# 3 BRAIN, MIND AND BODY

> The old [...] tradition, which is still in favour with many scholars [...] was based mainly on introspection. It considered mental events to be of a different nature than physical events. Yet it seems very hard to imagine how an immaterial mind could have arisen from a process of evolution by natural selection. Endowing the elementary particles that constitute matter with some kind of a psyche does not help much, and the conclusion is inescapable that mind is a product of brain organization in the same way that life is a product of molecular organization.
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> —François Jacob, *The possible and the actual* (1982)

## The mind/body problem

> [...]her pure, and eloquent blood
> Spoke in her cheekes, and so distinctly wrought,
> That one might almost say, her body thought
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> —John Donne, *The second Anniversarie* (1612)

Whatever one means by the term ‘mind’, it seems uncontroversial to say that depression is a disease of it—a ‘mental illness’.[1] What is controversial is the definition of ‘the mind’. Is it a separately existing non-material object, independent of the body? Or is it purely material, a part or function of the body (more narrowly of the brain)? It is obviously important, in a book about mental disorder, to take a position on this issue, and attempt some definition of what it is that the disease is located in, and therefore what steps might be most sensible for treating it.

This book, insofar as it deals with this and related issues, is set firmly within the paradigm of traditional Western reductionist science. I have only slight knowledge of other traditions; but I have sampled some, and made a deliberate choice because this is the approach I find attractive and convincing. This choice of course carries a set of biases; but they are respectable biases, those of contemporary neuroscience and biologically informed philosophy. I therefore have no hesitation about adopting them. So I take no account of alternative views, say Eastern or Christian (or religious of any sort), and exclude any concept that might be termed ‘spiritual’ or ‘metaphysical’ or having anything to do with ‘the soul’ or anything ‘immaterial’. Such a position in the treatment of mental phenomena may be unattractive or even perverse to many readers, so it requires some justifying argument. This chapter is mainly devoted to the kind of thinking that underlies the generally accepted view of mind among modern philosophers and neuroscientists, and a description of the machinery that the mind appears to be generated by or

[1]Uncontroversial except to those who don’t ‘believe in’ mental illness, but consider it to be a misinterpretation of the results of society not being suitable for the so-called ‘mentally ill’ to cope with it, or a conspiracy foisted on us by Big Pharma, or an invention of those interested in subjecting others to ‘mind control’. I ignore such positions, and follow the conventional medical (and lay) consensus that there is such a thing. I know: I have one.

be part of.

Since antiquity, philosophers and scientists have been intrigued by mind. What is it, and where (if anywhere) is it? Thinkers divide into two main camps. The older and traditional one is the dualists, who think mind is something special, non-physical, and though in some way perhaps 'resident in' or 'expressed through' the brain, is independent of it, literally 'meta-physical'. This picture of the mind has been sarcastically characterized by the English philosopher Gilbert Ryle (1984) as 'the Ghost in the Machine'. Dualism is at the core of 'folk psychology', the commonsense if unreflecting view of more people than not. It underlies the widespread belief in a separate 'soul', 'spirit', or whatever is supposed by some to animate, and by some also to survive the death of, the body.

The other group, now the mainstream among philosophers and neuroscientists, is the non-dualists, often referred to also as monists, physicalists or materialists. Whatever their technical disagreements (and there are bound to be many in such a complex field), they all believe that in some sense or other the 'mind' *is* the brain, or that the brain's activity (or the coordinated activity of the brain and the rest of the body) *is* the mind, and there is nobody else at home. This is a crucial issue, not only philosophically but medically. One's position on it largely determines one's construal of psychiatric illness, if not always one's philosophy of treatment. Though many details of the emerging view are still unclear, recent work in neurobiology and philosophy appears to me to have shown that dualism is (or certainly ought to be) dead as a serious philosophical or scientific position.[2]

The modern version of this debate goes back to the 17th century, to Descartes. He distinguished between what he called *res cogitans* ('thinking substance' or mind) and *res extensa* ('extended substance' or matter).[3] Descartes claimed an absolute and unbridgeable distinction between the two. *Res cogitans* is specific to humans: animals are merely clever machines, without mind or consciousness. But since our bodies are apparently controlled by our minds, there must be some interface where the two can meet. (Descartes thought it was the pineal body.) Cartesian dualism or 'substance dualism' and its children have been the source of enormous confusion and conceptual muddle, and are still a philosophical and medical plague.

How for instance, if the dualist claim is true, can there be 'psychosomatic' illness? If 'mind' is independent and non-material, how can it affect corporeal 'matter'? Even more basically, how can this non-material whatever-it-is control the gross movements of the body?

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[2] For a good picture of the non-dualist consensus see the (often quite different) treatments of the issue in Crick 1994, Dennett 1992, 1996,Cairns-Smith 1996, Pinker 1997, Damasio 1994, 2001. The most accessible of these are probably Pinker and Damasio;. Dennett is difficult, subtle and technical, but well worth the effort. I do not want to give the impression that there is no serious philosophy still being done in the dualist mode: see Antonietti *et al.* 2008 for a series of essays criticising the anti-dualist position and advocating various forms of dualism.

[3] *Discours de la méthode* (1637), *Meditationes de prima philosophia* (1641), *Principia philosophiae* (1644). English translations in Haldane & Ross 1967. For discussion, as part of the extended argument of what is perhaps the best available book on the history of concepts of mind, see Gregory 1984 [1993] : 463-8.

How does *intending* (whatever that means) to move your hand allow you to move it? Just saying it 'does so', mysteriously and in ways probably beyond our understanding, is not enough.[4] Actually Descartes has a partial, though not very good solution. The nerves that activate muscles in humans, as in animals, are perfused by 'animal spirit', which is a kind of *res extensa*, operating mechanically, 'tugging' at nerves. It is only strictly voluntary movement (which by definition is possible solely for humans) that requires some way for the *res cogitans* to get in touch with the material nervous system, via the brain. But if there is any interaction between some hypothesised nonmaterial entity and the material body, it would as far as we know only be able to occur through the transfer of energy from the nonmaterial to the material. Since the nonmaterial by virtue of having no mass also has no energy, this would appear to violate the law of conservation of mass/energy, and therefore be impossible in terms of modern physics.[5] I am not being anachronistic and criticising Descartes for not knowing modern physics; just noting that a now generally accepted property of nature probably makes dualism of his sort impossible.

A familiar demonstration of mind/body integration and mutual feedback, sufficient to make it pointless to distinguish the two, is the'placebo effect'. It is a well known (and still imperfectly understood) fact that a medication does not always have to be pharmacologically active to 'work'. A placebo (Latin 'I shall please') is an inactive substance that nonetheless can have potent effects, provided that the person taking it does not know or believe that it is inactive, or on the contrary believes that it is active. Placebos are used as controls in testing medicines; in a standard clinical trial a new drug is tested against an inactive substance (e.g. an identical-looking sugar pill). No subject knows whether he is getting the real drug or the placebo. (In a properly designed 'double-blind' trial, neither do the investigators: they only find out which patients have received the active drug and which the placebo after the results have been tabulated.) But typically a good percentage of subjects receiving the placebo experience the effects the drug is supposed to have. So if a new antidepressant is being tested, the patients will be told that this is a trial for antidepressant effect, and sometimes as many as 30% of the placebo-controls will respond, even though the drug itself (*qua* drug) is clearly not doing anything. There are even 'placebo side-effects'(technically called nocebo, Latin 'I shall harm'): if the trial population is warned that the new drug may cause nausea, a proportion of subjects may become nauseated.

But there are more striking indications of mind/body unity or inseparability—what might be called 'metaphorical pathologies'. These seem to have a symbolic dimension; complex

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[4] Some philosophers, known in the trade as the the 'New Mysterians', would rather not have such questions answered at all. They not only believe that mind cannot be grasped or explained physically, but do not *want* it to be. They are a kind of hangover from the romantic view that understanding things destroys their 'mystery', beauty, etc., and hence is undesirable. For a well written and eloquent attack on this position, and an (unconvincing) argument for the superior beauty of scientific understanding, see Richard Dawkins' odd but fascinating *Unweaving the rainbow* (1998). Of course the two are complementary, not mutually exclusive.

