1. Theoretical overview

1.0. Background

The result of the first attempt at examining the state of play in drug policy – looking at which countries have opted for a single drug policy and which seem to be moving in the direction of an all-encompassing policy that includes all psychoactive substances – prompted the next set of questions to be tackled.

The publication that resulted, *From a policy on illegal drugs to a policy on psychoactive substances*, outlined the development of drug policy in each country, taking into account on a national level the ratification of any UN conventions, the adoption of EU drug strategies and any major changes that may have influenced the path taken by the country concerned and resulted in the situation in that country today.

The development of drug policy was framed in the context of each particular country – the size of the country, its geographical position and its relation to its neighbours, the state of the drug problem and public opinion – and supported by the political context, that is, the political ideology of the time and place.

This has resulted in descriptions of the development of drug policy in each country and how the evidence from science has generally not been taken into account, with the exception of epidemiology. This, as recorded, may be because some countries put drug policies in place some time ago and the science then was not what it is now, especially in relation to cognitive neuroscience, which has provided new vistas on the way we view brain and behaviour, and more notably mental health.

The majority of the 17 countries opt for a separate policy for each psychoactive substance. The minority, those favouring an all-encompassing policy, were Switzerland, France, Ireland, Germany, Portugal, the Czech Republic and Norway. Norway appears to be the one country that has fully embraced integration; the United Kingdom

and the Netherlands seem steadfast in opting for separate policies on illegal drugs, tobacco and alcohol.

On the basis of these findings, Germany, Ireland, the Netherlands, Norway, Portugal, Switzerland and the United Kingdom were selected to participate in the empirical study that follows, which in turn reflects the fact that the UK and Norway are at opposite ends of the scale, with the other countries on a continuum between these two countries. Consequently the study asked two questions:

- What does the term "integrated policy" refer to in each of the seven countries?
- How is "integrated policy" operationalised in the country?

This study of the seven countries follows the overview, which looks at theoretical rationales of opting for a single policy or one that includes all psychoactive substances.

A key finding from the previous effort was that in all these countries the overarching policy consideration was health. For example, Norway makes it quite explicit why their policy includes both drugs and alcohol: it is because cognitive neuroscience has shown that all these substances affect the brain and behaviour and thus mental health status. The rationale for prevention is also made plain, being based on scientific findings that stopping early use prevents problems later on. In addition, harm-reduction measures – including substitution programmes and needle-exchange programmes – were introduced throughout Europe in response to the imminent health risks associated with injection drug use, which could have furthered the spread of HIV across Europe. Thus the threat to health of the citizens of Europe required policy responses that dealt directly with the problem. This latter example may have provided the foundations for a general move in the direction of basing drug policy on the health and well-being of the citizens in question.

On a more general note, the EU seeks to look after the health, security and well-being of its member nations; the Council of Europe seeks not only to secure their health and well-being but also to uphold the human rights of its 47 member states. Public policy seems the obvious domain through which to achieve these aims, so drug policy per se or a policy for psychoactive substances can provide a tool to address the health and well-being of the nations in question, as part of a comprehensive health policy.

A person's well-being can be related to their physical, social and mental state. In essence, these factors provide the basis for a person to live life

to the full and therefore be a fully active member of society. Some basic needs have to be met, but this is what public policy is all about – ensuring that they are met – while putting the individual at the centre of any policy development. Monitoring health status provides one of the indicators of well-being, and this monitoring should include determining the use of tobacco, alcohol and drugs, all of which can have a detrimental effect on health and well-being (Johnston 2009, Wilkinson and Pickett 2009). Consequently, focusing on the mental and physical state of the individual addresses two of the three aspects directly related to well-being; and the third in a sense may also be taken into account in policy indirectly by adopting the Zinberg 1984 model, which addresses the social domain.

On the same line of thought, it is said that all these substances, tobacco, alcohol and illegal drugs, are more than just chemical agents which affect the brain and behaviour, and thus mental state; one must also consider the personality, attitudes, expectations and motivations of the user, as well as the context, because these have a significant influence on the user and the patterns of drug use. All these factors are determined by the complex wiring of the brain that in turn gives rise to these characteristics and is at the basis of why decisions are made to use or not to use such chemical agents and thus affect mental health. A scientific understanding of those brain systems that give rise to personality, or for that matter to motivation, is thus at the core of evidence-based policy development in this field, with the aim of assuring well-being through a healthy mind and body. The fact that treatment works is a further endorsement for a better understanding of the brain systems involved in mental health and well-being, and for the use of findings from neuroscience as a base for drug policy or a substance-misuse policy.

1.1. Introduction

It is suggested that, in most domains, structure serves function or structure enables function. From a policy perspective having the appropriate ministries, departments and overall linking bodies provides the basis for policy implementation and monitoring. In the same way, the brain's intricate wiring system allows communication between the circuits within particular structures and is the source of our behaviour. Thus again it would appear that structure serves function. This first part of the book deals with the theoretical perspective for a single policy or a policy that integrates all substances, thus providing the background

for policy formulation, and thus it has overarching consequences for the structure–function approach.

Indeed the very term "integrated policy" conjures up different perceptions of what this could be. If one were only referring to an individual drug policy, then "integrated" would be understood to cover both supply of and demand for drugs. These then could be further broken down into their respective elements, namely from the supply standpoint, customs, police, the judiciary and the prison system; from the demand side, these elements could include prevention, treatment, harm reduction and social integration with an overall slant on research, evaluation and international collaboration. Thus from a single policy perspective, integration implies the inclusion of all necessary elements in a coherent manner.

If one were opting for a single policy for all psychoactive substances, then one's perspective on the term "integration" would be slightly different; the attempt here would be to include all psychoactive substances in an appropriate manner. Thus "integrated policy" tends to take on different hues depending, in the first instance, on which policy option has been chosen.

