Editor's Note

J. Greg Anson

To cite this article: J. Greg Anson (1990) Editor's Note, International Journal of Neuroscience, 51:1-2, 105-139, DOI: 10.3109/00207459009000516

To link to this article: http://dx.doi.org/10.3109/00207459009000516

Published online: 07 Jul 2009.

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Editor's Note

In August 1989, the Seventh International Australasian Winter Conference on Brain Research was held, once again, in Queenstown beside Lake Wakatipu in the South Island of New Zealand. Although snow conditions were less than favourable for experienced skiers, the majestic beauty of the alpine setting contributed significantly to the continued success of the conference. The 64 abstracts which appear in this issue of the International Journal of Neuroscience, represent the multidisciplinary and multinational flavor which is a recurring theme of the meeting. Participants from New Zealand and Australia were joined by representatives from West Germany, Japan, United States of America, United Kingdom, Sweden, The Netherlands and Canada. While the interdisciplinary theme of the conference remains its mainstay, symposia highlighting specific themes are encouraged. This year Neil McNaughton (University of Otago, New Zealand) and Gavin Andrews (University of New South Wales, Australia) organised a very successful symposium on Anxiety with sessions featuring epidemiology, threat, personality, clinical pharmacology and panic disorder. In addition other areas of interest to neuroscientists included sessions featuring Neuropsychology, Neurology, Cortex and Striatum, Neural Plasticity, Spinal Cord, Motor Control, Brain and Behavior, and Hippocampus. The success of the conference depends in part on external financial support. For this we are particularly grateful to the New Zealand Neurological Foundation whose contribution facilitated student participation. Contributions were also received from the Mount Cook Line and Gordon and Breach, Science Publishers, Inc. In August 1990 the Eighth International Winter Conference on Brain Research will be held, again in Queenstown, New Zealand.

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University of Otago
Effects of Subarachnoid Haemorrhage on Recognition Memory Ability

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Thirty-five subjects who presented with subarachnoid haemorrhage at Auckland Hospital were given Warrington's Recognition Memory Test (RMT) for faces and words. The RMT was administered prior to discharge and also at a six week follow-up session. In addition, neurological information on the presence of localised blood revealed by CT scan, and site and side of aneurysm was obtained. Results indicated that patients with blood in the Basal Cisterns were impaired relative to patients without blood in this region, whereas blood found in either the right or left Sylvian Fissures was not related to performance on the RMT. Side of aneurysm and presence/absence of an Anterior Communicating Artery aneurysm were also not useful prognostic indicators. Finally, subjects with no identified aneurysm had lower scores on the RMT compared to subjects who had their aneurysms clipped.

Factors Affecting the Decay of Long-term Potentiation in the Dentate Gyrus of Unanaesthetized Rats

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We examined how the decay of long-term potentiation (LTP) of the perforant path input to the dentate gyrus was affected by varying tetanization protocols at the time of LTP induction. Male Sprague-Dawley rats were surgically implanted with stimulating and extracellular recording electrodes. Two weeks later, baseline recordings to fixed perforant path test pulses were made for 1 week prior to tetanization. Responses were monitored 1, 2, 4, and 7 days post-tetanization and then weekly until LTP had completely decayed. Single negative exponential functions were fit to the decay curves for both the population EPSP and the population spike measures. LTP induced by 10 trains on one day decayed with a time constant of 2.8 and 3.0 days for the EPSP and spike, respectively. Fifty trains, in bursts of 5 trains 1 sec apart (1 min inter-burst interval) increased the LTP decay constants to 23.4 and 27.9 days for the EPSP and spike. Similar decay constants were found when 10 trains were given on 5 consecutive days. However when the 50 trains were delivered when the animal was anaesthetized with pentobarbital, the decay constant was similar to that following just 10 trains, i.e. 6.0 and 3.8 days for the EPSP and spike. These data indicate that the decay of LTP is variable, and a function of the tetanization parameters employed to induce it. The enhancement by pentobarbital of LTP decay suggests the possibility that there exists some mechanism, sensitive to this general anaesthetic, that is important for the development of very long-lasting LTP.
A Multi-phase Model of LTP Maintenance Based on Exponential Decay Functions

