3. INTRODUCTION

The Decade of the Brain (1990-99), launched by the President of the United States on 17 July 1990 (Proclamation 6158), was devoted to increasing our understanding and awareness of the function of the mind/brain in health and disease. This has resulted today in a number of significant initiatives that provided the basis for the mushrooming of neuroscience that would not have been entertained some ten years ago. For example, the OECD (2002), in its book *Understanding the brain: towards a new learning science*, addresses the issue of why it is we need to have an understanding of the working of the human mind if we are to better educate our young in the future. In addition, in the same year, the Society for Neuroscience released its publication entitled *Brain facts: a primer on the brain and nervous system* to specifically encourage research in neuroscience, to promote education in the neurosciences and, last but not least, to inform the public of the research findings and their implications. This was followed, in 2004, by the World Health Organization's *Neuroscience of psychoactive substance use and dependence*, which directly deals with the issue of the brain mechanisms involved in both the use of licit drugs, such as tobacco and alcohol, and illicit ones, such as heroin and cocaine for example, and the dependency that may follow.

All these three publications would appear to highlight the emergence of the field of neuroscience, through which it is now possible to ask questions and expect answers to some of the most complex issues such as why do some people who use such drugs become dependent on them while others do not. Of those who do, what is it about their brains which compels them to continue to use in spite of the sometimes debilitating effects on their health, as well as the unfavourable social outcomes? Moreover, will an understanding of the brain mechanisms that lead to dependence provide the means through which novel pharmacological/cognitive treatments can be developed to alleviate all drug-induced dependencies and not only those related to the opiates? In other words, will such endeavours increase the treatments available and in the long run reduce the potential for relapse. These questions typically address the end of the spectrum of drug use, that is dependency; the main focus being to identify what has been termed the "molecular switch".

Moreover, the virtual completion of the Human Genome Project has also provided us with the fact that some 30 000 genes are responsible for assembling a human and that 70% of these are required for putting together the organ of the mind, the brain. This piece of information may provide further insight into those more predisposed to substance abuse and might provide part of the answer as to why some people are more

prone to experiment with drugs in the first place and then are at an increased risk of developing dependency. In addition, the Human Genome Project heralded the promise of gene therapy but as yet this has not been forthcoming and will not be so for some time yet as we still have to understand how development actually ensues before tinkering with some of the basic elements. Gene silencing may provide alternatives to gene therapy as such but it is still in the early stages of development as is antisense technology (see section 5.3) as well as stem cell therapy. Pharmacogenomics, an offshoot of the Human Genome Project, has at its core, the concept of personalised medicine. In itself this would mean, for example, better use of medicines in the relief of dependencies, in that the present drugs do not all work efficiently on everyone, probably as a result of the fact that the different receptor subtypes that these medicines target are somewhat differentially responsive in all of us due to the different combinations that appear as a result of slight differences in the codes (polymorphisms) that lead to their production. For example, there are at least two types of D2 dopamine receptors within the brain that are found in the "reward circuitry"; a high affinity and a low affinity one in which some of the population may have a preponderance of the former that may result in a poor response to a medicine that specifically targets this type of receptor.

On the other hand, questions such as why do most people who are not genetically predisposed in the first place resort to trying these substances would appear to be an issue addressed mainly by social psychology or the social sciences in general. Korf et al. (2005) look at this particular issue in more detail but it is now becoming more adroit in the field of neuroscience to also include this particular issue as witnessed by the publication of *The neuroscience of social interaction* by Frith and Wolpert (2004). This book was published following the first conference in 2001 related to the area that has come to be known as "social cognitive neuroscience". Moreover, it is now emerging that if one wishes to address behaviour in all its contexts then the social aspect has to be integral to any theoretical framework that seeks to explain the complex issue of drug use (see, for example, Hartnoll, 2004).

Moreover, in terms of prevention of use this should further strengthen the evidence base upon which such programmes are developed that highlight the understanding of the risk and protective factors for experimental use and relapse.