Once such a decision has been taken, the term "integration" may then be applied to a second level, namely that of structure–function: that is, what structures are required to be in place before the policy can be implemented to provide the necessary outcomes. This has been addressed by the empirical study that follows, which gives some insight into how policies in this field have been implemented. It is discussed in Chapter 3, which also looks at the overall conclusions arising from both this overview and the empirical study.

The next question that arises is why bother with science in this policy domain? Epidemiology over the years has been the mainstay of most research done in the drugs field, and even more so in relation to alcohol. Thus from government, the main question has always been the size of the problem of use of psychoactive substances and their impact on society. Epidemiology has provided a means to estimate the size of the problem through population surveys, school surveys and snowball surveys, for example, that provide estimates of use over a lifetime, the past year and past month. These three, lifetime use, past-year use and past-month use, may be interpreted as trying the substance/s once, irregular use and regular use. Mathematical estimates may also be used to calculate numbers, for example of problem drug users that may need direct intervention and numbers in treatment, that show how well the said policy is having its desired effect. Finally, treatment outcomes may further support the policy in place.

Thus epidemiology has provided a means to determine the size of the problem. At the time of writing, the figures for drug use in Europe indicate that about 23 million people have used cannabis in the past year (irregular use), some 4 million people have used cocaine, 2.6 million have used ecstasy and 2 million used amphetamine. Problem drug users or users of heroin and cocaine, the drugs that cause most harm and the most health and social costs, number about 2 million and there are approximately 7 500 fatal drug overdoses each year related to such problem drug use. There is also a high co-morbidity between drug use and mental disorders, both serious and more common.

In the case of alcohol use, Europe remains the heaviest drinking region in the world with a yearly capita consumption of 11 litres of pure alcohol, which is double the world average. It is estimated some 55 million Europeans drink harmful levels of alcohol; of these 23 million are considered to be dependent. Such levels of harmful drinking are estimated to be responsible for some 195 000 deaths each year across Europe as a result of cancer, liver cirrhosis, neuropsychiatric conditions, suicides, road traffic and other accidents, and homicides (European Commission 2009a). We may note that those road-traffic accidents where alcohol use is a contributing factor are predicted to rise to fifth place overall in the leading causes of death in 2030, from ninth in 2004 (1.3 million to 2.4 million). The World Health Organization have announced that all 193 member countries agree to confront the harmful use of alcohol by adopting a global strategy; its ten target areas include health services, community actions, pricing policies and reducing the health impact of illegal alcohol production (WHO 2010).

Tobacco-related deaths worldwide in 2004 totalled 5.4 million and these are expected to rise to some 8.3 million by 2024, which would account for 10% of all deaths (WHO 2004). Tobacco use also contributes to cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease and some cancers. Moreover, the three leading causes of death worldwide in 2004 were ischaemic heart disease, cerebrovascular disease and lower respiratory infections.

Thus the prevalence of tobacco, alcohol and drug use in Europe is, to say the least, a problem that needs to be redressed because of the impact of these substances on mental and physical health and thus overall well-being.

As referred to above, use of these substances has an impact on our whole physiology and plays a major role in our health and well-being, and thus our ability to live productive lives. Epidemiology has provided the means of estimating the global burden of disease,

but in addition it has extended the concept of the disability-adjusted life year (or DALY) to incorporate "potential years of life lost due to premature death to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability" (WHO 2004). Biomedical research has now started to provide us with the ability to understand the mechanisms that give rise to use in the first place and the changes that result in a switch to dependence and the consequences. Cognitive neuroscience is the field of research that is at the forefront of brain research tackling such issues.

One caveat needs to be mentioned before we look at the brain systems thought to be at the centre of substance use. This is the fact that these psychoactive substances also have effects on other body organs; thus, for an integrated policy, these too should be taken into account. To some extent, as highlighted below, these effects will be considered, but not in all cases, so one should keep this mind when trawling through this text.

Psychoactive substances are so named because they primarily interact with the workings of the brain and thus alter behaviour. This implies that the brain is made up of a number of functional regions each specifically responsible for generating a particular aspect of our cognitive abilities to enable us to make decisions and behave in the appropriate manner in the context we find ourselves.

Which cognitive abilities do they affect? These types of substance seem to interfere with our ability to take decisions, make value judgments and restrain our behaviour, and with our faculties of learning, memory, emotion and interoception. Hence, altering such functions may result in pathological behaviour, which has become the typical diagnostic criterion used to determine dependence (American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, revd 2000; WHO 2003). These cognitive abilities also result from brain regions that sub-serve such functions; they include the frontal cortex (for decision making) and the hippocampus (for particular types of learning and memory). Moreover, the findings from scientific literature that these cognitive abilities become compromised in patients with damage to such areas of the brain are further evidence of the role of these specific areas.

Before addressing each of these psychoactive substances in the next part of this overview, we need to examine briefly how these substances can affect brain function by interacting with neuronal communication. The brain is made up of some hundred billion cells – nerve cells – which in effect are the wires that make up the circuits within regions

of the brain and also connect all these regions in one way or another. Unlike the wiring in your house, which normally requires that an electrical device be plugged into the mains to connect it to the supply of electricity, nerve cells are individual components – that is, they are not joined. But they need to pass electrical signals to one another and, to get around this problem, they make use of "chemical signalling". An electrical signal is changed into a chemical signal to get it across the gap between the nerve cells and is then converted back to an electrical signal in the next cell.

The machinery of chemical transmission uses the lock-and-key concept: after the electrical signal arrives at the terminal, the nerve cell needs to produce and release the appropriate chemical; and the following cell needs to have in place the lock, the receptor, through which the key (the chemical) may open the gate. Understanding these mechanisms gives us the opportunity to come up with medicinal drugs that can correct aberrations in these processes, aberrations that have resulted in brain diseases ranging from depression to drug dependence itself. There are some one hundred brain chemicals, known as neurotransmitters, that are released from nerve cells, and there are some hundred trillion connections operating on this principle. It is akin to having the wiring of the whole telephone network serving North and South America packed into some 1·2-1·3 kg of matter – that is what the brain weighs – mainly nerve cells, forming 2% of body weight.