[5]This, if properly developed, might be the strongest argument against a non-material mind, but I do not know enough physics to follow it up.

physico-chemical processes respond to 'mental' properties like imagery, thought, knowledge, fear, desire. A relatively simple example is the 'conditioned immune response':some hayfever sufferers will show allergic symptoms on seeing a plastic rose. Apparently the immune system and the parts of the brain that control it 'know' that roses cause allergy, and even in the absence of the pollen antigens that (chemically) provoke the response they appear to read the plastic replica as close enough to the real thing so that reaction is appropriate.[6]

But perhaps the most telling examples are those where attitudes or wishes apparently recruit huge portions of a person's biology 'in order to' achieve some end. Consider for instance pseudocyesis or 'false pregnancy'. In this disorder, a woman's physical resources are utilised in extraordinarily complex ways to mimic a pregnancy, without there having been any fertilisation (or even intercourse), or any fetus *in utero*. Even doctors have been fooled. Here is a description by a clinical neurologist:

> Some women who desperately want to become pregnant—and occasionally some who deeply dread pregnancy—develop all the signs and symptoms of true pregnancy. Their abdomens swell to enormous proportions, aided by a sway back posture and the mysterious deposition of abdominal fat. Their nipples become pigmented, as happens in pregnant women. They stop menstruating, lactate, have morning sickness and sense fetal movements. Everything seems normal except for one thing: There is no baby.[7]

The 'mind' acts on the 'body' powerfully enough to produce a desired (or not desired) condition, by coopting surrogate mechanisms. Much of the abdominal distension is produced by swallowing air and alterations in sphincter tone, leading to the retention of enormous quantities of gas in the digestive tract (hence the Victorian term 'wind egg'.) A related phenomenon, even more bizarre, is the rare 'couvade' or 'sympathetic pregnancy' syndrome, in which the *male* partners of pregnant women develop abdominal distension, cravings for odd foods and may lactate and have morning sickness and labour pains (see Ramachandran 1999: 218).

On a dualist view, not only is the mind distinct from the brain, but the personality or self is a kind of 'whole', self-existent, a mixture of behavioural, temperamental and moral traits, independent of any physical ground. Such a belief would be necessary for instance to allow dead selves to return as ghosts, still possessed of all the unique personal attributes that were theirs in life. ( I am deeply puzzled by the fact that even dualists who believe in ghosts are not disturbed by the fact that they often appear as *clothed physical bodies* with voices. Even a hard-core dualist ought to quail at the notion of a 'spiritual larynx'.) Here is a story that should make us think very

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[6] On the plastic rose phenomenon and other examples of immune conditioning (even in animals), see Ramachandran 1999: 219ff.

[7] Ramachandran, 213. See this chapter for further references, and a discussion of the physiological mechanisms involved. The labour pains often start precisely nine months after 'conception', and the symptoms disappear immediately after 'delivery'. This is a complex and unresolved phenomenon: some (but definitely not all) instances may be due not to 'mental' phenomena, but to tiny endocrine tumours that produce prolactin (the hormone that induces lactation). Something like this must be the explanation of false pregnancy in dogs, which is not uncommon, and certainly does not involve (as far as we know) a bitch 'wishing' to have puppies.

carefully about the possibility of an independent and detached/detachable mind.

In the year 1848, Phineas Gage, a 25-year-old foreman working for the Rutland & Burlington Railroad in Vermont, was preparing a hole for blasting. A premature explosion drove a 3.5- foot iron tamping rod through his left cheek and frontal lobe. Surprisingly, Gage survived the accident; the rod was removed, and after treatment of infection he seemed to recover completely, and was perfectly functional. Except, interestingly, that his personality had changed radically. The former sober, well-organised, trustworthy and in all ways exemplary citizen turned into 'someone else'. I can do no better than to cite the retrospective description given by his doctor, John M Harlow, some two decades later:[8]

> The equilibrium of balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference to his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans for future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. Previous to his injury, though untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart business man, very energetic and persistent in executing all his plans of operation. In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was "no longer Gage."

The naive dualist question would be: where did the Old Phineas go to, and where did the New Phineas come from? How does a self turn into another one? The non-dualist answer is that the Old Phineas 'as a person' was simply his undamaged brain, with two functional frontal lobes working together and with the rest of his brain; the New Phineas was what was left when the 'downward' control or inhibition that used to be exerted by the damaged frontal lobe was destroyed, to reveal 'the other half': a more primitive, disorganised, uninhibited Gage. 'Unified' selves are the products of fully functional brains. The effect of the brain damage was rather like a permanent state of drunkenness (Gage also took to uncontrolled drinking). There was of course no real 'transformation', no 'new' Gage at all; it was just that one of the physical structures underwriting the old Gage was gone, and all that was left was what the undamaged structure could do, and this was perceived as 'someone else'.

The evidence then supports not just a 'connection', but an identity of the 'mental' and 'physical', at levels of complexity from the virtually reflex (allergy to plastic roses) to that of an entire personality. But there is also a major logical difficulty with the dualist view. The classical dualist image is of a little 'self' sitting inside the brain somewhere, and watching over, observing and interpreting the events going on in what Daniel Dennett (1992) calls the 'Cartesian Theatre'. This observer is 'you'. But if he does all these things, acting for all the world like a human observer and reporter and moderator, then *he too* must be conscious and have a self, so he has to

[8] Harlow 1868, quoted in Valenstein 1986: 90. For a detailed study of the Gage case, see Damasio 1994.

have another Cartesian Theatre inside his head. And that of course requires another self-as-observer, etc., *ad infinitum*. Dualism leads to an infinite regress. These examples only scratch the surface of a tangle of very subtle and complex issues. The mind/body relation will continue to arise as a major theme throughout this book.

There is a solution, as we will see later; but for now it is worth simply noting that this debate has its therapeutic reflexes. It underlies the split between two theoretical extremes among psychiatrists. On one side are the nondualist 'biological psychiatrists', who see mental disorders simply as a special, complex, and as yet poorly understood and difficult subset of physical ones, i.e. mind disease is brain disease. On the other are many psychoanalysts and others who believe, even if there are biological 'roots' to mind, that talk therapies, treating the mind directly by communicating verbally with it, are the only appropriate therapeutic approach to the mental. (This is an expository caricature of course; there is a vast range of approaches in between. And anyhow the best psychiatrists do not let their theoretical stances get too much in the way, and will use drugs, which are about as physical as you can get, along with other therapies.)

But whether dualist or not, no sane person doubts, to put it as conservatively as possible, that 'mental activity' (not only mood, but consciousness, thought, intention) is at least *located*, even if contingently, in the brain, and that purely physical causes can produce mental effects. One's consciousness, to take an everyday example, can be startlingly altered by drugs; probably the most familiar is alcohol. These may even produce states in which one 'isn't oneself' (a temporary version of what we might all the 'Gage Effect'). Even more extreme examples easily come to mind: e.g. the sensory derangements produced by hallucinogens, where people end up seeing and hearing things that 'aren't there' but that their brains manufacture under chemical stimulus. Such drugs can produce hallucinatory and delusional states that mimic schizophrenia and other psychotic disorders. These effects must be mediated solely by the physical and chemical state of the brain—there are no other variables.

So our mental lives are at least *played out* in a physical arena, the brain. Even if one wants to reserve judgement on the dualism issue, it would seem that before talking in more detail about disturbances of psychological function we ought to know something about the brain, what it does and as far as we know, how it does it.

