the central, peripheral and autonomic nervous systems vary enormously in form and function, they can be classed into three broad groups: *sensory neurons*, which convey information into the central nervous system; *effector neurons*, which carry information out of the central nervous system to muscles

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and other effector organs; and *interneurons* within the central nervous system, which link the sensory and effector neurons and also have links with one another.

Information is conveyed *within* individual neurons by electrical means—generating nerve impulses that can be recorded and displayed on an oscilloscope. In the twentieth century it was shown that information is conveyed *between* neurons predominantly by chemical means. When a nerve impulse (an action potential) travelling along the long extension (axon) of a neuron arrives at a junction (synapse) with another neuron, it causes the release of a neurotransmitter chemical from the pre-synaptic cell. This chemical affects the electrical properties of the post-synaptic neuron through its interaction with specialized receptor proteins embedded in the surface membrane of the post-synaptic cell. It has been shown that there are numerous kinds of neurotransmitter chemicals that, depending on the specific receptors involved, can either cause an electrical change that enhances the possibility of an action potential occurring in the post-synaptic cell or, alternatively, decreases that possibility. Various chemical mechanisms ensure that the neurotransmitter is cleared from the synaptic area, so that its effect does not persist and so that another action potential in the pre-synaptic neuron can exert its effect in turn.

This then is the basis for modern insights into how the brain—and therefore behaviour—can be manipulated by chemical means. Clearly, as our understanding of the neuronal circuits underlying specific behaviour increases, and we understand more about the neurotransmitters and receptors functioning in such circuits, we have more chance of helping people who are suffering from various malfunctions of the nervous system (mental illnesses). It has to be accepted, however, that such information may be misused by those with malign intent.

POST-TRAUMATIC STRESS DISORDER

According to the standard *Diagnostic and Statistical Manual of Mental Disorders* you have Post-Traumatic Stress Disorder (PTSD) if:

You have been exposed to a horribly traumatic event that made you feel extremely fearful, helpless, or terrified.

You keep reexperiencing the event in different ways, such as upsetting memories or nightmares; flashbacks that it is happening again; or having a severe reaction whenever you are exposed to anything that reminds you of it.

You avoid things that are associated with the traumatic event; cannot remember the details of what happened; feel detached from everyday life; or feel like you will never have a normal life again.

You are jumpy and hypervigilant, have trouble sleeping, have angry outbursts, or have trouble concentrating.

These symptoms persist for at least a month and cause either severe distress or problems with school, work, or other people.⁶

The human species has evolved mechanisms to ensure that dangerous events are well remembered for the obvious good reason of avoiding such events, or taking great care about them, in the future. If this response gets out of hand we call it PTSD, and it clearly causes great distress to those who suffer from it. There is every reason to try to understand how it comes about and to find better ways of dealing with it.

It is not too difficult to discern that PTSD involves at least two components: learning and memory. These concepts may be defined in this way: the acquisition of reproducible alterations in behaviour as

a result of particular experiences is *learning* whereas *memory* is the storage of the altered behaviour over time. We are clearly dealing here with learning about aversive events and strengthening (consolidation) the memory of such events. The basic elements of the system for dealing with fearful events is built into all mammals so if we hear a loud explosion we will exhibit a startled response and freeze momentarily before the “fight or flight” response kicks in.⁷ As one of the main investigators of the fear response, Joseph LeDoux, explained:

In a situation of danger, a variety of physiological responses occur. Blood is redistributed to the body parts that are more in need (the muscles). This results in changes in blood pressure and heart rate. In addition, the hypothalamic-pituitary-adrenal, or HPA, axis is activated, releasing stress hormones. In general, the body is readied to move quickly. In addition, the brain activates the release of natural opiate peptides, morphine like substances that block the sensation of pain ...⁸

It is possible to gain much insight into the human fear system from investigations of those in other mammals, like the rat.

It is relatively easy to study the impact of fear on the rat through what is called classical fear conditioning. The rat is repeatedly subjected to a sound (which it does not fear) followed by a mild electric shock (to which it does react with fear). Soon it learns to react to the sound alone in anticipation of the shock. Investigators like LeDoux knew that sound picked up in the ear is processed in the auditory mid-brain, then the auditory thalamus and finally in the auditory cortex (the highest relevant level of the brain).