1.2. Scientific evidence

1.2.1. Psychoactive substances

In the main, all psychoactive substances – that is, alcohol, tobacco and other drugs – interact with nerve cells to alter the way in which neuronal signalling takes place. More specifically, alcohol gets into most tissues or cells of the body as it is miscible in water and carried round the body in the bloodstream after it is absorbed following oral ingestion. The greater the blood supply to a particular organ, the greater the chances that alcohol gets into that organ – the brain, for example. Tissues, cells or organs that do not have such a good supply of blood take longer to absorb any alcohol through passive diffusion; however, when most of the alcohol has moved from the blood to parts of the body that have a rich supply of blood, then the reverse happens. Since alcohol in these tissues or cells is in a higher concentration than in the blood, some of it now moves back into the blood.

All in all, alcohol seems to get into most organs of the body, but it has specific effects on the nervous tissue found in the brain. Once in the brain, it interacts with nerve cells that release the inhibitory neurotransmitter gamma amino butyric acid (GABA for short) and these nerve cells' corresponding receptors known as GABA A receptors; the effect is to prevent inhibition in some areas of the brain. Consequently, alcohol is thought to be a stimulant because it relieves some inhibition – for example, self-restraint – but in truth it is a depressant: further intake of alcohol disrupts speech, locomotor activity and fine co-ordinated movements. Alcohol also elevates mood and interacts with the reward pathway by removing inhibitory inputs via the GABA system; thus one gets an elevation of the reward-signalling neurotransmitter dopamine, resulting in the feel-good factor as explained below.

Alcohol also interacts with other neurotransmitter systems in the brain to modify their signalling. In particular, it is known to increase the release of opioid peptides that are involved with feelings of euphoria and pain relief (or analgesia). For this reason the opioid receptor-blocker (or antagonist) naltrexone is used in treating alcohol abuse. This is a good example of how one may bolster the effect of one drug, such as heroin, by ingesting alcohol as well. Such drug interactions are common and may provide the basis for polydrug use in which the user gets to learn the effects of different drugs and combines them in the manner to ensure the "best effect" while perhaps ignoring detrimental effects – such as respiratory depression being amplified – when the two are combined. This may also arise when alcohol is combined with anti-anxiety medication such as diazepam; it is believed that alcohol inhibits the breakdown enzymes and thus increases the concentration of diazepam in the blood stream with the result once again of increased depression of respiration, which may result in total arrest.

Alcohol also results in vasodilatation of the peripheral blood vessels, causing the sensation of warmth and flushed skin, and is thus frequently used in cold weather. This may be dangerous because this feeling is due to the release of body heat for a short period and the inhibition of the reflexive, cold-induced vasoconstriction of the same peripheral vessels, so that now the person ends up colder than before.

Chronic alcohol use has other effects on the peripheral system. Those of concern include cancer of the tongue, mouth, stomach and liver, as well as impotence in males and ovarian dysfunction in females. Fetal alcohol syndrome results in developmental problems in the unborn child, which are manifested at birth as physical malformations and mental retardation.

Nicotine is one of several compounds found in tobacco; it is a stimulant, as is caffeine for example. The main reason why nicotine seems to produce dependence is the fact that, on inhaling a cigarette, within seven seconds 25% of the stimulant has already reached your brain – this is about twice as fast as when administered intravenously. In effect, the link between smoking and the feel-good factor is so nearly instantaneous that the habit easily becomes reinforced and this is the reason for its highly dependence-inducing nature.

Nicotine in the brain acts on what are termed nicotine receptors, though they would normally respond to the neurotransmitter acetylcholine. In general, nicotine acts on the reward system in which these receptors are present, receptors that give rise to the same euphoric feelings as those produced by other known stimulants such as cocaine and amphetamine. Although the mechanism through which these act is not the same, the overall outcome is the same – euphoria. Nicotine also has effects elsewhere throughout the nervous system in the rest of the body and thus is said to contribute to four of the five major causes of death highlighted above, including cardiovascular diseases, lung and other cancers, stroke and chronic obstructive pulmonary diseases. In 2010 it was reported that lung cancers in smokers harbour some 50 000 mutations or changes in their genetic material, compared to non-smokers (Lee et al. 2010).

The most-used psychoactive substance, other than alcohol and tobacco, is marihuana whose active naturally occurring cannabinoid is tetrahydrocannabinol, or THC for short. THC acts on the brain by interacting with cannabinoid receptors of which there are two types, CB1 and CB2. It is CB1 that is of main interest in that stimulation of this receptor leads to increased levels of dopamine in the reward pathway. Consequently, activation of these receptors again results in euphoria as well as altered sensations and memory impairment. Spice products that contain cannabinoids and the increase in THC concentrations obtained from the plant *Cannabis sativa* seem to be of major concern at present.

The most notable stimulants are cocaine and amphetamine and both usually have a direct effect on the main neurotransmitter in the brain involved in generating feelings of euphoria. They act in turn by locking onto the dopamine transporter that is responsible for the uptake of dopamine back into the synaptic cleft after its release and interaction with its receptors on the next neuron. In doing so they elevate the levels of dopamine to such an extent that some have described the feelings of euphoria that are produced following the ingestion of cocaine as greater than anything they have experienced. Both cocaine and amphetamine may induce visual and auditory hallucinations and

paranoia, symptoms typically attributed to schizophrenia. In the laboratory, high-dose amphetamine administration has been used to model the symptoms of schizophrenia with the aim of trying to unravel what brain circuits may be responsible for that condition and what neuronal changes characterise the behaviour.

Cocaine also has effects on the peripheral nervous system and the organs that are innervated by what is known as the sympathetic nervous system. Thus, following ingestion of these stimulants, an increase in blood pressure occurs alongside an increased heart rate, heightened metabolic and respiration rates and elevated body temperature, and all these seem to be a result of either the effects of these stimulants on nor-adrenaline uptake, which is similar to dopamine, or the direct effect of these agents on the brain centres that control sympathetic outflow.