## What Brains Do

> [...] the ability to make sensations such as pain and hunger was perfected by natural selection because these sensations were useful [...] Now the ultimate means of production of any evolved function lies in material genes, in messages written in DNA molecules, and the only thing that DNA molecules can do is to organise other molecules. Therefore consciousness comes from an organisation of molecules. It is part of the material world, the world of molecular machinery, quite as much as the ability to contract a muscle or convert the energy of sunlight into fuel. They are all evolved functions. They are all on a par.
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> – A.G. Cairns-Smith, *Evolving the mind. On the nature of matter and the origin of consciousness* (1996)

Brains appeared quite early in the evolution of animal life. The most primitive multicellular organisms, like jellyfish, have nervous systems of a sort, but they are simple networks, with no central director. Certainly before the Cambrian Explosion c. 550 million years ago, proper brains developed, particularly in animals that moved about under their own steam, rather than being planted in one place or floating. The brain is normally at the front end, where among other things it integrates the complex and disorderly input from sense organs. Adaptively speaking, that is where a brain ought to be anyhow, since an animal's most important tasks are feeding, escaping predators and breeding. (Or as it is sometimes coyly put, 'the three F's: food, flight and reproduction'.)

The earliest brains, like those of earthworms, are little more than clots of nerve cells, simple bulges off a central nerve-cord rather than the immensely sophisticated devices found in 'higher' animals. But the more recently evolved an animal type is, it appears, the more complex its brain. We have exceedingly large brains; according to the average brain/body ratio in mammals, ours are about three times the size they ought to be. An adult body has about ten trillion cells in all, of which some ten billion are in the brain. The brain is also metabolically greedy: though it makes up only about 2-3% of total body weight, it uses 20% of the body's oxygen and glucose. And this rather unprepossessing mass of podgy, wrinkly material makes us what we are; it is a horrendously complex and as yet poorly understood organ, often said in enthusiastic textbooks to be 'the most complex object in the universe', which it might just be.

The brain is often modelled as something like a fantastically intricate parallel computing device. This serves for some purposes, but misses the important point that brain function is not digital. There are not just two states for any nerve cell, 'on' and 'off', but a huge number of possible finely graded states and state-transitions that can be provoked by neural activity. Some idea of the complexity of what neuroscientists have to model is given by David Horrobin (2001: 168):

> Analogies, although almost always misleading to some degree, can be useful in conveying the scale of things. Imagine the largest supercomputer in the world. Imagine that at each switch point, instead of a digital 0 or 1, all open or all closed, about 100,000 variable positions were available. And finally imagine that the whole computer were bathed in a fluid containing well over a thousand different chemicals, each of which could modify the functioning of the switches and each of which could vary with time, with season, with stress and with a myriad other influences. You would then begin to get a feel for the complexity of the brain.

The brain's ten billion neurons are constantly engaged with each other and the rest of the body in an almost inconceivably elaborate dialogue. A standard estimate is that there are some ten trillion interconnections just inside the brain itself, let alone the rest of the nervous system. All of this activity is mediated by two primary kinds of processes: electrical impulses travelling down neurons, and chemical cascades triggered inside them and causing the release of special 'messenger' chemicals (neurotransmitters), which in turn may trigger the actions of other, more complex substances. These matters are crucial for understanding (as far as we can) mood and

mood disorder.

The brain has both receptive and/or interpretive, and executive functions. Both can be internal or external. For instance, via the inputs from external sensors (e.g. eyes, ears, skin) it monitors the outside world, and—within the capabilities given to it by evolution—constructs a representation (a simplified and species-specific picture or model) of this world. This may at first sound over-complicated: common sense would have it that the sense organs just register 'what's out there'. But this clearly cannot be true.[9] For instance, ultraviolet radiation is 'out there', as we can tell indirectly every time we get sunburned; but we cannot see it, though bees can. Many flowers that appear monochrome to us actually have elaborate nectar guides and patterns for attracting insects that are visible only if photographed under ultraviolet light, but are surely part of the 'outside world' for the insects that pollinate them. We however cannot even *imagine* what UV 'looks like', because our brains have no wiring for interpreting it. Only a small part of the electromagnetic spectrum is available to our sense organs. Bats can echolocate with extraordinary precision: the high-frequency echoes bouncing off and discriminating between obstacles and prey are also 'out there', but only for bats.[10]

A brain perceives and models what it has to, given its ecological setting, and what its history has made it suitable for. Like any complex organic structure it is an adaptation (or suite of adaptations), and therefore a product of the demands of its evolution. But it perceives indirectly and 'theoretically', not directly. We think we see with our eyes; but in fact no photon gets any further than the retina; the impulses set off by light impinging on the retina travel through a complex set of pathways to the *back* of the brain, which is where we do our basic seeing, though the signals from the back go forward again, and are integrated in other places. These operations however are hidden from us; we have the illusion that our eyes are doing the work, even though it is really being done at the opposite end of the head in a moist and fleshy darkness, where no light can possibly reach. What we 'see' is coming back in the other direction, a reflection and processing of the interpretations the brain makes of the patterns sent to it by the light-induced firing of retinal neurons. A lot of the experiences we think are coming from the outer world are coming from the inner (and often inaccessible) one.

I will illustrate this with two phenomena, one so familiar that we normally pay it no attention, the other on first encounter close to surreal. First the familiar one. Think of some object in your house that is green. If you look at it in the morning it is green, and if you look at in the afternoon or evening it still is (to you). But in fact as the day goes on the incident light becomes redder, and the wavelengths of the light reflected from the object make it 'objectively' redder

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[9] Smythies 1992 calls the notion that we simply perceive 'what's out there' Naive or Direct Realism, as opposed to the more sophisticated Representational Theory, in which perceptions are representations constructed by the brain out of selective interpretation of sensory input and innate predispositions to make certain kinds of 'theories', to impose structure on that input.

[10] See Thomas Nagel's intriguing essay, What is it like to be a bat? (1974). For a slightly perverse but fascinating reply, Dennett 1992: chapter 14.

too. But your brain *knows* it is green, and as it were counterfactually holds its colour constant, until some threshold is reached where all colour disappears. The brain can be described as having 'a theory of colour constancy'. But 'you' (whoever that may be) have no idea that your brain holds this theoretical position, and indeed there is no way for you to access it. Yet your brain is part of you, or you are part of the complex whole made up of your brain and the rest of you.

Damage to the visual cortex can often result in blindness, even though the eyes remain intact and functional. This by itself makes perfect sense; we can interpret it simply as a disruption of information-pathways, so the coded signal from the eye fails to get to the place (or from the place) where it is 'seen'. It is even less odd if you think of the experience of 'seeing stars' when struck on the head: visual phenomena that are certainly not 'outside' (except in comic strips) are produced by jarring the brain.

But now consider the strange condition called 'blindsight' Certain patients with damage to the visual cortex appear paradoxical. They present with total blindness in one or both visual fields, depending on the lesion. They act blind in these fields, report being unable to see, to all intents and purposes cannot see at all. Yet when the (apparently blind) visual field is presented with some stimulus and the patient is asked to identify or locate it, the percentage of correct responses is significantly better than chance. When however the patient is asked about the identification, he says that he guessed, and is totally unaware of having 'perceived' anything. Nonetheless there clearly has been some kind of perception, or the percentage of correct responses would eventually cluster around the random mark. So the patient, with intact eye and damaged brain, is actually seeing, *but does not know that he is seeing*, and is unable to account for his own correct perception except as guessing. A complex brain system is apparently working properly, and the patient is performing what must be a 'mental' activity ('this is a vertical line'). But there is no contact between this activity and the patient's consciousness: two normally cooperating systems have been decoupled. The seeing, that is, is being done by what Ramachandran calls a 'zombie': an autonomous system working away on its own, just as it would if its connections to the higher cortex (where we *know* that we are seeing) were intact.[11] The inverse of blindsight, as it were, is the experience of detailed visual hallucinations, often of exquisite colour and great complexity, by all of us when totally blind, i.e. in dreams where there is no visual input from the outside. Rather than seeing (with the eyes) but not knowing it, we know that we are seeing, but not how. Here the optical cortex *does* connect with experience, but without input from the peripheral visual system. Less exotically, the same thing occurs when we recall the appearance of anything visual while conscious but not in its presence. Call up the image of a face or a picture. Right now: you can see it, but where is it?