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Although long-term potentiation (LTP) has long been regarded as a long-term information storage mechanism in the central nervous system, little is known about how long LTP actually lasts and the factors that influence its decay. Racine et al., (Brain Research, 1983, 260, 217-232) reported LTP decay to be described by two negative exponential functions, with decay constants of about 1.5 hr and 5 days, while Barnes and McNaughton (Behavioral Neuroscience, 1985, 99, 1040-1048) reported a decay function with time constant of 37 days. Recent work from our laboratory (see Jeffery & Abraham abstract, this volume) has confirmed that a variety of LTP decay functions can be obtained, depending on the induction protocol. When decay constants for perforant path to dentate gyrus LTP are pooled from the literature (values either directly available or calculated from published data), three discrete groupings are observed, with time constants of 2.1 hr, 4.1 days and 23.8 days. No major differences between EPSP and population spike decay have been reported. These groups may be referred to as LTP1, LTP2 and LTP3 in Racine's terminology, and appear to represent serially organized phases of LTP maintenance. Pentobarbital, given at the time of LTP induction, prevents the appearance of LTP3. Anisomycin, a protein synthesis inhibitor, prevents both LTP2 and LTP3. It is clear from the literature that LTP1 is a protein synthesis-independent phase, while LTP2 is protein synthesis dependent. We suggest that LTP3 involves a qualitatively different biochemical mechanism, such as a change in gene expression perhaps initiated by depolarization-mediated activation of proto-oncogenes.

The Suppression of Water Intake by a Dopamine Agonist, Pirebedil

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Dopamine (DA) is a weak dipsogen when injected IVT or subcutaneously (sc). In this study we examined the effect of a DA2 agonist (pirebedil) on the water intake of rats and whether the subfornical organ is essential for its effect. We used 14 300-400g male Wistar rats. The rats were anaesthetised with Equithesin and electrolytic lesions made stereotactically in the subfornical organ (7) or the cerebral cortex (7). Two weeks later the rats were housed in individual cages and deprived of water from 5.30 p.m. The next morning pirebedil, 1mg/ml/kg, or normal saline was injected sc in a volume of 1ml/kg. Fifteen minutes later the rats were given free access to water from a calibrated burette with a drinking spout. The volumes drunk at 15, 30 and 60 min were noted. Experiments were repeated at three day intervals. Rats, after pirebedil injections, whether they had had control (cortical lesions) or subfornical organ lesions, drank significantly less (p < .05) at 15, 30 and 60 min than they did after saline injections, suggesting the subfornical organ is not necessary for the action of pirebedil.
The Responses of Guinea Pig Vestibular Nucleus Neurons Following Chronic Unilateral Labyrinthectomy: An Electrophysiological Study in Vitro.

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The recovery of oculomotor and postural disorders following unilateral labyrinthectomy (UL), is correlated with a return of resting activity to neurons in the medial vestibular nucleus (MVN) on the deafferented side, possibly as a result of the intrinsic properties of the neurons in the deafferented MVN. In this study we examined the single unit extracellular responses of MVN neurons in brainstem slices from guinea pigs with both labyrinths intact compared with those from guinea pigs 6–8 weeks following a UL. Albino guinea pigs were etherized and decapitated and the brains removed to ice. Brainstem slices were cut by hand and incubated in a slice chamber for 1 hour prior to recording. In the slice chamber the slices were continuously perfused with standard artificial cerebrospinal fluid (ACSF). A total of 63 neurons were recorded: 15 from control animals, 48 from animals with a chronic UL. To test the effect of blocking synaptic transmission on resting activity, neurons were recorded before, during and after perfusion with 15mM MgCl₂ ACSF. Since the majority of MVN neurons ipsilateral to the UL were not silenced by high Mg⁺⁺ ACSF, our results suggest that the regeneration of resting activity in the ipsilateral MVN may be due to change in the deafferented MVN neurons themselves.

Responses of Subfornical Organ Neurons to Dopamine: An Electrophysiological Study In Vitro

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The subfornical organ (SFO) is one of the circumventricular organs; located on the ventral surface of the fornix, it protrudes into the third ventricle at the level of the interventricular foramina. Neurons in the SFO have been found to respond to changes in the osmolarity of the extracellular fluid, and it has been hypothesized that these neurons are involved in the initiation of drinking behaviour. In this study we examined the extracellular single unit responses of SFO neurons to dopamine (DA).
Male Wistar rats were decapitated and the brains quickly removed to ice. An explant of brain tissue containing the SFO was dissected out and incubated in a slice chamber for 1 hour prior to recording. In the slice chamber the explant was continuously perfused with artificial cerebrospinal fluid (ACSF) containing (in mM): NaCl 126, KCl 5.0, KH2PO4 1.25, MgSO4 1.3, NaHCO3 26.0, glucose 10.0, CaCl2 0.5 at pH of 7.4. Forty neurons were tested for responses to DA by recording activity before, during, and after perfusion with ACSF containing DA (10^-4 M). Sixteen neurons decreased activity, 7 neurons increased activity and 17 showed no change in response to DA. When tested with the D2 agonist Quinpirole (10^-6 M) or the D2 antagonist Remoxipride (10^-6 M) the activity of the DA sensitive neurons was also modulated, suggesting that the D2 receptor is involved in the responses of SFO neurons to DA.