Surprisingly, when lesions were made in the auditory cortex it was found that rats could still associate the shock and sound and were therefore reacting with fear to the sound alone. The auditory cortex is clearly not required to support such behaviour. Further investigation showed that lesions in either of the sub-cortical levels (auditory mid-brain and auditory thalamus) eliminated the fear conditioning. The information was obviously being processed somewhere beyond the thalamus, but not in the auditory cortex, in order that the fear reaction occurred. This location was found to be the amygdala region of the brain—which was not too surprising since the amygdala has been known for years to be important in emotional responses. LeDoux continued his explanation as follows:

The low road, or the thalamo-amygdala pathway, is a quick and dirty system. Because it doesn't involve the cortex at all, it allows us to act first and think later. ... We freeze first, and that gives us a few seconds to decide what to do: Run away? Hold still? Try to fight?

If we are in a forest and see a stick that might possibly be a snake we are better reacting immediately as if it were indeed a snake. However, “The cortex—the high road, so to speak—also processes the stimulus, but it takes a little longer”. While the amygdala pathway prepares for action, the cortex pathway is simultaneously processing the information, and if it decides that what is seen is actually a stick and not a snake little effort is wasted as it can switch off the emergency response. So the amygdala is involved in the learning process. However:

In addition, there is a strong consensus that the amygdala is involved in mediating the effects of emotional arousal on memory. Findings of many studies indicate that the amygdala mediates the consolidation of long-term explicit memories of emotionally arousing experiences by influencing other brain regions involved in memory consolidation.⁹

It is this second process of memory consolidation that is surely of more interest in relation to PTSD.

A variety of evidence shows that the amygdala is not the site of long-term memory. For example, “[l]esions of the amygdala ... induced between one week and one month after aversive training do not block inhibitory avoidance performance”.¹⁰ So something more complex is happening than the amygdala operating in isolation. In fact, the system is very complex and is far from completely understood. Enough is known, however, to suggest that biologists will decipher it rather quickly.

It is well known that under stress the hypothalamus (the central link between the nervous system and the hormonal system of the body) through a complex process causes the secretion of glucocorticoids (steroids). At the same time the sympathetic (alerting) part of the autonomic nervous system activates the secretion of adrenaline. These two agents, glucocorticoids and adrenaline, have significant effects on the body, but they also affect the functions of the amygdala. There is considerable evidence that adrenaline, despite not being able to pass the protective blood-brain barrier, still has an indirect impact, which leads to enhanced output of a closely related neurotransmitter known as noradrenaline in the amygdala.¹¹

However, the noradrenaline does not act alone in this respect. The glucocorticoids released also have an effect in the consolidation of memory of stressful events. Glucocorticoids are able to pass the blood-brain barrier and there they have multiple effects. In particular, glucocorticoid effects on memory consolidation require them to act on the amygdala. Infusion of glucocorticoid agonists (substances that have the same effect) into the amygdala after training enhances retention whereas infusion of antagonists (substances having a blocking effect) impairs retention. Again it can be concluded that the amygdala is the location for the impact of glucocorticoid enhancement on memory consolidation.¹²

A full account of the circuits involved in the total stress response will be very complex,¹³ but it is clear that the amygdala is on one of the pathways leading to the initial readiness of the body to respond to danger signals. Subsequently, input from the body leads to noradrenaline and glucocorticoid activation of cells in the amygdala, and output from the activated cells has a considerable impact on the enhancement of memory consolidation by other brain structures. Furthermore, consolidation enhancement via the amygdala can be interrupted by the use of chemical antagonists that interfere with these processes in the amygdala.

What then does this have to do with treatment of people suffering from PTSD? It has been found, first, that less technically detailed studies on humans produce similar results to those on animals.¹⁴ Neuroimaging also shows that the amygdala is selectively activated when negative emotional stimuli are being processed and in fear conditioning. This and much other evidence support the view that the amygdala plays a similar role in humans to that in animals in dealing with frightening situations.

Whilst the events are much more complex than in animals, it can be considered that noradrenaline neurotransmission is crucial in humans too because very traumatic events would lead to overproduction of the transmitter and thus overconsolidation of the memory of these events. As the traumatic memory causes the events to be relived in flashbacks and nightmares a feedback system could therefore lead to the further consolidation of the memory as the body responded again and again to the stress.