The brain perceives more than the external world; it keeps a vigilant eye on the internal one as well, monitoring heart-rate, blood-pressure and temperature, blood-sugar and hormone levels, the pH of the stomach, the state of the immune system, the positions of joints, the relation

[11] The classic description of blindsight is Weiskrantz *et al.* 1974; for more details and neurological commentary see Ramachandran 1999: chapter 4.

of the body to gravitational forces. And—the executive function I mentioned above—not only does it receive these countless messages, it acts on them. If (via your eyes) it perceives an object hurtling toward your face it puts programs in operation that make you get your head out of the way. Certain properties of your blood chemistry make it send a complex series of messages to many places that result in your feeling hungry and trying to obtain food. If some threat suddenly arises, it activates a cascade of reactions which tell your pituitary to send a hormone to your adrenals, which in turn secrete a hormone that raises your heart-rate and blood-pressure, turns the stored glycogen in your muscles into glucose, shuts off your digestive, sexual and excretory functions, dries up your saliva, dilates your pupils and gets you ready for 'fight or flight'.

None of this of course is really 'mental' (though there are emotions and feelings, even thoughts, that go along with many of these activities); but the mind is an inextricable part of this system, and a 'mental insult' can act like, or in fact *be*, a 'physical' one—if for no other reason than that the same machinery and processes are involved. (Think of the way you feel, physically, when grossly insulted or embarrassed or verbally threatened.) Most importantly, we are unaware of most of what the brain is doing, and there are many apparently 'mental' phenomena (like a blindsighter's correct identification) that cannot be accessed by what we normally think of as 'mind'—at least if we take that to mean consciousness.

I have so far considered only the brain's relation to impinging stimuli; but of course the most definitively human part of its behaviour consists of its talking to itself, and generating thoughts, attitudes, moods, emotions, memories, desires, ideas, works of art. We know much less about how it does most of these things than we do about its receptive and executive functions; but enough to let us talk fairly intelligently about mood. Though I must warn the reader that the approach will be somewhat roundabout: mood is very complex, and there is a lot we do not know about it.

## How the brain talks to itself and others

Even for the 'normal', mood is less under control than other aspects of mental state. It typically seems to be 'imposed' by external forces. This is unsurprising; from the point of view of consciousness, the unconscious activity of the brain *is* pretty much external. At least it is beyond our reach and control: we do not invent our dreams. The reason for this, as for so much of our behaviour and mental functioning, is broadly evolutionary. Mood is largely initiated by brain modules much older than those controlling the 'higher' functions—thinking, planning, the representation of a cognitively alive, conscious 'us'. It has been suggested, half as metaphor and half as historical fact, that we really have three brains (Maclean 1990). First (and geographically lowest, closest to the spinal cord) is the old primitive reptilian brain: this consists of the brain-stem and a few higher structures, and controls breathing, heartbeat, arousal and certain stereotyped responses. Above this is a 'primitive mammalian' one, the palaeocortex, 'emotional brain' or limbic system (nothing to do with limbs: Latin *limbus* 'border'). And spread over the top of this evolutionary complex is a high-powered newer mammalian brain or neocortex, the

fragile two-millimetre-thick convoluted layer that makes up most of the brain's surface. Our emotional lives are largely lived at the older levels, in structures we share with all other vertebrates; they move along trackways predating our emergence, using chemicals that may be nearly as old as life itself. Our conscious, cognitive lives, though coloured, manipulated and partly controlled by and partly controlling these older brains, are centred in the evolutionarily newest structures. But no part of the brain is isolated from the rest: chemical and electrical messages pass along trillions of connections among billions of neurons that connect just about every part of the brain with every other, and ultimately with the rest of the body. And there are numerous pathways projecting from the 'primitive' parts to the higher centres, and in the reverse direction. For convenience I will use terms like 'emotional' and 'cognitive' throughout as if they represented quite separate domains; but there is no cognition without emotion, and no emotion without cognition.[12]

Viewed from above, the brain is a roughly oval symmetrical object, divided into two wrinkled hemispheres by a groove running from front to back; it rather resembles a large, soft three-pound walnut, unclearly divided into a set of lobes. If we look at it from the side, at the bottom (in back) is a smaller and slightly brain-shaped structure called the cerebellum ('little brain'), which is mounted atop the brainstem, a swelling of the top of the spinal cord. From this aspect we see both the evolutionarily oldest and newest parts of the brain. The brainstem and cerebellum are ancient structures, concerned mainly with functions common to all vertebrates like control of breathing, heartbeat, fine movement, balance and orientation (though recent research implicates the cerebellum in language and learning as well). The lobes form the cerebral cortex or neocortex, which makes up some 60% of total brain weight. And roughly between the two, hidden from view by the cortex, is the old mammalian or limbic system.

It is often difficult to specify precisely what part of the brain does what. It seems that specific functions are not exclusively located in particular pieces of anatomy; but rather that these loci are crucial to the execution of these functions within an integrated whole-brain system. All discussion below concerning the localisation of function is to be taken in this sense. The legs are 'the organs of walking', no doubt; but they do not perform this function very well if detached from the hips and the spinal cord. It is also impossible to give an intelligible answer to the question 'Which part of the leg walks?' The flexings of the leg at hip, knee, ankle and toes are crucial—but it is the leg as a whole (or better as one of a pair), cooperating with our senses of balance and orientation and perception of gravity, that walks.

So the various structures are at least associated with particular functions, and are for the most part connected to other structures associated with different functions. And now, with sophisticated techniques of real-time brain imaging, we can often see what parts of the brain are active in performing a particular task, and how activity travels around it during performance. These techniques usually measure glucose uptake or blood-flow and oxygenation as a function of activity (the more work a part of the brain is doing, the more energy it uses).

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[12]See Damasio 1994, Ratey 2001: chapter 6.

A brief sketch of the major parts of the brain might be in order, so that when they are mentioned again there will be something to look back to.

A. CORTICAL

(1) *Frontal lobes*. Behind the forehead. These are the 'newest' parts of the brain, more highly developed in humans than other primates. They control the 'higher' cortical functions: thinking, planning, much of consciousness and control of emotion. The most anterior portion, called prefrontal, seems to be concerned with 'conscience' and abstract ideas. The frontal cortex as a whole also controls certain kinds of memory, the perception of states of mood and emotion, awareness and arousal, planning of actions (including assessing their consequences), and maintenance of 'personality'.

(2) *Temporal lobes.* Over the temples and ears. These orchestrate most of language and hearing, as well as aspects of face- and voice-recognition. The final integration of visual information and the identity of objects is achieved here by feed-forward transfer from more posterior parts of the brain (the so-called 'what pathway', which identifies objects as being particular things, drawing on temporal memory resources. The 'how' pathway, which identifies objects as being in particular places or moving in particular ways, but not 'as' objects, is in the parietal lobes).[13] The temporal lobes are the primary seat for autobiographical memory, the kind that constitutes the ongoing narrative defining the 'self'. Bilateral damage (especially the medial parts and certain underlying structures) leads to amnesias. Other functions include aspects of religious sensibility; electrical stimulation of the temporal lobes can produce visions and experiences that feel religious to the subject, and temporal-lobe epileptics are often inclined to hyperreligiosity.[14]

(3) *Parietal lobes*. Over the temporal lobe and meeting at the top of the brain. They integrate visual and other sensory information, generating a spatial map, recognizing objects 'conceptually' if presented from unfamiliar perspectives. They are also concerned with spatial orientation, direction-finding, face-recognition, voice recognition, arithmetical calculation and awareness of body position and orientation. A good deal of parietal function, like frontal-lobe function, appears to be integrative—gathering together bits of information from other parts of the brain and constructing perceptions.

(4) *Occipital lobes*. At t he back of the skull. These deal with vision and related tasks. In addition to forming visual images out of fragments, they cooperate with the language centres in the temporal and frontal lobes in linguistic/visual tasks like reading.

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[13] On the what and where pathways, see Ramachandran 1999: 77-82.

[14] See Ramachandran 1999: chapter 9, called 'God and the limbic system'.