Also included in this group of stimulants are the two members of the amphetamine family, MDMA (or ecstasy) and khat. At this juncture we focus on MDMA, which has been more popular than khat and mainly used at rave parties. Ecstasy acts mainly on the serotonin system to enhance release and inhibit the uptake of the said transmitter and this in turn results again in mild euphoria and a sense of well-being as well as increased sensory perception and a willingness to interact with others. Excessive use of ecstasy is said to result in a form of neurotoxicity that results in damage to the serotonin neurons and thus a loss in their numbers as well as to some degree a form of memory impairment. On a more acute level, ecstasy also increases the heart rate and blood pressure, elevates body temperature and increases sweating and salivation and it is these peripheral effects that put the individual in danger at rave parties where they are made worse by physical activity. Thus the "chill room" allows the user to stop dancing, cool down and take in the required water to replace that lost.

Last but not least, the opiates, such as morphine, interact with the opioid system in the brain, which is largely responsible for pain relief and the sense of well-being and euphoria. This class of compounds, in which heroin is a prime example, interact with opiate receptors of which there are three subtypes, mu, kappa and delta. Direct stimulation of the mu receptor in the reward pathway of the brain by heroin is thought to be responsible for the feelings of euphoria it generates. Heroin seems to act by mimicking the effect of the endogenous opiate, enkephalin, and thus with repeated use the system shuts down the synthesis of enkephalin so that, on stopping use, the brain does not contain any significant amount of the said neurotransmitter which now results in dysphoria and heightened pain perception.

Methadone, another drug that mimics the effect of enkephalin but not so effectively, is used in heroin detoxification to reduce these major side effects but by decreasing the dose in a systematic way it gives a chance for the brain to restart the synthesis of enkephalin once again so that after three weeks the individual may be weaned off methadone altogether. A more recent medication used in the treatment of heroin addiction is buprenorphine, more frequently known as subutex. Once again this partial agonist has a maximal effect of around 65%, less than that of heroin but enough to enable the system to start functioning again in adverse circumstances.

This short résumé of the pharmacological and physiological effects of alcohol, tobacco and other drugs, all psychoactive substances, is intended as a prelude to the next section. (For more information, see Meyer and Quenzer 2005; Feldman, Meyer and Quenzer 1997.)

1.2.2. Reward system

A critical underlying mechanism that enables behaviour, especially goal-directed behaviour, is what is termed the reward system within the brain. This system, found just below the cortex, is thought to provide the mechanism that makes us likely to do things more frequently because these have resulted in rewards that make us feel good about what we have done. In simple terms, if eating, drinking and reproducing did not make us feel good, none of us would be here today. More long-term goals – for example, obtaining a higher degree or indeed obtaining positive policy outcomes – require consistent behaviour over a period of time that finally results in the rewards such as a degree or re-election. So some rewards are obtained now (instant gratification), others are obtained over an extended period of time (delayed gratification) and these alter our behaviour accordingly. Psychoactive substances seem to alter the reward pathway in a way that leads to instant gratification and not delayed gratification.

The reward system in the brain is a circuit that arises from the midbrain and terminates in an area known as the ventral striatum. A number of neurons make up this circuit, releasing a variety of chemical agents to enable communication between them, but the principal neurotransmitter that seems vital to providing some form of reward signal in this area is dopamine. It has been shown that stimulation of these nerves to release dopamine in this circuit is integral to providing the feel-good factor and that the behaviour leading to this is likely to be repeated in order to obtain this very outcome. In effect the final common pathway through which all psychoactive substances act,

even though they may not directly enhance dopamine release, is via increased release of dopamine in this reward pathway. Thus, on acute administration, or taking the substance the first time, the dopamine signal is enhanced in this pathway, with the result that the behaviour leading to this is reinforced with the likelihood that it is repeated.

Some may argue that this in itself is not a bad thing, considering the sometimes mundane nature of life, but the risks that ensue include the development of addiction and dependence in which the sole form of reward is substance use because this provides greater pleasure than anything that is normally on offer such as that afforded by relationships or the joy of watching a sunset by the sea in summer. In addition, for such a scenario to ensue, this does not happen overnight as changes in the brain occur gradually as a result of such use – but, more to the point, behaviour becomes altered as do certain cognitive abilities such as the ability to attend to stimuli and the ability to make what may be termed correct decisions in the prevailing circumstances.

The key point here is that psychoactive substances of all classes, be they alcohol, tobacco or drugs of abuse, hijack the brain-reward pathway by greatly amplifying the reward signal as provided by dopamine, which then results in the risk of further use that may lead to other consequences, such as poor decision making, that compromise behaviour. Repeated use over time leads to counteractive mechanisms in the brain coming into play, by which the impact of the reward signal is diminished and craving for the substance is increased. Consequently, other natural rewards are now less likely to activate the system and the likelihood of repeated use is further enhanced to keep the individual from feelings of dysphoria or depression rather than euphoria following first use.

The brain mechanism for this current scenario is thought to arise from the increase in dopamine signalling within the reward pathway; this comes into play by altering the firing pattern of the relevant neurons. In effect, the dopamine nerve cells operate under two conditions, tonic activity or phasic activity: the firing rate for these states is low for the former, some 2-5 times per second, whereas in the latter it may rise as high as 20 times per second. The implication of this is that the release of dopamine is low in the tonic state but high in the phasic state. All psychoactive substances have the property of shifting the bias of dopamine firing to the one known as phasic activity and thus to enhanced levels of dopamine when such substances are on board.

