

underlying the generation of brain pathology, we have studied the possible involvement of these molecules in the cognitive effects induced by glucocorticoids. Our results have highlighted CAMs regulation at the level of the hippocampus and the frontal cortex, as a correlate of time-dependent effects of stress and glucocorticoids on learning and memory processes.

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<p>Symposium 12: Behavioural disinhibition and its relation to affective disorders Organized by A. Roberts</p>

Symp 12/1

NEURAL MECHANISMS UNDERLYING THE BEHAVIOR OF PATIENTS WITH VENTROMEDIAL PREFRONTAL CORTEX LESIONS

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Patients with bilateral damage to the ventromedial prefrontal cortex (VMF) develop severe impairments in personal and social decision-making, in spite of otherwise largely preserved intellectual abilities. This class of patients can be described as intelligent and creative before their brain damage. After the damage, they begin to pursue actions that often lead to losses of diverse orders, e.g., financial losses, losses in social standing, losses of family and friends. The choices these patients make are no longer advantageous, and are remarkably different from the kinds of choices they were known to make in the pre-morbid period. These patients often decide against their best interests. They are unable to learn from previous mistakes as reflected by repeated engagement in decisions that lead to negative consequences. Hence, we ascribed to them the term “acquired sociopaths”. For many years, the condition of these patients has posed a double challenge. The first, although the decision-making impairment is obvious in the real life of these patients, there had been no laboratory probe to detect and measure this impairment. The second, there had been no satisfactory account of the neural and cognitive mechanisms underlying the impairment. Over the past few years, we succeeded in overcoming these challenges by, first, the development of the “gambling task” which enabled us to detect these patients' elusive impairment in the laboratory, measure it, and investigate its possible causes. Second, by making progress in understanding the nature of this impairment at the behavioral, physiological, and cognitive levels. In this paper, we review evidence suggesting that decision-making is a process guided by emotional signals (somatic states), which we define as the bio-regulatory responses that are aimed at maintaining homeostasis and ensuring survival. Damage to the VMF precludes the enactment of emotional (somatic) states in anticipation of future consequences, and consequently lead to disadvantageous decisions. The nature of this defect is discussed in relation to other mechanisms of the frontal lobe, including working memory, impulsiveness and response inhibition.

Symp 12/2**SEROTONIN, DOPAMINE AND IMPULSIVE DECISION MAKING***J. Evenden**Astra Arcus USA, Three Biotech, One Innovation Drive, Worcester, MA 01605 USA*

Impulsive behaviour is fairly common in everyday life, and may have both positive and negative results. Pathological impulsive behaviour is prevalent in a number of psychiatric and neurological disorders, and although some success has been obtained with the selective serotonergic reuptake inhibitors as yet there is no adequate treatment. Cognitive psychology postulates that prior to impulsive behaviour a process of decision making must have taken place which can also be characterised as impulsive. Many different aspects of cognition, such as memory, attention, motor control or reward and punishment, can contribute to this process. Given what is known about the neurobiological basis of these, it is reasonable to assume that the neurobiological factors giving rise to an impulsive decision must be very complex, and might be different depending upon the type of decision to be made. However, these have been very little studied in practice. The hypothesis that low levels of brain serotonin underlie much pathological impulsive behaviour has gained credence based upon human studies (CSF sampling and more recently PET studies) and animal studies (mainly brain lesions). A simple explanatory model suggests that there are three important and discriminable ways in which impulsive decision making can affect behaviour: in the preparation for action, in the execution of a chain of actions, and in the evaluation of the outcome of a planned action. The present author has devised three operant behavioural procedures employing rats as subjects to examine these: an uncertain visual discrimination (preparation), a paced fixed consecutive number schedule (FCN, execution), and a variable delay of reinforcement procedure (outcome evaluation). These procedures use the same response (lever pressing), the same motivational state (food restriction), and the same reinforcer (food pellets). The dopaminergic drugs amphetamine and haloperidol had the greatest effects on responding in the paced FCN procedure, in which both drugs increased impulsivity. Haloperidol increased impulsivity at the same doses as it reduced the amount of behaviour, which may suggest why antipsychotic agents are not particularly useful for treating impulsivity in the clinic. The effects of the serotonergic drugs were different amongst the three tests which suggests that serotonin can modulate separate aspects of impulsivity differently depending upon the receptor subtype mediating the effect. For example, the 5-HT₂ agonist DOI increased impulsivity in the paced FCN procedure, but reduced impulsivity in the uncertain visual discrimination. Further experiments are needed with chronic drug administration and selective brain lesions to confirm this picture.