Consequently, the "biopsychosocial model" refers to a comprehensive model of drug use and dependency that may now be replaced by the framework provided by social cognitive neuroscience. Thus, it is crucial to differentiate between the factors involved in experimental use (these

in turn would appear to be mainly social) from the those factors that lead to maintenance and dependency. Petraitis et al. (1995) have suggested three factors and three levels for experimental drug use that can be framed in a three by three matrix. The three factors are: (i) social/interpersonal, which include the well-known peer pressure; (ii) cultural/attitudinal, which include beliefs that the benefits of use outweigh the risks; and (iii) intrapersonal, which includes, *inter alia*, the belief that one is in control of one's use. The levels *per se*, proximal, distal or ultimate, relate to how closely specific factors influence experimental use and as such it is the proximal ones that have the most direct effect whereas the ultimate ones are at the other end of the scale. From the neuroscience perspective, it is personality traits commonly associated with substance use – for example, impulsivity and novelty seeking – that may provide some insight into why one starts to experiment with such drugs.

Development and maintenance of drug seeking and drug use has clearly been the domain of cognitive neuroscience over the past twenty years with millions of papers resulting from the millions of dollars of funds apportioned to the field mainly in the United States. However, it would appear that the factors related to dependency can be best described as drug related in that they involve positive reinforcement, subjective effects, conditioned stimuli and aversive effects (Stolerman, 1992). Indirect influences, such as sociocultural, psychological and genetic factors, are considered as risk factors or protective factors..

The concept of reward is at the core of research into drug dependency in that drugs of abuse would appear to entrap the brain system cum "reward circuitry" that processes such information, which in turn influences most of our decisions. In a world where hedonism seems to drive most things, the very fact that such drugs in both animals and humans seem to accentuate directly the pleasure that ensues, following the stimulation of such a pathway, it is no surprise that neuroscience has permeated most subject areas involved in the understanding of human behaviour. On the other hand, it has been suggested that mental disorders – such as depression, with one of its cardinal symptoms, the inability to experience pleasure – result from a dysfunction within the "reward circuitry" (Willner et al., 1991). That substance abuse/dependency is also now considered a disorder/disease as per the ICD 10 (*International statistical classification of diseases and related health problems*, 10th revision, World Health Organization, 1992) or DSM IV (*Diagnostic and statistical manual of mental disorders*, 4th edition, text revision, American Psychiatric Association, 2000) has stemmed from the fact that dependency is associated with loss of control as suggested by the disease model propounded by Jellinek in the 1960s for alcohol dependency.

One may add at this juncture that the DSM IV is now more used by the research fraternity, and increasingly so by clinicians, whereas health statistics are still reported in accordance with ICD 10. Over the years there has been a call for better integration of both these classification systems and the agenda for the revision of DSM IV to V for 2010 is that such an undertaking will in effect be conducted (Kupfer et al., 2002). It is imperative to have a clear and concise description of the syndrome in question, namely substance abuse, and the accompanying symptoms if one is to model the disorder in an attempt to gain a better understanding of the aetiology and pathophysiology. It is also the case that research *per se* in this area could better facilitate the description of the symptoms based on a better understanding of brain function.

Prior to expanding on some of the issues raised above in the format of popular themes in drug research in neuroscience today and those of tomorrow and the accompanying methodologies or technologies that will enable such themes to be addressed, one may add that current practice in science involves constructing a theoretical framework, from which it is then possible to start one's endeavours. It is of very little use to conduct a study just to state that a particular medication for example has an effect on a particular cohort without relating it to the conceptual framework. As such, it is also quite demanding to expect that an experiment incorporate everything, that is the genetic make-up of the cohort under test, the molecules, systems, brain regions and the social context under which a particular behaviour is central to the study. Thus, the expanding domain of neuroscience under which drug research clearly sits is governed by the type of question one is willing address. However, social cognitive neuroscience, behavioural/systems neuroscience, clinical neuroscience, molecular and cellular neuroscience, and the genetics of dependence may provide the most suitable stages to address issues related to use, abuse and drug dependency in the field of drug research.