If this were all that occurred following the ingestion of such substances, one would expect all to revert to normal after use, but repeated use

continues to bias the system to phasic activity while the increasing propensity of the dopamine receptors to be less active is an attempt by the brain to counteract the effect of increasing levels of dopamine in the reward pathway. Thus, with prolonged use, the overall output of the system is turned down in that the increases in dopamine release are countered by the reduction in dopamine receptors. This is why it is thought that the user needs to keep using just to keep a "normal" level of functioning which otherwise would tip the other way, to dysphoria rather than euphoria, which is typical of what happens when the user stops using and more so in cases of withdrawal.

Consequently, stopping use results in a stage that is characterised by the emergence of symptoms typical of depression and also anxiety and irritability. This state is stressful to say the least and thus the brain systems that give rise to these feelings come into play as a result of the alterations in the reward pathway that have impacted on these systems (for further information see Koob and Volkow 2010).

The underlying message would appear to be that psychoactive substances have a major impact on brain chemistry with an initial effect on the reward pathway that makes them so attractive. The brain is a dynamic organ and attempts to counteract the effects of these substances and thus the consequences of those effects. Learning takes place and memories are formed, which in turn affect the overall functioning of the individual.

1.2.3. Learning and memory

As hinted above, the repeated use of psychoactive substances starts to lead to a state where the impact of the reward is diminished and the wanting or craving for the substance increases. At first this is a consequence of the reward threshold rising and thus the stimuli or cues associated with use are given greater prominence: the cues, usually the paraphernalia of use, become better linked with substance use and therefore are more noticeable to the individual now. Before people begin using a substance, these cues do not alert them or focus their attention. This increased salience of such cues is thought to be a prominent aspect of craving and a means to guide behaviour to obtain the substance, to the detriment of other natural cues.

This is akin to the feeling one gets when hungry, when one's attention becomes alerted to visual presentations of food or just the smell of food; these cues take on more significance when one is hungry and guide one's behaviour to obtain food to satisfy this need. Once food is consumed and the body has taken up the necessary nutrients, signals

are sent to the brain to alert it that this has happened, and the cues that had taken on extra significance when hungry lose their significance till the next hunger pangs set in. Here we need to note two things: first, that we learn through conditioning what cues are associated with hunger that then successfully guide our behaviour to satisfy that specific need; and second, psychoactive substances seem to use the very same system of learning and cueing to guide us to the behaviour that obtains these substances, to the detriment of natural rewards like food and water.

The amygdala seems to be responsible for carrying information related to the various aspects of the cues used to guide behaviour. This structure is made up of a number of nuclei and it feeds into the reward pathway, so that the cues become better associated with the behaviour taking place. One can show that, after repeated pairings, the cues themselves will initiate the specific behaviour that prior to pairing they would not have done. In addition, in the laboratory, animals will continue to work or perform in the presence of these cues even if the reward, the psychoactive substance, is withheld. This again reinforces the view that these cues have a significant impact on behaviour.

It has been argued that the mechanism responsible is sensitisation. By repeated association this strengthens the pathway linking cue-related information to reward-outcome information; thus the resulting aberrant learning and memory hold the key in guiding future behaviour.

There are several molecular mechanisms that have been suggested to account for learning and these in the main have been gleaned from work on another brain structure involved in learning and memory related to context or the spatial domain – the "where". The hippocampus is thought to be the brain structure that provides for episodic memory or, more colloquially, the ability to recall personal experiences that depend on the "what", "where" and "when" (see Dickerson and Eichenbaum 2010). Information about where is encoded in the hippocampus and this is also sent to the reward pathway, so now the whole picture can be put in perspective, namely taking in the substance in question in its defined context together with inputs of the particular cues (amgydala input) that accompanied the rewarded behaviour. Thus, places where the substance has been used, as with the cues mentioned above, may take on greater significance for the user and provide the same urge to use the same substance when in the same contexts or places. Thus memories of places or episodes associated with substance use may in turn bias behaviour or decision making to further use. This again may be the setting shown by the Zinberg 1984 model referred to above (see also Chapter 2).

Thus the question of why does the use of all psychoactive substances have such an impact on future behaviour may be answered to some degree by the apparent aberrant learning and memories that are stored after such use, which then have a great impact on guiding future behaviour. Moreover, the mechanism thought to give rise to such memories in the hippocampus and other parts of the brain, such as the reward pathway, is related to what is known as long-term potentiation (or LTP for short) in which neuronal connections are strengthened, making them more likely to contribute to neuronal activity in the future and thus guide behaviour.

1.2.4. Decision making

The ability to make the correct choice under the prevailing circumstances is what drives behaviour forward. Information reaches the frontal cortex, the site at which decisions are made, from the reward pathway through the thalamus, which appears to be the main gateway through which most stimuli gain access to this higher structure. It is worth noting that, from an evolutionary perspective, the cortex has evolved more than any other other brain structure.

Information from sub-cortical sites such as the striatum, amygdala and hippocampus may also flow directly into the cortex; as well as activating the reward pathway, this information may at the same time activate the cortex. Thus, coincident activation takes place of all the structures in question, which biases decision making by the frontal cortex in support of those behaviours that to one degree or another provide the best outcome in the specific context. Thus the goal of any substance user is to feel very good and now behaviours that support such an outcome are given prominence, irrespective of the negative consequences if they do exist.

In a number of studies that explicitly examined this phenomenon – studying, for example, the choice between an instant small reward and a larger one that is delayed in time – most people on any substance opt for the small instantaneous reward. In some studies this has been taken a step further, to determine whether the person will work to obtain a reward that is also linked to a negative outcome, the outcome being that they will still work for such a reward. Consequently, the use of psychoactive substances biases the decision-making process of the frontal cortex even if the outcome is also partly negative, as long as the final result is achieved – namely, obtaining the substance.

It is interesting that substance users, when making decisions, appear to behave in ways very similar to patients who have a damaged frontal

cortex for one reason or another: they make choices that bring instant reward at the risk of incurring loss of reputation, job, home and family (Rogers et al. 1999). Moreover, impulsive behaviour – which again seems to stem from a problem with the circuitry in the frontal cortex – is a major risk factor for the use of psychoactive substances and especially for substance dependence (but see below).