The Effects of NMDA Receptor Antagonists on Eye Movement and Vestibular Nucleus Activity Following Unilateral Labyrinthectomy in the Guinea Pig.

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The NMDA receptor is involved in many forms of cortical plasticity. We have conducted a series of behavioural and electrophysiological studies examining the role of the NMDA receptor in the neural plasticity which follows surgical unilateral labyrinthectomy (UL). Guinea pigs (n=40) received a UL and the disordered eye movements which resulted from this operation (spontaneous nystagmus, SN) were measured up to 3 months afterward. Intraperitoneal injections of the NMDA receptor antagonists CPP (1.0, 5.0 mg/kg) or MK801 (0.5, 1.0 mg/kg) were given at various times after the UL. Normally, SN has disappeared by 52 h post-UL. An injection of CPP or MK801 resulted in an increased SN, or a return of SN, up to 1 week post-UL; thereafter these drugs had no effect. Our recordings from medial vestibular nucleus (MVN) neurons in vitro, in brainstem slices from guinea pigs compensated for UL, show that approximately 60% of neurons ipsilateral to the UL show a decrease in firing in response to CPP (10^-8 M) or MK801 (10^-6 M). These results suggest that the NMDA receptor may contribute to the neural changes responsible for vestibular compensation.
The Role of Dopamine in Prism Adaptation, Tested In Parkinsonian Subjects

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The hypothesis has been advanced (Miller, International Journal of Neuroscience, in press) that dopamine plays a role in acquisition of motor control similar to the dopaminergic reward signal believed to be involved in instrumental conditioning in animals. Experiments are currently in progress to test this hypothesis. The rate of adaptation of a reaching response is being studied when vision is distorted using prismatic lenses. Accuracy of reaching for a target, with a rapid ballistic movement is assessed before, during and after wearing prismatic lenses. The subject never sees the reaching arm or hand. While wearing the lenses, information to facilitate adaptation of the reaching response is provided in one of two ways: (i) after each reach subjects are allowed to see the position their arm has reached ('knowledge of results': KR). (ii) Alternatively, while wearing the lenses, subjects periodically view hand and forearm during a slow self-paced tracing movement (not directed to any target). In the latter condition no specific KR is provided. However, the former condition seems akin to reward-mediated learning, as defined by Thorndike's Law of Effect (Adams, Journal of Motor Behavior, 1971, 3, 111-114). Results so far show that mildly Parkinsonian subjects fail to adapt during the first exposure condition, while in the second exposure condition adaptation is less severely affected. Acquisition of motor control by KR seems to be impaired when striatal dopamine is depleted.

Two Neurodynamic Modes in the Mammalian Striatum, Under Cholinergic/Dopaminergic Control: (1) Basis in Experimental and Clinical Literature.

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The principle neurons in the neostriatum are medium spiny neurones, which send inhibitory connections to each other and to various outflow sites. There is also a small minority of large cholinergic neurones whose projections are confined to the striatal neuropil. Electrophysiological experiments (Rebec & Curtis, Synapse, 1988, 2, 633) show reciprocal inhibition between populations of striatal neurones. However after
administration of the D-2 dopamine antagonist haloperidol, this pattern disappears, and is replaced by co-activation of these striatal neurones. Functional parallels of these results are apparent in the differences between motor function in normal subjects and in Parkinson's Disease (PD): Under normal circumstances, antagonistic pairs of muscle groups are activated by reciprocal inhibition, and therefore movements are free. In contrast, in PD, there is co-contraction of antagonistic muscle groups, leading to the symptom of rigidity. We propose that the striatum represents events (such as muscle activations) which tend to be mutually antagonistic. However, for such representations to be realized in neural activity, adequate dopaminergic tone in the nigrostriatal pathway is required. Dopamine, acting at D-2 receptors inhibits tonic activity in the cholinergic interneurones. Modulation of cholinergic activity in turn can control the degree of rigidity/mobility in the limbs. We therefore suggest that under high and low cholinergic tone, striatal neurodynamics correspond to co-activation and reciprocal inhibition respectively. The biophysical mechanism by which acetylcholine achieves this switch is unknown, and is dealt with in the companion paper.