Symp 12/3**THE NEUROCHEMISTRY OF THE PREFRONTAL CORTEX, AMYGDALA AND VENTRAL STRIATUM IN THE MODULATION OF AFFECTIVE RESPONSES***J.D. Jentsch**Section of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven Connecticut 06520-8001 USA*

The net behavioral response of any mammalian organism is likely a multivariate function of interactive and competing brain processes that include arousal and perception, autonomic, unconditioned and conditioned responses and cognition. The neural substrates of these independent facets of behavioral regulation are somewhat understood, but less is known about

the interactions between these brain systems. The current presentation will address interactions between the prefrontal cortex, amygdala and ventral striatum in the generation and cognitive modulation of stimulus-reward associations and will highlight the role of dopamine and associated cellular signalling pathways within each of these key structures. The relevance of these effects to the affective disturbances of schizophrenia and drug-addiction will be stressed. Our original studies demonstrated that long-term exposure to the psychotomimetic drug-of-abuse phencyclidine (PCP) produced performance deficits on the acquisition of an object retrieval/detour task by monkeys, and these impairments were correlated with reduced dopaminergic transmission within the prefrontal cortex. Likewise, subchronic PCP administration to rats produced impairments on a discrimination reversal task. We further measured acquisition of a new response for a conditioned reward (CR) and found that PCP-treated rats produced more responses for CR than did saline-treated controls. These data suggest that long-term PCP treatment produced impairments in the ability to regulate responding towards conditioned and unconditioned reward. We then hypothesized that this form of drug-induced impairment in inhibitory control could have relevance for drug addiction, in general. We have examined the effects of repeated treatments with d-amphetamine or cocaine on incentive learning and responding for CR. Chronic cocaine or amphetamine enhanced Pavlovian approach behavior towards a CR and augmented lever pressing for a CR. Parallel studies suggest that these effects may be dissociably mediated by alterations in dopaminergic transmission and protein kinase A activity within the prefrontal cortex, amygdala and ventral striatum. Our studies suggest that the affective impairments of drug addiction and schizophrenia may be explained, in part, by altered interactions between the amygdala and prefrontal cortex within the ventral striatum, resulting in alterations in incentive learning, conditioned reward and inhibitory control. Dopaminergic transmission, and its effects on protein kinase A, within each of these areas may contribute to the behavioral changes.

Symp 12/4**PREFRONTAL CONTRIBUTION TO INHIBITORY CONTROL AND AFFECTIVE BEHAVIOUR: NEUROPSYCHOLOGICAL STUDIES IN MARMOSETS***A. Roberts**Department of Anatomy, University of Cambridge, Cambridge, CB2 3DY, UK*

The medial and orbital prefrontal cortices have been implicated in the inhibitory control of behaviour as well as specifically, in the expression of emotional and social behaviour. Humans or non-human primates with damage to these regions may exhibit impulsiveness and inflexibility, emotional disturbances and anti-social behaviour. In addition, a variety of neuropsychiatric disorders such as depression, obsessive compulsive disorder, schizophrenia and sociopathy are associated with dysfunction in these regions. However while the precise relationship between inhibitory control, affective processing and the prefrontal substrates underlying these processes is poorly understood recent findings in the common marmoset, a new world primate, have begun to shed light upon these issues. This presentation will describe the dissociable behavioural effects of excitotoxic lesions of the medial and orbital prefrontal cortex on a range of affective and inhibitory control tests including object retrieval, food preference and extinction of a rewarded response. Overall, the results are consistent with the hypothesis that both medial and orbital prefrontal cortex may be involved in the control of affective processing but their roles are differentiated through the nature of the associations governing behaviour.

Symposium 13: Cerebellar plasticity during development and at adult age: structural and behavioural effects
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Organized by P. Strata and A. Gramsbergen
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Symp 13/1**THE EFFECTS OF OLIVARY DESTRUCTION AT EARLY AND LATER POSTNATAL STAGES ON CEREBELLAR DEVELOPMENT AND MOTOR BEHAVIOUR IN RATS**

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The inferior olivary nucleus together with the climbing fibre system at adult age plays an important role in the processing of information from the spinal cord. Both the climbing fibre system and the mossy fibre system develop late in neuro-ontogeny and mature functioning of both input systems has been demonstrated to occur from the end of the second week of life. This is further illustrated by our finding that cerebellar hemispherectomy at ages before the 10th postnatal day (P10) leads to motor handicaps only from P15. The problem of the present research is how this late development is related to the compensational capacity of the cerebellum after selective lesions. We concentrated upon the