A conceptual framework has been formulated to understand how information reaching the cortex via other brain structures guides behaviour and thus choice. This suggests that the reward pathway is responsible for converting incoming sensory signals to some common "reward currency" that is in turn transformed by the cortex with the help of the reward system into a value presentation of the said stimuli. This value is then mapped onto the probability of available choices of behaviour. Psychoactive substances may bias this process so that stimuli related to use are given more value in reward currency than other, more natural stimuli. It is akin to money markets, where it is often perceptions of the strength of a particular currency that cause more people to invest in that currency than others with less perceived value.

Once a decision has been made to act, the required motor programmes in the brain need to be enabled in order to execute the intended actions. Here again the motor cortex communicates with a sub-cortical structure, namely the dorsal striatum, which is thought to be primarily responsible for influencing the motor cortex in selecting the appropriate actions. A current theory for addiction/dependence invokes the dorsal striatum, primarily because of its role in maintaining habits – be they good or bad. In a state of dependence, information processing in this structure is biased to favour selection of those actions that lead to obtaining the substance of interest (Everitt et al. 2008). Compulsive behaviour also involves the dorsal striatum and thus it is suggested that use in the first instance may kicked off by a predisposition to be impulsive, as this is one of the risk factors, but then later on repeated use is supported by the formation of habit, which in turn becomes compulsive (see section 1.2.5 below).

1.2.5. Addiction/dependence

First and foremost, the epidemiological evidence to date suggests that not all people who try a psychoactive substance become addicted to it. Moreover, it has been estimated that – of those who try such a substance once – the chances that addiction/dependence will set in are 1 in 10 for marihuana and 1 in 3 for tobacco, with other substances

falling in between. Thus the tendency to become addicted/dependent should not be the only measure of the impact of these substances on bodily health, as outlined above, but the problem of addiction/dependence is still there for all to see and needs redress.

Based on our current understanding it would appear that there is some molecular switch within the system that turns occasional drug use into uncontrolled compulsive drug use with the known consequences. A protein molecule known as Delta Fos B has been identified as the molecule that may provide this switch, because quantities of this protein increase following the intake of any type of drug of abuse. More importantly it is activated following repeated use and thus the response does not adapt or habituate; hence it may be this molecule that enables the transition to long-term sensitisation of the striatal dopamine function that is said to be responsible for people craving or wanting a substance. This particular protein is synthesised from the activation of what is known as an immediate early gene, the c-fos gene, following drug stimulation and in turn the product of this gene, Delta Fos B, may switch on or off conventional genes that may be responsible for the long-term effects associated with chronic drug use (Nestler 2008).

Repeated use results in tolerance to the rewarding or pleasurable effects that these substances produce. To overcome the effect of tolerance, further drug use ensues in an attempt to obtain the original effect. Thus with repeated drug use the reward threshold is increased and not decreased, and on stopping use the individual goes into a state of dysphoria rather than euphoria as a result of the tolerance or down regulation of the dopamine receptors within the reward circuit. Consequently stimuli with greater impact are required to activate the reward system. To offset this condition the user would seek to obtain and take in more drugs, setting up a sequence of events that gives rise to compulsive drug use (Koob and Le Moal 2008).

Among the consequences of repeated drug use are dependence/addiction and strengthening of the circuits in the brain involved in habit formation. Thus compulsive drug use, like addiction, arises from a series of steps or conditions that alter what is known as the striatal circuitry to give rise to the aberrant behaviour observed in the clinic. However, initiation of drug use is under the control of the ventral striatum, most notably the nucleus accumbens core region that processes information related to motivation/reward. With repeated use of the drug over a long period, the maintenance of or switch to drug dependence/addiction occurs as the dorsal striatum takes over. This is primarily involved in the selection of action as pointed out above.

Impulsivity also increases the likelihood of addiction and relapse. In subjects selected for impulsivity, findings from the laboratory show that they learn to administer cocaine in the same way as the control group, but they then take on board more and more of the drug than their counterparts. It has also been shown that they have low D2 receptor availability in the ventral striatum, as do human drug addicts (Volkow et al. 2004) and also when abstinent (Volkow and Wise 2005). Thus impulsivity per se may predispose one to use drugs in the first place and then facilitate the switch between occasional use and drug dependence/addiction, and finally also render abstinent addicts more susceptible to relapse.

Thus our current understanding from science indicates that addiction/dependence only sets in with individuals who repeatedly use these substances. There may be a molecular switch that is flipped at a certain point in time and instantiates the decreased sensitivity to rewards and increased craving with the accompanying behaviour changing from impulsive to compulsive.

1.2.6. Psychiatric disorders

It has been suggested that impulse-control disorders resemble addictions; some writers have even gone as far as stating that these disorders may be considered addictions (Brewer and Potenza 2008). Impulse-control disorders are said to fall along a continuum in the impulsive–compulsive domain. They include pathological gambling and kleptomania, and are usually repetitive and pleasurable. Impulsivity per se may be a key factor in some psychiatric disorders, including impulse-control disorders and addiction/dependence. The characteristics of impulsivity include lack of premeditation and sensation-seeking, but key to its resemblance to dependence/addiction is the definition given by Moeller et al. (2001): "a predisposition to rapid unplanned reactions … with diminished regard to negative consequences".

From a genetic standpoint it is uncanny that family and twin studies account for up to 60% of the variance for risk of dependence/addiction (Kreek et al. 2005). In relation to specific factors in human and animal studies, it appears that the reduction in availability in dopamine D2 receptors is a possible basis for a mechanism for both impulsiveness and the development of addiction/dependence.

The presence of substance dependence is also associated with affective disorders, anxiety disorders, attention-deficit disorder and personality disorders and it is more likely to abound in this cohort than in the general population. Major depression, anxiety and personality disorders are thus found more commonly among those with substance

dependence than in the population at large (Couwenbergh et al. 2006; Ross et al. 1988; Merikangas et al. 1998).