This idea of a direct relationship between noradrenaline and memory for emotional events has been tested in humans. Healthy subjects were either given a placebo or propranolol (which passes the blood-brain barrier and opposes the action of noradrenaline) one hour before viewing a series of either neutral or emotionally stressful scenes. One week later people who had received the placebo had significantly better memories of the emotional slides but those who had received the propranolol did not remember them any better than the neutral ones.¹⁵

Such results have obviously led to efforts to prevent people from developing PTSD, in one example giving victims of car crashes propranolol quickly after the event. Some observers, however, are concerned that such treatment might be used to enable people to carry out dreadful actions and retain no

memory of them. Dr Leon Kass, chairman of the President's Council on Bioethics in the United States, has been quoted as saying "It's the morning-after pill for just about anything that produces regret, pain, or guilt."¹⁶

A national co-ordinator for Vietnam Veterans Against the War agreed and argued that such treatment could "make men and women do anything and think they can get away with it". A different possibility, of course, is that those with malign intent might find means—through a chemical agent—to enhance PTSD, not prevent it. Imagine how debilitating it would be for any organization—civil or military—if a large percentage of its members were made very susceptible to PTSD even in relation to relatively minor stressors?

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NARCOLEPSY

We have discussed something of the neurobiology of fear and cognition—but such higher functions rest on a whole set of more automatic homeostatic functions that maintain the body in its normal state. No animal could operate without effective regulation of, for example, its temperature or blood pressure. These kinds of functions are normally regulated from centres in lower parts of the brain near the junction with the spinal cord. Here we will consider an aspect of one regulatory system—sleep—and, in particular, one of its malfunctions, *narcolepsy*. Before discussing narcolepsy and how its investigation will likely lead to means of helping sufferers but also open up new roads to misuse, a brief review of modern knowledge of biological clocks will be necessary.

Many of our basic physiological functions exhibit a circadian (daily) rhythm. Most noticeably, we tend to sleep each night for about eight hours, but other functions—core temperature and production of pituitary hormones, for example—also exhibit such a rhythm. If sensory cues, most importantly light, are eliminated then our sleeping/waking cycle will elongate from twenty-four to about thirty hours. It is therefore clear that sensory inputs affect the basic circadian cycle, but what has been dramatically demonstrated recently is that the basic rhythm is driven by an internal clock located in a group of nerve cells (the superchiasmatic nucleus, SCN) of the front part of the hypothalamus. The output from this intrinsic clock then flows to complex circuits in other parts of the brain to regulate the various circadian cycles. Light input direct from the retina synchronizes the output of the SCN with the twenty-four-hour cycle.¹⁷ What is particularly important is not only that the genetic basis for the cyclic form of output from the SCN (with neuronal firing peaking during the day) has been elucidated, but how this output is integrated from the single cell through the SCN, the brain and then the behaving animal is also increasingly being understood.¹⁸ From the neurobiologists' viewpoint, it is also crucial to note that the role of the different neurotransmitters in circuits governing the various physiological functions is being steadily clarified.¹⁹

Sleep, of course, is not just a quiescent state the opposite of wakefulness. During the second half of the last century a great deal was learned about what happens when we sleep from recordings of the electrical activity of the brain picked up from electrodes placed on the scalps of volunteers. When we are awake these electroencephalography (EEG) recordings are of low amplitude and high frequency. When we fall asleep we pass through four phases of what is called slow wave sleep in which the EEG recordings have high amplitude and low frequency. If awoken from such sleep, people are confused, find it difficult to think clearly and easily go back to sleep. However, at about ninety-minute intervals a quite different type of sleep appears. This type of sleep is called rapid eye movement sleep (REM) or paradoxical sleep (because the EEG resembles that of the awake state). In this kind of sleep people dream and muscle tone is absent apart from the extraocular eye muscles producing rapid eye

movements.²⁰ Again, the mechanisms underlying this behaviour are being elucidated—even if we still cannot explain *why* we sleep.

Despite much effort to find cures, there are many people who suffer from sleep disorders such as insomnia, obstructive sleep apnoea and narcolepsy so there is every good reason for further investigation of the underlying neuronal mechanisms.²¹ Narcolepsy is characterized by four essential features:

... excessive daytime sleepiness (EDS), catalepsy (sudden loss of muscle tone in response to strong emotion such as laughter or anger), hypnagogic hallucinations (dream-like experiences occurring at sleep onset), and sleep paralysis (the inability to move while falling asleep or upon awakening)²²

The total amount of sleep and REM sleep is of the same order as in people without narcolepsy but, clearly, the control mechanism is severely disrupted with two main problems: “first, an inability to maintain wakefulness, and second, intrusion of REM sleep into wakefulness or at sleep onset resulting in hallucinations, sleep paralysis, and possibly catalepsy”.