**Two Neurodynamic Modes in the Mammalian Striatum, Under Cholinergic/Dopaminergic Control: (2) Results of a Computer Simulation**

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A reciprocal inhibitory relationship exists between principal output neurons of the striatum. Competition among these neurons may function to prevent coactivation of neurons which represent incompatible actions. There is indirect evidence that excess acetylcholine levels favour coactivation over competition. We consider a possible explanation for this. Prominent among the effects of acetylcholine described in the striatum and elsewhere is a prolonged change in a membrane potassium conductance ($G_K$). We simulated the effects of different $G_K$ values on the responses of a simplified model of a striatal neuron in which the membrane potential ($v$) obeys the equation:

$$\frac{dv}{dt} = \frac{(V_E - v)G_E + (V_L - v)G_L + (V_I - v)G_I + (V_K - v)G_K}{C}$$

where $G_E$, $G_L$ and $G_I$ are excitatory, leak, and inhibitory conductances (respectively) with reversal potentials $V_E > V_L > V_I > V_K$ and $C$ constant. Increasing $G_K$ hyperpolarized the resting membrane potential, reduced EPSP peaks, and reversed the sign of the IPSPs. These characteristics were incorporated into a model of a domain in which all the neurons were mutually inhibitory. Increasing $G_K$ decreased competition and increased coactivation. In networks larger than one inhibitory domain, alternating zones of excitation and inhibition form spontaneously at low $G_K$, but give way to more uniform activation at high $G_K$ values. This trend was robust. These effects of $G_K$ on striatal neurodynamics are sufficient to explain how a switch between coactivation and competition occur. If Parkinsonian rigidity is due to excess of acetylcholine, then a testable prediction of the model is that the relevant effect of acetylcholine on striatal output neurons is an increase in $G_K$. There is as yet no conclusive evidence on this point.
The assessment of attention deficits in head injured persons lacks a coherent theoretical model. As a result, there is often confusion about what sort of attention is being evaluated and how it relates to other sorts. This creates problems both for adequate assessment of attention deficits and for choice of appropriate remedial procedures. In particular, laboratory-type tasks used for testing and training attention may have little to do with the attention problems encountered in normal daily activities. Evidence suggests that this is particularly true of computerized ‘cognitive rehabilitation’ programmes, contrary to the claims of the burgeoning software industry. The paper proposes a model for evaluating generalizability of procedures for assessment and remediation of attention deficits in head injured persons. Illustrative data are presented from research in progress.

Age Related Changes in Exploration, Passive Avoidance, Radial Maze Learning and Structure of the Dentate Gyrus in Wistar Rats

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Wistar albino rats aged 9 months (young adult), 18 months (middle aged) and 24 months (old) were given behavioural tests designed to relate to functioning of the hippocampus. In a passive avoidance task, immediately after one shock in a previously safe compartment, the middle aged group avoided more successfully (with longer latencies) than both other groups. However the old group performed better than the young group 24 hours later. Both older groups were also more cautious and slower to explore a new environment. In the early acquisition stage of an 8 arm radial maze task with 4 arms baited, the old group made more errors, both to never rewarded arms and to previously rewarded arms, compared to young and middle aged groups. However there were no group differences on number of trials taken to reach criterion nor were there any differences on a reversal of this task. On structural measures of activity in the dentate gyrus, there were no differences in volume densities of mitochondria but older animals had significantly greater surface densities of synapses, compared to young rats.
Longitudinal Assessment of IQ Following Head Injury: Some Conceptual Guidelines

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It is often necessary for clinical neuropsychologists to assess a client’s IQ across time and this frequently involves the use of different tests. Recent theory and evidence suggests that, all else being equal, IQ points are gained as a test ages. This needs to be considered when examining changes in test performance. To allow quick adjustment for such age-of-test effects a table of adjustment values was derived for five Wechsler Intelligence Tests. Evaluation of the proposed adjustments by applying them to previous research findings showed that most observed IQ discrepancies across tests no longer reached significance when adjustment for the age of the tests is made. Similar adjustment values were also derived for subtest scores and their use will be briefly examined. Some cautions concerning the application of this procedure in the individual case will also be outlined and some case examples will be presented.