This description suggests that the right and left hemispheres of the brain do identical things. This is not the case: much function is 'lateralised', i.e. primarily centred in one hemisphere or another. Normally (in right-handed people and most left-handers) for instance language function is centred in the left hemisphere; the right hemisphere has some language capacity but not much. In general, the left hemisphere controls the linear and 'intellectual' functions of consciousness, the right the more 'holistic' and emotional. There is hemispheric disparity in mood disorder as well: dysfunction of the left frontal cortex is associated with depression, dysfunction of the right with mania.

B. SUBCORTICAL

The intricately convoluted neocortex, the site of the higher cognitive functions, is folded over a complex core of highly differentiated, evolutionarily older structures. This layered configuration is Maclean's 'triune brain'.The oldest part, the brainstem, controls basic arousal and automatic life-sustaining processes, like breathing and heartbeat; without it we would not be alive at all. It also receives primary sensory information via ancient input pathways, before passing them back to the cortex for processing. With only the brainstem but no other part of the brain functioning, we are in a 'vegetative' state: a working brainstem with no communication with any other part of the brain may keep some functions going, but the owner could no longer be called a person. This is not to say that the brainstem has no relation to higher functions; some of the crucial chemicals that mediate our emotional lives are produced there.

From the point of view of mood and emotional function, the most important set of structures is the newer but not newest 'old mammalian' brain, the limbic system. It is conventionally marked off from the rest of the brain by its own cortex, a region bounded at the front and above by the cingulate gyrus, at the sides by the hippocampus, and at the bottom by the hypothalamus; this structure in its entirety is often called the 'limbic lobe', and wraps round the brainstem. Its outer edges lie just beneath the neocortex, and some of the significant structures are located just beneath, or could be said to be part of, the temporal lobes. This 'emotional brain' as it is often called mediates a large number of functions, having to do, in general, with our emotional and sexual lives and what Peter Whybrow has called 'housekeeping'— fine-tuning endocrine function, blood glucose levels, need for nourishment, temperature, heart-rate, blood-pressure, sexual desire, and adjusting the internal chemical landscape to sources of danger and other significant properties of the environment. As we will see, it is primarily limbic disturbances or dysregulations that underlie what the higher cortical centres perceive as mood disorders. The most important components of this system, for our purposes, are the thalamus, hippocampus, hypothalamus and amygdala.

(1) The *thalamus* [15]is the primary integrating and distribution station for information coming in

[15] Recall that the brain has two hemispheres, and though one says 'the thalamus', 'the amygdala', in each case there are two of these structures, right and left.

from outside, and has two-way connections with most of the rest of the brain. Different parts of it receive sensory input and pass it on to the relevant areas for further processing. The thalamus is also an important part, along with the hippocampus, of the system that establishes and retrieves memories. It may also be the primary enabler of consciousness; the intralaminar nuclei in its interior are involved in elaborate feedback loops with the rest of the brain, and probably play a major part in establishing the 40Hz 'background oscillation' of neuronal firing that is uniformly present except in the deepest sleep.[16]

(2) The *hippocampus* is primarily involved with memory and mood. It organises short-term memories into long-term memories that are stored elsewhere, and aids in their retrieval. It is also involved in orientation, particularly path-finding (not surprising, since this also involves short-term memory). Damage to the hippocampus appears in many amnesias and dementias; it is one of the areas that degenerates most severely in dementias of the Alzheimer type. It also, importantly for our purposes, shows damage in depressive disorders. It is intimately connected with mood, in that 'normal' mood requires an undamaged and fully functional hippocampus. Depressed patients typically show loss of hippocampal neurons, and often a smaller hippocampus than undepressed controls, and regeneration of hippocampal neurons (one of the actions of antidepressant medications) is associated with improvement of depression.

(3) The *hypothalamus*, at the base of the brain, secretes hormones that instruct the pituitary to send messages to glands like the thyroid, gonads and adrenals, and thus orchestrates a good deal of our endocrine function. It is also responsible for temperature regulation, hunger, water balance (hence thirst), the organisation of sleep, initiation of the stress response and sexual arousal. Hypothalamic dysregulations like insomnia, disordered eating, persevering stress are exceedingly common in mood disorders; I return to the function of the hypothalamus and the recipients of its messages below.

(4) The *amygdala* is primarily concerned with recognition, arousal, fear and aggression; Whybrow calls it an 'emotional sentinel'. Among other things, it mediates fear and anxiety responses (whether desirable or not), stores traumatic memories (hence is activated in the flashbacks of Post-Traumatic Stress Disorder), and is part of the system that recognises the emotional tone of facial expressions and speech, as well as the difference between familiar and unfamiliar faces and voices. Damage to the amygdala can result in striking delusions due to the failure to identify the 'familiar': one of the most bizarre is the Capgras delusion, in which the patient is convinced that familiar people like parents, partners, children are clever replicas

[16] Hz ('Hertz'—after the famous 19th-century German physicist) = cycles per second. The 'background oscillation' consists of brain-wide waves of regular neuronal discharge at 40Hz; particular activity (such as attending to or intending something) recruits groups of neurons into faster firing. For discussion see Ratey 2001: 134ff.

inhabited by alien selves. The lack of emotional grasp of familiarity provokes this kind of story as a sort of 'adaptive response': if they *look* identical to my parents /wife/sibling and yet *feel* totally unfamiliar, they must be impostors. [17]

There are also limbic subsystems, projecting to higher cortical centres, which regulate 'reward' and 'punishment'. The reward system (primarily activated by the neurotransmitter dopamine: see below) consists of a set of pathways connecting the hypothalamus and a region called the septum, just at the front of the limbic system, and with important projections to a small structure called the nucleus accumbens; the punishment system involves the brainstem and (most importantly) the amygdala. Both systems have an intimate two-way connection to the frontal cortex. The current view is that hyperactivation of the reward system is associated with elevated mood states, and the opposite for the punishment system. To state an important point in a preliminary way, our emotional lives are lived in the limbic system, but are generally perceived by the neocortex, particularly the frontal lobes. And by means of descending projections, the frontal lobes can act to inhibit or otherwise control the limbic system. Cortical-limbic balance constitutes a good deal of what might loosely be called 'mental health'

Much pop-neurology literature tends to superimpose a kind of Freudian geography on the brain, equating the neocortex with 'consciousness' and the limbic system with 'the unconscious', thus making a neat division between a conscious brain and an unconscious one. This is simply wrong; even 'higher consciousness' is exquisitely sensitive to limbic disruption, and there is considerable evidence that the limbic system has its own kind of knowledge and cognitive functions, and is typically activated first in many processes that appear 'conscious', e.g. face-recognition. Victims of prosopagnosia (the inability to recognise faces), if shown sets of pictures of arbitrary unknown faces and ones that ought to be familiar, like those of family members, cannot consciously (i.e. 'as far as they can tell') distinguish one from another. But careful monitoring can show differential limbic response to the familiar ones, e.g. changes in skin-conductance (associated with emotional, i.e. limbic, arousal), and slight blood-pressure and pulse-rate rises— the signs normally picked up by so-called 'lie-detector' or polygraph tests. This is the same kind of 'unconscious cognition' that occurs in blindsight. As Pascal presciently said, 'Le coeur a ses raisons, que la raison ne connaît pas'.[18]

## Information flow in the brain

The brain is not just hardware and software; it is also 'wetware'. Any information-transmitting

[17] Severe limbic detachment may produce even more distressing delusions: perhaps the worst is the Cotard delusion, in which the patient becomes so divorced from a feeling of familiarity even with his own body that he draws the conclusion that he is dead. For discussion of these and other 'reduplication misidentification syndromes', see Weinstein 1996, Ellis & Szulecka 1996 and Young & Leafhead 1996. One of the overall functions of the amygdala and the rest of the limbic system may be to invest percepts with affective significance.

[18] 'The heart has its reasons, which reason does not know'.

system needs some kind of carrier for the information, and a channel to broadcast it on. In the nervous system the information-bearers are chemicals, generically called neurotransmitters and neuromodulators, and the channels are neurons. We will now take a brief look at the actual structures that carry the brain's messages, and some of the chemicals mediating this transmission.