In addition, those diagnosed with substance dependence are more at risk than the general population of developing a related addictive disorder at some point in their lifetime. Moreover, their first-degree relatives are also at greater risk than the general population of developing an addictive disorder, which includes substance dependence.

Which comes first, the psychiatric disorder or substance dependence? It has been demonstrated that disorder predates dependence by typically five to ten years (Couwenbergh et al. 2006; Shaffer and Eber 2002). It has also been reported that there are significant predictive associations between primary mental disorders, first substance use and dependence among problem drug users. However, in practice it appears that anxiety disorders – and, to a lesser extent, depression – precede and increase the risk for substance use. We may thus infer that substance dependence does not arise as result of the lifestyle that may be attributed to the syndrome but from some underlying neurobiological dysfunction.

1.2.7. Genetic predisposition

It is now understood that dependence/addiction – or the vulnerability to developing this disorder – is influenced by the type of genes we inherit from our parents. That is not to say that the social context does not have a say in the development of dependence/addiction but genetic heritability is some 50% independent of the substance in question. It may be higher for specific substances: for heroin, it is reported to be in the region of 70%.

Recent studies in this field have suggested that dependence/addiction is heterogenous from a genetic standpoint, as well as polygenic. This implies that in the first instance a set number of genes acting independently may together produce vulnerability to dependence, but that seems to provide only a small propensity to develop dependence and polygenicity appears to be the main factor. Polygenicity in this case means a number of genes acting in concert to produce the vulnerability, with no single gene responsible. In the light of these findings, it has been proposed that it may prove to be more fruitful to examine the genetic influence on a particular feature or trait that has a corresponding biological substrate and thus be able to account for the single genes responsible (see below). This has proved to be challenging except for example in the case of some particular sub-typing with respect to alcohol. Accordingly, this sub-typing of

alcohol dependence has produced a more homogenous grouping and thus reduced the overall number of characteristics that may be attributed to this disorder (Wong and Schumann 2008).

1.2.8. Psychological traits

There appear to be five personality traits. One of them is extraversion, which includes the more specific trait impulsiveness, and that seems to increase the risk for developing substance dependence. Specific traits within the extraversion grouping – impulsiveness, sensation-seeking, risk-taking, low stress tolerance and nonconformity – normally predate the use of psychoactive substances. It has been suggested that such traits are heritable and that normally genes and environment contribute equally to the development of any such trait, which is rather stable throughout life. Thus it would appear that the trait of impulsiveness, which in effect is non-pathological (which is not the case in psychiatric conditions), is a risk factor for the initiation of substance use.

Impulsiveness, it is argued, may also be divided into a number of subtraits, such as urgency, lack of perseverance, lack of premeditation and sensation-seeking (Lynam et al. 2006). The dimension of urgency – that is, negative urgency, the tendency to give in to strong impulses specifically when accompanied by negative emotions, which may take the form of anger, anxiety or depression – was found to be the main factor in a group of substance dependants. Sensation-seeking is also related to initiation of substance use; it can be described as the need for novelty or seeking activities that provide intense stimulus, such as skydiving. Research using constructs that are able to measure this trait has shown over the years, in studies of alcohol users, that sensation-seeking is correlated with greater quantity and frequency of alcohol use. In addition, in the laboratory it has been shown that exposing the young to alcohol or cocaine enhances novelty-seeking and thus it has been argued that novelty-seeking per se may cause people to further engage in substance use.

The trait of impulsiveness, like other personality traits, is also considered to be influenced by both biological and environmental determinants. It may be that, in individuals who tend to be impulsive, it is the lack of impact from normal rewarding stimuli – a lack of impact that may be caused by a down regulation of their dopamine receptors within the reward pathway – that leads them to seek more intense stimuli to get their reward system up and running as required. It has also been proposed that it is some alteration to the frontal cortex

circuitry that enables impulsiveness, because results from people with lesions to this area show that, in choice tests where the subject may either take a small reward with no delay or a large reward following a delay, the small reward is always chosen.

1.2.9. Sociological determinants

Each of the big five personality traits is made up of what may be called sub-traits, and they all include an element of what it is to interact with our environment, especially with other people. This notion of interactivity, or more specifically the ability to co-operate with others, is at the essence of what it is to be human. The way in which the environment and the individual interact then provides the basis for the building of family units (whatever the definition of these), communities and society at large. Thus the environment or culture per se may impact on societies and the individual participating in them.

To be able to behave in this way, a scientist would argue, one must "have a theory of mind" to be able to read other people's minds or mental states, because these mental states determine behaviour. Mental states vary in type and form from the long-term to the short-term – for instance, trustworthiness as opposed to flippancy or, in the short term, anger versus happiness. There are also desires, which can take one form or the other and are usually goal-directed, and beliefs, which govern our behaviour even though they may be false. The point is that these "mental states" – both our own and those of others – are strictly speaking not physical phenomena, though they very much depend on the neuronal workings of the brain.

To this end the brain structures that help instantiate the ability to have theory of mind include the frontal cortex, the limbic system (involved in reward processing) and the superior temporal sulcus. The limbic system provides information on emotional content, enabling us to read people's emotions and helping us to empathise with loss or share in the glory of one's football team winning the world cup. Without this ability to read people's emotions, society would be in a bad state, unable to recognise such signals, just as computing in the field of Artificial Intelligence has not been able to do so far.

The underlying mechanism that enables theory of mind within this circuitry in the brain is thought to be based on what may be termed "mirror neurons" that are activated by our own ability to express emotions; but crucially these mirror neurons are also activated when other people express their emotions. Using this basic mechanism, it is thought, we can experience the same emotion as that expressed by the

other person, even though at that instant we may not know the basis for their feelings. The inference is that the mirror system is best placed to track changes in mental states, such as emotional states and intentions of others, that per se may lead to alterations in behaviour.