Whilst this condition is quite widespread and debilitating, until recently very little was known about its causation. It was known that some dog families exhibited very similar symptoms to those of human narcolepsy, and this suggested a genetic basis for the disease. However, as there was also a strong link with aspects of the immune system, an autoimmune disorder was also strongly suspected and this, of course, might have an environmental trigger.

This whole field of research was revolutionized over a few years at the turn of the century through the discovery of two new transmitters produced by cells of the hypothalamus. These new transmitters are called hypocretins (Hcrt-1 and Hcrt-2), and are clearly the key to understanding narcolepsy and a good deal of the normal sleep mechanism. The dog narcolepsy cases are associated with genetic mutations of this system, mice with targeted deletions of the gene for these transmitters display symptoms of narcolepsy, and the majority of humans with narcolepsy and the associated immune system characteristics lack hypocretins in their brain.

The hypocretins and their associated receptors were discovered in 1998.²³ Progress in elucidating the nature of narcolepsy has been phenomenal since these discoveries. Human Hcrt-1 and Hcrt-2 are very similar to those found in other mammals. These transmitters have been strongly conserved during evolution, suggesting important functions. In all experiments carried out so far, hypocretins have had excitatory effects on post-synaptic cells. For example, the brain noradrenergic neurons, which are important components of the arousal and vigilance systems, are densely packed with receptors for hypocretins.

Narcolepsy affects twenty to sixty people per 100,000 of the population in western countries. This is about the same level of incidence as Parkinson’s disease or multiple sclerosis, but unlike those diseases it usually begins in the teens or twenties when it is very debilitating at a crucial formative period and continues to be so for many years. At present most patients require drug treatment, such as stimulants or modafinil, to combat their excessive daytime sleepiness.²⁴ Other symptoms have to be treated with other drugs and none are free of side effects. The need to find better treatments is obvious and research will clearly continue to achieve this end.

Work on dogs with narcolepsy has supported the view that a noradrenaline neurotransmitter mechanism is involved. High activity of cells producing this neurotransmitter occurs in wakefulness. In normal sleep, as the characteristic synchronization of the EEG occurs, noradrenaline and other associated transmitter activity decreases. During REM sleep there is little noradrenaline activity. Clearly, drugs that affect REM sleep can have profound effects, as can natural agents such as the hypocretins, which

strongly affect the noradrenergic (arousal) neurons and have excitatory effects. In particular, human beings with narcolepsy have low or non-existent levels of hypocretins in their brains and thus would lack this excitatory input to the noradrenergic neurons. These would therefore be much less active, which probably explains many of the symptoms such as excessive daytime sleepiness. Certainly, direct application of Hcrt-1 onto cells of the noradrenergic neurons leads to an increase in wakefulness and a decrease in sleep in rats.²⁵

In some dog families narcolepsy is caused by a gene mutation. In humans there may be a genetic susceptibility in some people, but an autoimmune causation—presumably with an environmental trigger involved—is the most likely explanation for most human cases. If this is indeed found to be the correct explanation, given the ongoing elucidation of the mechanisms of normal sleep patterns and the abnormal sleep patterns of narcolepsy, it is not impossible that means will be found to trigger narcolepsy. Such a disruption of normal functioning would, of course, be profoundly debilitating for an individual or groups of people affected.

To those who find that idea far-fetched, it has to be pointed out that the drug Provigil (modafinil), which is used to help people with narcolepsy keep awake during the day, is now being used by some armed forces as a means of prolonging the hours that troops can stay awake while on active duty.²⁶ Thus intentional modification of behaviour related to knowledge of narcolepsy is already being carried out.

Conclusion

It has to be stressed again that these are but two examples of our growing understanding of the molecular basis of human behaviour and that there are many other such examples. The rapidity of the recent elucidation of the causes of narcolepsy is quite startling and should remind us that new knowledge can be discovered very quickly. Fundamentally, however, what the work on PTSD and narcolepsy illustrates is that much of that growing knowledge is dual-use and could be subject to hostile misuse if the prohibitory norm embodied in the 1925 Geneva Protocol, the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC) is not upheld in coming decades. One urgent requirement, if that objective is to be achieved, is for neuroscientists—along with everyone else involved in the life sciences—to regard it as central to their work to uphold the norm against the hostile use of their science and technology. For that reason the BTWC meetings in 2005 related to codes of conduct for scientists are of immediate and critical importance.