The functional work of the brain is done by billions of neurons or nerve-cells: while there are many different kinds, they all share a basic structure. The cell body is more or less like that of any other cell, with a nucleus containing a full complement of genes, and all the other appurtenances. It puts forth a long process, the axon, which may extend several centimetres or more, and is the output end or terminal. At the cell-body end of the neuron are dendrites, little branching structures, which make innumerable connections (in total in the trillions) with the terminals of other neurons. The transfer mechanism is the sending of an electrical impulse down the axon, which causes complex chemical events at the junction of axon terminals from one neuron with dendrites from another. These junctions are called synapses. They are not direct physical connections, but tiny spaces (synaptic clefts), across which the inter-neuron signalling takes place. I will use the activity of a single neuron as a model, but practically nothing in the brain is done by one neuron: it is assemblies of neurons that act, triggered by other assemblies.

Let us call the neuron sending a signal the upstream or presynaptic neuron, and the receiver the downstream or postsynaptic neuron. At the end of the upstream neuron's axon at a given synapse is a terminal button, containing a number of tiny vesicles (little bubbles of fat) filled with neurotransmitting chemicals, which have been manufactured by the neuron. When a downstream neuron receives a sufficient number of specific kinds of inputs from upstream neurons, connecting to different dendrites, it fires; neurotransmitters are released into the synaptic cleft, and bind to structures on the dendrites of the next downstream neuron called receptors. These are protein-molecule 'locks', designed to accept certain chemicals as 'keys', on the basis of agreement in molecular shape.[19]

When a neurotransmitter binds to a downstream receptor, it triggers an impulse (the information it carries depending on the particular neurotransmitter involved, and the particular variety of receptor), and a complex series of events occur in the cell, signalled by the bound receptor.[20] I will not go into detail here, but it involves among other things the turning on of genes which produce a chemical cascade of proteins and other 'messengers' that eventuates in

[19] The 'fit' is not necessarily exact, and much of modern pharmacology (and recreational drug use) depends on this. For instance, morphine, heroin and other opiates bind to receptors designed to accept morphine-like chemicals made by the body (called endorphins); the fit is good enough, and these drugs can compete with or mimic the effects of the body's own products. Many drugs work by binding to receptors for other chemicals and either blocking their normal receptivity by occupying them ('antagonists'), or enhancing their activity by having a stronger effect than the body's natural products ('agonists').

[20] The commonest type of receptor is a complex protein molecule, inserted in the external cell membrane and extending down into the cell itself. The outside structure is the 'lock'; in general the molecule binding to the receptor causes the internal part to send a signal or series of signals to structures within the cell. The substance that binds normally does not enter the cell itself. For a very clear if technical introduction to receptors and cellular signalling, see Downward 2001.

the downstream neuron firing (or not).When the downstream neuron has done whatever it is supposed to do, most of the effecting neurotransmitter is taken back out of the synaptic cleft by 'transporter' proteins through a gate in the terminal button (the 'reuptake pump'). Within the neuron, and to some extent in the cleft, the excess is degraded by various enzymes, which turn the neurotransmitters back into simpler chemicals or precursors out of which they can be built again when needed. Many terminal buttons also bear 'autoreceptors', which recognize which neurotransmitter has been released, and in what quantity, and act as a feedback control.

So regulation of neural activity is largely controlled by chemicals that either tell neurons to fire (excitatory neurotransmitters), or tell them not to (inhibitory neurotransmitters). The rate of firing however is controlled not by a single neurotransmitter input, but normally by a cocktail of chemicals reaching the dendrites at one time. If the majority of the inputs are excitatory, the neuron will fire; if the majority are inhibitory, it will not. But at a certain threshold it will fire, and the inputs control the speed and organisation of its output. These chemicals however not only trigger the simple on/off activity of neurons: they *modulate* the signals, through a complex system of 'messengers' within the neuron that determine the kind of information that the current running down the axon imparts to the downstream neuron.[21] Messenger activity controls the turning on and off of genes in the cell body of the downstream neuron, which plays a major part in determining the content of the received and transmitted messages. Activation of gene expression in the downstream neuron can result in instructions to carry a particular kind of content, and also in rewiring and restructuring of connections. 'Arborisation', the growth of new dendrites and connections is also possible (this happens whenever learning takes place, and as an effect of certain antidepressants for instance); there is also 'pruning', the removal of connections. A good deal of the brain's circuitry is plastic, and is constantly changing.

There is another oversimplification here: our ideal neuron had a single axon, whereas real axons may divide into fantastically complex bundles of branches and sub-branches, each with its terminal buttons connecting with a different downstream neuron; and by the same token the dendrites of any neuron will be parts of many different synapses, often activated by different neurotransmitters (there may be more than 10,000 synapses on a single neuron). A given firing then may be triggered by a host of impulses from upstream neurons, using different neurotransmsitters that act in synergy or opposition. And different synapses are of different 'strengths': i.e. they take different amounts of input to activate them.

There are many kinds of neurotransmitters, of different chemical structures, serving many different functions. The most important for our purposes are the so-called 'bioamines'. Three of these appear to be crucially implicated in the maintenance of mood: serotonin, noradrenaline[22]

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[21] Actually much of the modulatory and information-carrying work is done by other chemicals which interact with the major neurotransmitters: the term 'neuromodulator' is often reserved for neuropeptides (small proteins such as the various endogenous opioids), and other chemicals like nitric oxide and perhaps carbon monoxide.

[22] A terminological confusion. In 'British-speaking' countries, (nor)adrenaline is the normal technical usage; in the US (nor)epinephrine is used instead. Actually both mean the same thing: *ad-ren*-- is Latin and *epi-nephr*-

and dopamine. There seems little doubt now of the central role played by these chemicals in depressive illness. Neurons carrying these transmitters project not only to other parts of the brain, but throughout the rest of the body as well, and control or influence many different physical and mental activities. In summary:

(1) *Serotonin* (amine)[23] helps control the flexibility of arterial walls, and receptors for it are found on platelets (tiny cell-fragments involved in clotting). Deficiency of serotonin uptake can lead to faster clotting time, and may be involved in coronary artery disease, hypertension, and immune dysfunction. It also helps regulate motor behaviour, the vomiting reflex, the setting of body clocks, the relaxation phase of sexual activity, appetite and mood. Serotonin dysregulations may lead to depression, sleep disorders, carbohydrate craving, altered pain thresholds and sexual dysfunction, impulsivity, anxiety, compulsiveness, aggressiveness and suicidality.

(2) *Noradrenaline* (amine) controls aspects of metabolic regulation and homeostasis, and regulates arousal; it is sometimes referred to as 'the brain's adrenaline', and is a major actor in the stress response. It appears to increase the signal-to-noise ratio in the brain, so that impinging stimuli are sharpened. Noradrenaline dysregulation can lead to excessive pleasure-seeking, panic, hypervigilance, excitement, and decreased food intake, or on the contrary depression, lack of energy and alertness.

(3) *Dopamine* (amine) is involved in the control and initiation of voluntary movement (degeneration of dopamine neurons is the primary cause of Parkinsonism), feelings of reward and punishment, sexual excitation, the production of nausea and vomiting, and the establishment of memories. Dysregulation can lead to mania, psychosis (most antipsychotic drugs are dopamine antagonists), psychomotor slowing or speeding-up, involuntary movements or tics (Tourette's syndrome is normally treated with a dopamine antagonist), sexual problems and alterations of the ability to experience pleasure.

A number of other neurotransmitters may be implicated in psychiatrically important phenomena:

(4) *Acetylcholine* (amine) is involved in attention, learning, memory, and the operation of the parasympathetic nervous system (see the next section). Deficiency of acetylcholine is one of the major chemical dysfunctions in Alzheimer's disease.

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Greek for 'on or near the kidney', which is where the adrenals are.

[23] An amine is a simple organic chemical that has an ammonia-like nitrogen and hydrogen group attached to it.