Because this ability to attribute mental states to self and others is seen as an important determinate of behaviour, it is hardly surprising to learn that problems in this circuitry in the brain lead to problems in interacting with others. On the extreme end of the scale, autism is a condition where theory of mind has been disabled and it has been suggested that the mirror-neuron system is to blame in part for the emergence of the symptoms of this disorder. Autism is an example of the emergence of problems as a consequence of developmental problems, whereas disorders like schizophrenia that develop later on in life are said to result in problems in applying theory of mind to form coherent relations with others and the world. The long-term use of psychoactive substances may result in symptoms comparable with those associated with schizophrenia, as sometimes noted with amphetamines and cocaine, which in turn may result in loss of the ability to attribute mental states to oneself and in some cases to others. The mechanism for such a loss is believed to arise from a dysfunctional inhibitory pathway from the cortex to the sub-cortical structures forming part of the limbic circuit, which is responsible for processing information related to emotions.

Personality traits may be one of the risk factors for starting to use a psychoactive substance, apart from the well-known phenomenon of peer pressure. Among these traits are expectancy, a well-known psychological construct that includes the belief that the benefits of use outweigh the risks, and finally the belief that one is in control of one's use. So all in all, sociological determinants are very much influenced by the underlying brain system through which choices are made, but in truth a decision to initiate substance use in the first place depends on the workings of the individual mind, as does (in a number of people) the switch to dependence.

1.3. Discussion

The foregoing overview of the impact of psychoactive substances on the brain and behaviour has attempted to show that the evidence from science has come a long way. This in turn should raise our understanding of why people use such substances in the first place and why

some users unfortunately go on to become addicted/dependent with the resultant problems.

It would appear that the crux of the issue is the finding that these substances have a major impact on the reward pathway, such that the mental states or feelings of euphoria they generate continue to attract a fair number of individuals to experiment with these substances. It is also worth noting that the majority of users seem to be in the younger age groups, starting at 16 years old, and this is a problem in itself because the frontal cortex – the part of brain mainly responsible for decision making – only fully matures at the age of 20.

It is understood that our mental states – one of them being our beliefs – in turn determine our actions or behaviour. Beliefs are synthesised in our minds by the assumption that knowledge depends on experience; thus, for example, in order to obtain happiness (a short-term mental state) the path one takes may involve the use of psychoactive substances to create this false belief. It is possible that our make-up or psychological traits may predispose some of us more than others to try such substances, and this is starting to be borne out by the findings that our genes give rise to our psychological traits, whatever they are. It needs to be emphasised that not all is clear-cut and the big five psychological factors are broad categories and thus not as good at predicting or explaining behaviour as are the sub-types or lower-level traits.

Of all the traits, impulsiveness seems to be the one that provides most risk for substance use in the first place and risk of dependence thereafter and this trait falls under the larger domain of extroversion. That impulsiveness per se may be in part understood to arise from the reward circuitry in the limbic system being down regulated by the lack or insensitivity of D2 receptors demonstrates that neuroscience is beginning to provide us with new insights into how such brain circuitries may instantiate such behaviour. Again, the issue needs to be viewed in its total context in that correcting such behaviour with medication alone is not the whole answer. Recent cognitive findings, in which memories have been altered, provide a way forward in which both medication and cognitive therapy may bear better outcomes.

One last note: the emerging discipline of social cognitive neuroscience – which merges such disparate fields of study as sociology at one end, neuroscience at the other and cognitive psychology in between – has been described by Ochsner and Lieberman as seeking to

> to understand phenomena in terms of interaction between three levels of analysis: the social level, which is concerned with the motivational factors and social factors that influence behaviour

and experience; the cognitive level, which is concerned with the information processing mechanisms that give rise to social-level phenomena; and the neural level which is concerned with the brain mechanisms that instantiate the cognitive level processes.

1.4. Conclusion

Following the first attempt to understand in descriptive terms what led to the development of policies on alcohol, tobacco and other drugs, it was clear that epidemiology was the main consideration, not social cognitive neuroscience. It appears that this now needs to be redressed irrespective of whether a single policy or an integrated policy for all is the choice.

The main issue raised in sections 1.0 and 1.1 above was health and well-being. It was stated that most institutions aim to have policies that provide for the health and well-being of their citizens. In addition, the social domain was taken into account as the third pillar that public policy seeks to address. Public policy is also relevant here because it supplies the over-arching umbrella under which such items as alcohol, tobacco and drug use may shelter. The findings of the first study pointed to health as a major consideration in deciding what type of policy to have on the use of psychoactive substances. It is also clear here that measures of health, well-being and the global burden of disease – measuring, for example, lost days due to ill health or premature deaths – have been an important advance in evaluating how well policy has been implemented. The most recent findings from social cognitive neuroscience provide insights into what determines our health and well-being – in either the absence or presence of psychoactive substances – and as such should be taken on board in developing and implementing policy in this domain.

Policy-makers looking to ensure health and well-being might also want to consider what elements could constitute a healthy lifestyle and promulgate these to the whole population, but most importantly to those who are at most risk of developing practices that are unhealthy or may jeopardise health and well-being in the future. Secondary prevention may be used as a tool, for example in campaigns targeting youngsters with specific psychological traits like sensation-seeking that guide their decisions. It is also acknowledged that preventing use when young reduces problems related to use later on.

Policies related to health and well-being also need to include the latest findings from science when attempting to address those who

have become addicted/dependent with repeated use. Harm-reduction policies came into being as a result of the need to tackle emerging health problems, mainly those related to the spread of HIV. In general, national policies followed only after measures on the ground proved positive, but in future this pattern needs to be reversed because policy makers should take cognisance of current scientific evidence earlier on. Treatments in this field are advancing at a considerable pace: at the time of writing, a cocaine vaccine will be available within the year and a nicotine vaccine shortly thereafter.

Whether we opt for a policy for each substance or an integrated one for all now seems to need further consideration in the light of scientific findings and what actually happens in practice. The second part of this book attempts to understand the current state of play by an empirical analysis of practice and the reasons for it.

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