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Notes

1. G. Poste, 2002, *Advances in biotechnology: promise or peril*, at <www.upmc-biosecurity.org/pages/events/2nd_symposia/transcripts/trans_post.html>.
2. I. Hacking, 2004, "Big ideas—the race against time: Neuroscience", *New Statesman*, Special Issue, 26 July, at <www.newstatesman.com/site.php3?>>.
3. M. Dando, 2002, "Scientific and technological change and the future of the CWC: the problem of non-lethal weapons", *Disarmament Forum (UN Institute for Disarmament Research)*, no. 4, pp. 33–45.

4. M. Wheelis, 2003, "'Nonlethal' chemical weapons: a Faustian bargain", *Issues in Science and Society*, Spring, pp. 74–78.
5. G. Poste, op. cit.
6. Quoted from the 4th edition of 1994 (DSM-IV) in A. Frances and M.B. First, 1998, *Your Mental Health: A Layman's Guide to the Psychiatrists' Bible*, Scribner, New York, pp. 109–16 (Chapter 5, "Exposure to Traumatic Events").
7. J. LeDoux, 1999, "The power of emotions", in R. Conlan (ed.), *States of Mind: New Discoveries About How Our Brains Make Us Who We Are*, New York, John Wiley and Sons, pp. 123–50.
8. Ibid.
9. J.L. McGaugh et al., 2002, "Amygdala modulation of memory consolidation: Interaction with other brain systems", *Neurobiology of Learning and Memory*, vol. 78, no. 3, pp. 539–52.
10. B. Ferry and J.L. McGaugh, 2000, "Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage", *Acta Pharmacologica Sinica*, vol. 21, no. 6, pp. 481–93.
11. J.L. McGaugh and B. Roozendaal, 2002, "Role of adrenal stress hormones in forming lasting memories in the brain", *Current Opinion in Neurobiology*, vol. 12, no. 2, pp. 205–10.
12. B. Ferry et al., 1999, "Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between b- and a₁-adrenoceptors", *Journal of Neuroscience*, vol. 19, no. 12, pp. 5119–23; B. Roozendaal, 2000, "Glucocorticoids and the regulation of memory consolidation", *Psychoneuroendocrinology*, vol. 25, no. 3, pp. 213–38.
13. E. Vermetten and J.D. Bremner, 2002, "Circuits and systems in stress: I. Preclinical Studies", *Depression and Anxiety*, vol. 15, no. 3, pp. 126–47.
14. R. Grossman et al., 2002, "Neuroimaging studies on post-traumatic stress disorder", *Psychiatric Clinics of North America*, vol. 25, pp. 317–40.
15. S.M. Southwick et al., 1999, "Role of norepinephrine in the pathophysiology and treatment of post-traumatic stress disorder", *Biological Psychiatry*, vol. 46, no. 9, pp. 1192–1204.
16. E. Baard, 2003, "The guilt-free soldier: New science raises the spectre of a world without regret", *The Village Voice*, 22–28 January.
17. A. Longstaff, 2000, *Instant Notes: Neuroscience*, Oxford, BIOS Scientific Publishers (section 3, Brain Biological Clocks).
18. H. Okamura, 2003, "Integration of mammalian circadian clock signals: from molecule to behaviour", *Journal of Endocrinology*, vol. 177, part 1, pp. 3–6.
19. H.D. Piggins and D.J. Cutler, 2003, "The roles of vasoactive intestinal polypeptide in the mammalian circadian clock", *Journal of Endocrinology*, vol. 177, part 1, pp. 7–15.
20. A. Longstaff, op cit., (section 4, Sleep).
21. W. McDowell Anderson, 2002, "Top Ten list in sleep", *Chest*, vol. 122, no. 4, pp. 1457–60.
22. S. Taheri et al., 2002, "The role of hypocretins (orexins) in sleep regulation and narcolepsy", *Annual Review of Neuroscience*, vol. 25, pp. 283–313.
23. L. de Lecea et al., 1998, "The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity", *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 1, pp. 322–27; T. Sakurai et al., 1998, "Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behaviour", *Cell*, vol. 92, no. 5, pp. 573–85.
24. Taheri et al., op. cit.
25. P. Bourgin et al., 2000, "Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons", *Journal of Neuroscience*, vol. 20, no. 20, pp. 7760–67.
26. I. Sample, 2004, "Wide awake", *The Guardian*, 29 July, at <www.guardian.co.uk/print/0,3858,4980696-111414,00.html>.