(5) *Glutamate* (amino acid)[24] is the main excitatory neurotransmitter, and plays a part in arousal along with noradrenaline; it is also necessary for learning and the laying down of long-term memories, and most likely for the sustaining of positive mood.

(6) *GABA* (gamma-aminobutyric acid) is the major inhibitory neurotransmitter, preventing neurons from firing, or damping down their activity. GABA receptors bind opiates and alcohol, and are the main mediators of the effects of sedatives and tranquillisers.

As even the brief description above suggests, it is quite unreasonable to ask of a brain chemical X 'what does X do?' and expect a simple answer. This is an unbiological kind of question—one cannot even depend on a substance of great importance for the brain operating only in one place, or binding only one type of receptor . The proper kind of question is rather 'What does chemical X do when it binds to receptor-type Y in location Z?' For instance, there are about 15 different types of receptors for serotonin alone, in different places. Only one of these is primarily involved in mood. Others mediate serotonin's effects on blood-vessel tone in the genitalia, the vomiting reflex system, and appetite and weight-regulation.

The amine systems are highly interactive. Serotonin, for instance, exerts a feedback control on the noradrenaline system. If the latter is hyperactive, as may be the case in anxiety disorders, serotonin reduces its activity; if it is underactive, as in some (perhaps all) depressions, serotonin stimulates it. Therefore a drug that primarily alters serotonin output or uptake will almost certainly affect noradrenaline as well. (Some serotonin neurons in fact synapse directly onto noradrenergic ones, and some bear noradrenaline receptors.) One of the more serious problems in understanding neurochemistry is the fact that very often the same neurotransmitter may have both excitatory and inhibitory effects, depending on the chemical ecosystem it is released in, and which receptors it binds to.

Returning for a moment to the 'three brains', the architecture of the amine systems themselves says something of considerable evolutionary interest. These substances are produced in three primary areas, all in the older parts of the brain. All of these (or close analogues) occur in the nervous systems of other vertebrates, and these posterior sources suggest that they are very ancient indeed. But these transmitters do not just stay in the older structures. Each main source has a complex set of projections (neurons activated by and carrying the transmitter) to other parts of the brain, including both the limbic system and the higher neocortical centres. Thus both 'primitive' and 'advanced' structures and functions are fed by the amines; this makes it unsurprising that depression, for instance, is a disease not only of the emotions but of the more 'intellectual' functions of the brain as well.

The point of this description is both simple and critical: the older or 'primitive' parts of the brain have upward projections to the most recent and highly evolved parts, so that the thinking, conscious or cognitive brain, the neocortex, is flooded with information and orders

[24]An amino acid is a weak organic acid that is the main building block of proteins.

'from below'. The reverse is true as well; the brain is full of bidirectional loops, e.g. thalamus-to-cortex/cortex-to-thalamus, etc. Very little traffic is entirely one-way. The whole brain is a single tightly-knit system, though its owner (to speak in the traditional way) is directly aware of only the tiniest fraction of what is going on inside it.

**Stress and the autonomic nervous system: the hypothalamic-pituitary-adrenal axis**

The brain, particularly the limbic system, controls much of the body's endocrine activity. At the lower edge of the limbic region is the pituitary, often called in textbooks the 'master gland', since its signals control the functioning of other parts of the system. But the pituitary is not an independent agent; it is part of the limbic system, an outgrowth of the hypothalamus. This suggests that in principle at least some aspects of endocrine function should be related to mood or similar properties of the 'psychological' brain. And, less directly, perhaps (assuming the whole business is tightly enchained, as bodily systems typically are), that anything controlled by endocrine glands should in principle be capable of responding to mental state, and vice versa.

One important example of this intimate enchaining, central to the understanding of depression, is the stress response. The term 'stress' has many different meanings. In everyday usage it is what you are under when you work too hard, your boss is a bastard, things are going wrong in your life, you are subject to anxiety, danger or trauma. True enough. But there is a good side to stress as well; what makes you feel miserable and helps give you ulcers and coronaries is the malfunction, under inappropriate ecological conditions, of ancient adaptive survival-systems. No animal is going to live long enough to reproduce if it is not wired with internal devices that mobilize it to escape predators and other dangers. I will return to these issues in chapter 4, in an attempt to answer the question of why the stress response appears to be capable of causing so much harm.

The stress response begins with the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. This system controls the body's (hence the brain's), or the brain's (hence the body's) longer-term response to stress, both physical and mental. The stress response has two main stages, the first relatively simple, quick and short-term, the second more complex, slower and potentially long-term. When information passed to the hypothalamus results in the perception of some kind of threat (physical or psychological), a cascade of events is set in train preparing the body for survival under pressure: the 'fight or flight' response. The first stage is direct recruitment of the autonomic nervous system by the hypothalamus. The autonomic ('self-regulated') nervous system consists of two branches, the sympathetic and the parasympathetic. The former, when stimulated, dilates the pupils, inhibits salivation, peristalsis and bladder and sexual function, dilates the bronchi, raises heart-rate and blood-pressure, and increases the uptake of glucose by muscles. That is, energy, reactivity and alertness are maximized, and less important functions are temporarily put on hold. These effects are mediated by adrenaline and noradrenaline, produced by the adrenal medulla (the inner portion of the gland). The parasympathetic system, activated mainly by acetylcholine, does more or less the opposite, e.g. slows heartbeat, lowers blood-

pressure, stimulates the gut and bladder. The two work as complementaries, controlling the online regulation of body functions, under the instruction of hormonal messages from the limbic system and in some cases the spinal cord. (E.g. the parasympathetic system relaxes arteries and allows erection and lubrication; the sympathetic produces orgasm.)

The immediate autonomic activation is followed by a much more complex set of events, induced by another cascade of chemical signals. The aroused hypothalamus produces corticotrophin-releasing hormone (CRH), which is sent to the pituitary. CRH instructs the anterior pituitary to produce adreno-corticotropic hormone (ACTH), which passes via the circulation to the adrenal cortex (the outside layer: the inner medulla has already poured out adrenaline), and tells it to release cortisol, often referred to, along with adrenaline and a few others, as a 'stress hormone'. This has a number of effects, all useful in the short term, but some potentially damaging in the long term. Cortisol maintains a continuing stress-reactivity, putting the entire body in a more stable fight or flight mode. It does this in a number of ways: partially suppressing insulin output so that more glucose is available for quick energy, releasing fatty acids from the liver into the bloodstream to produce energy, increasing blood-flow through vital organs, diverting white cells from the circulation to cut down on energy consumption, and acting as an anti-inflammatory agent. Ideally, when the situation triggering stress in the first place has gone, the body should return to its normal functional mode, and cortisol levels should drop. And indeed this is what generally happens.

If however stress is chronic, or the individual is particularly vulnerable, cortisol levels may remain high. This can lead to dysregulations of neurotransmission, and an extremely complex effect on the immune system, involving both partial hyperarousal and long-term suppression. But the overall long-term effect is partial inhibition of the immune response. In this sense cortisol acts rather like its chemical relatives, cortisone and other steroid hormones. The release of fatty acids into the circulation may also be dangerous in the long term, as this will raise general lipid levels, and increase the likelihood of coronary heart disease. So an abnormally prolonged or chronic stress reaction could potentially produce a great deal of damage (see the following section).

Recent research has shown that CRH, which used to be thought of as mainly a signal to get the HPA into gear, actually plays a far more complex and significant role. It displays considerable activity within the brain itself, and is not merely a hormonal messenger, but a neurotransmitter. It is found in a number of sites outside the hypothalamus, in particular the higher cortex, the amygdala, and the brain stem. The CRH neurons in the amygdala project back to the hypothalamus, and to the brain stem as well; in the brainstem they project to the regions that produce serotonin and noradrenaline. So release of CRH affects the amine systems, in particular sensitising them beyond their normal thresholds to stress-related trauma. We will see how important this is in the next chapter.

## Stress, mind, immunity and death

> Challenge is no longer the hovering of eagles, but [...] triggered by a rich imagination and personal memories. These abstract forms for many individuals cast shadows equally as terrifying as the presence of the primordial beast. What is remarkable in the human experience of stress is not the linking neurobiology, for that is in keeping with our primitive ancestry, but the myriad ways in which learning, experience, and social attachment can initiate the physiological arousal that leads to stress.
>
> ——Peter H. Whybrow, *A mood apart* (1997)

Here is a provocative and probably unfamiliar fact. In Israel, and among certain Jewish communities elsewhere, the normally steady death-rate among the elderly and chronically ill shows a marked fall just before Passover, and a compensatory rise (overshooting the norm) just after. The same thing has been observed, especially in elderly women, at the time of the Chinese Harvest Moon Festival. In the latter case, there is a 35% fall in expected death rate during the week before the festival, and a 35% rise in the week after, so that the expected annual rate is 'normalised'. The interesting thing is that these strange rises and falls do not occur at these particular times of the year among non-Jews and non-Chinese. It turns out that in both instances the festivals are of particular symbolic importance, with a strong focus on family unity and reunion.[25]

Well-studied cases like these make certain kinds of anecdotal reports rather more convincing than they might otherwise be. We are probably all familiar with occasions where people somehow mysteriously manage to die precisely on the anniversary of the death of a loved one. These rather creepy occurrences may be coincidences; on the other hand, as the evidence above suggests, they may well not be. And if they are not, they illustrate again the subtle interaction of mind and body. The mechanism is unclear; but if the evidence is really as good as it seems to be, then there is some way (undoubtedly not fully available to or controlled by the conscious mind) for a person to postpone, for particularly important reasons, effects that the mind/body somehow 'knows' are going to happen; and 'let go' of this control when the occasion for exercising it is over. (Recall the limbic-cortical-brainstem feedback loops.) Whatever the 'will to survive' and the 'will to die' may be, they clearly operate on a virtually seamless mind/body system: otherwise they would not be able to exert such powerful effects.

These are macro-effects whose actual mechanisms at finer levels of resolution are not accessible. But there are many studies that suggest what the possible mechanisms might be, and a great deal of statistical correlation that makes sense in the light of what we know about stress and its effect on the immune and other systems. Let us return to Israel, which during the Gulf War was bombarded by Iraqi missiles. On 18 January 1991 Saddam Hussein began a series of

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[25] Martin 1997: 5-6. I have seen no studies suggesting a similar phenomenon among Christians at major holidays like Easter or Christmas, or Muslims at Ramadan. There is however some evidence that terminally ill people can postpone death for short periods for financial reasons. See Kopczuk & Slemrod 2001.

SCUD attacks. During the first, nobody was killed (in the whole series there were only two deaths); but on 18 January the overall Israeli death rate rose some 58%, particularly in those areas whose inhabitants knew or felt that they were within in range of the missiles (Martin 1997: 3-5). Virtually all the 'extra' deaths were due to cardiovascular events: heart attacks or strokes. This again supports a piece of conventional or cliché knowledge: it is possible to be scared to death. Clearly the physical effects were being mediated through the victims' 'states of mind': and there is nothing like a good dose of adrenaline and a rise in blood-pressure to wreck an already compromised heart, or burst a weakened blood-vessel. Stress can have effects very similar to those of inappropriate exercise: mental as well as physical activity can produce an 'adrenaline rush'.

Examples like these could be multiplied at will. I mention one more here, just to give a view of the longer term effects of cortisol-mediated stress, and the interrelations between mind and body via the immune system. This connection has now been so well recognized that there is now a medical speciality with an enormous and proliferating literature, called psychoneuroimmunology.

One particularly interesting set of observations emerged from the famous Three Mile Island reactor accident in Pennsylvania in 1979. Though there was originally considerable anxiety about a nuclear catastrophe, it turned out that the accident was well contained, and that no significant amount of radiation had been released even into the immediate environment. But there was a great deal of speculation and apocalypse-mongering in the media, and this plus the core of knowledge, expectation and apprehension that people quite properly have about anything nuclear, generated some interesting and startling effects.

Beginning in 1985, a series of studies were carried out on the inhabitants of an area within a five-mile radius of the Three Mile Island reactor. These people were compared to controls living considerably further away, in their own view outside the 'danger zone'. The first finding was that those within the danger zone had distinctly impaired immune function: e.g. fewer circulating white blood cells than expected and a loss of control over latent Herpes infections. They also displayed higher levels of anxiety, higher average blood pressure and pulse rates, and raised noradrenaline, adrenaline and cortisol levels. In addition, there was a short-term rise in all types of cancers in the study population, as high as 50% above expectation. It was clear that any radiation released was at levels far too low to have any carcinogenic effects (this was not a Chernobyl); but the actual mechanisms behind this enormous rise are still somewhat ambiguous, if clearly important. The consensus seems to be that there were two reasons for the increase: (a) a direct effect of stress-induced reduction of immune function (the immune system plays an important role in destroying certain potential cancers and controlling existing ones); and (b) a greater anxiety about health in general, which led to people being more suspicious and visiting doctors earlier than they might have, so that at least part of the effect was due to increased

diagnosis.[26] But overall the rise is far too high for that to be the only cause: as in most interesting things, a multicausal model would be more appropriate. Even lacking precise details, however, we can be sure that stress-related immune suppression played an important role.

**A word of caution**

I have argued here that there is nothing in the central nervous system that is not physical. The evidence overwhelmingly supports this view, as do general conditions on doing good science. That is, one must not invoke entities superfluous to one's explanatory goals,[27] and one must avoid the 'miraculous' and the metaphysical. This could be taken as indicating that I think (or anybody thinks) that the hard problems concerning the mind/body relation are solved. They are not. We have a good idea of what they are, but not a clue about the crucial mechanisms and relations.

We know an enormous and ever-increasing amount, in finer and finer detail, about the brain and central nervous system, neurotransmission, and the experiential and physiological correlates of neural activity. We have some idea of how the limbic system and higher cortex are organised, and how they relate to each other and the rest of the brain and body. But there is a crucial gap: we probably do not even know how to talk sensibly about the interface between brain activity and experience. We see the neural activity 'from below', and the phenomenology of experience (mood, thought, etc.) 'from above', but we have no more idea of what the interface between them looks like than Descartes did. This is probably the most glaring lacuna in our knowledge of ourselves, and the most exciting, important and frustrating area in neuroscience (and philosophy). As John Maddox, former editor of *Nature*, has written (1998: 276):

> [...] the cruel truth is that the central objective of the now majestic research program in neuroscience remains beyond reach: there is only the most shallow understanding of how the brain, and the human brain particularly, engenders mind—the capacity to reflect on past events, to think and to imagine [...]That is not a scandal. The question is truly perplexing.

This has not of course been a 'conclusive' treatment of the mind/body relation. Given the amount of thinking and writing that has been done on the topic, as suggested in the tip-of-the-iceberg references to this chapter, it could not be. It is a beginning, though. The main point has been to show what the brain does and can do in relation to the rest of the body, and how phenomena that we generally consider 'mental' have their physical obverses, and probably for the most part vice versa, and that there is no evidence for the participation of anything nonphysical in the workings of the brain/mind. In the next two chapters I will begin once more

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[26]Martin 1997: 83-85, plus references. There is a detailed treatment of the relation between mood, attitude and cancer in his chapter 9.

[27]That is, good science is guided by 'Occam's Razor', the principle enunciated by a mediaeval English philosopher that *Entia non sunt multiplicanda praeter necessitatem* 'Entities are not to be multiplied beyond necessity'.

to focus on depression itself, its possible causes and the major treatments. But this has not been merely an interlude—it is the conceptual basis for everything that follows, and the groundwork of what preceded. The attitude I want to encourage has been nicely summed up by the English neuroscientist Susan Greenfield (2008: 89):

> For a neuroscientist, the old dualism of 'mental' and 'physical', indeed of 'mind' and 'brain', is as unhelpful as it is misleading. The mind, far from being some airy-fairy philosophical alternative to the biological squalor of the physical brain, *is* the physical brain— more specifically the personalised connectivity of that otherwise generic brain.