Dynamic System Theory and EEG-Activity

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Recent Dynamic Systems theory has revealed a wide range of structure in previously intractably complicated phenomena. These structural features include bifurcation points, and chaotic attractors. Tools for determination and qualification include the estimation of the correlation integral C(r) and the Lyapounov-exponents and K-entropies. Treatment of EEG-Signals with these methods has indicated the existence of strange attractors. These tools allow inference of the minimum parameter set which is required to define the systems dynamic differential equations, although it is not possible to derive the equations explicitly. The foetal sheep preparation offers a special opportunity to obtain estimates of dynamic systems parameters for EEG, over the time in which the brain matures. Electrocortical activity can be recorded in foetal life, from about 100 days gestation, to birth at about 140 days. During this time the sheep brain undergoes extensive myelinization and develops slow wave, and rapid-eye movement, sleep. Together with autoregressive parameters, the above mentioned non-linear analysis methods may permit identification of the minimum dynamic properties to be explained by a mathematical neural network theory, for each stage of neural maturation.
Assessment and Classification Using the McCarron Neurodevelopmental Battery

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Methods of assessing neuromuscular development and delay are still hampered by limitations in our understanding of motor control and learning. A shift in emphasis from product to process measures has led to the development of batteries which include quantitative and qualitative assessment of movement such as the McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1982). This paper reported preliminary Australian norms for the MAND based on 246 children enrolled in one primary school. They ranged in age from 4 to 12 years. Using the American norms 2.4% of the population demonstrated a neurodevelopmental profile considered moderately delayed/disabled, while a further 12.5% exhibited a mild disability. Normal development for age was observed in 73.0% and 12.1% demonstrated superior levels of co-ordination. The performance of all children in this sample aged 6 to 9 years (n = 130) was then compared to the initial MAND assessment of 99 children aged 6 to 9 years who had attended or were attending a remedial movement programme. Multivariate Analysis of Variance showed a highly significant difference between the groups on the MAND \( F_{10,218} = 30.86, p < .0001 \) with all 10 fine and gross motor variables able to separate the samples. Discriminant function analysis using the 10 variables was able to successfully classify 87.9% of the movement impaired sample and 90.8% of the school based group.

Movement Difficulties Experienced by Dyspraxic Children

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Children considered dyspraxic or clumsy are initially identified by the awkwardness of their motor performance. Comparisons of their movement patterns with normally performing age matched peers have shown problems at the temporal, kinematic and kinetic levels of analysis. This study of sprint running expands on the description of impaired movement processes in clumsy children. Fourteen poorly coordinated (PC) and the same number of well coordinated (WC) children were identified using the gross motor section of the McCarron Neuromuscular Development battery. The subjects were filmed for two trials, using a high speed Photosonics camera set at 100 fps, between the 15 and 20 metre section of a maximal effort 50 metre run. The well coordinated children were also filmed at reduced speed comparable to the mean maximal velocity of poorly coordinated children obtained in a pilot study. As expected, comparisons of velocity during the filmed segment of the faster trial confirmed that the WC children had a significantly higher velocity than their PC peers. An Analysis of Variance of preliminary data showed that the relative time spent in support by the PC group \( (M = 33.9\% \pm 4.1) \) was significantly longer \( (F_{1,26} = 15.59, p = 0.001) \) than the WC group \( (M = 29.1\% \pm 2.1) \). By contrast the flight time of the PC group \( (M = 32.3\% \pm 8.0) \) was significantly less \( (F_{1,26} = 23.16, p=0.001) \) than
their WC peers ($M = 42.9\% \pm 2.0$). The increased percentage of cycle time spent in flight by the WC group ($M = 41.0\% \pm 6.2$) was maintained while performing at the controlled velocity. Differences in performance will be considered in relation to the movement patterns and functional estimates of anaerobic power.

An Ultrastructural and Immunocytochemical Study of Bronchopulmonary Paraneurons in the Bandicoot

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A class of paraneurons have been described in the epithelium of pulmonary alveoli and bronchioles of the Bandicoot lung. These Bronchopulmonary paraneurons are thought to act as airway chemoreceptors and are ideally situated to perform such a function. Ultrastructural analysis has revealed at least two distinct types of nerve profiles innervating these paraneurons. The first type contained predominantly mitochondria with a few agranular vesicles and were thought to be sensory. The second type contained large numbers of synaptic vesicles which were characterised as adrenergic fibres and were probably efferent. Antibodies raised against serotonin (5HT) and Calcitonin Gene Related Peptide (CGRP) and fluorescence microscopy was used to study the distribution of these two putative neurotransmitters. 5HT- and CGRP-like immunoreactivity (-LI) was observed to be co-localized in most of the paraneurons, although some of them showed 5HT-LI only. Furthermore, fibres with CGRP-LI only were often observed in close association with these groups of paraneurons. Ultrastructurally, the Bronchopulmonary paraneurons contained numerous large granules 80nm-140nm in diameter. Using protein A gold probes 5HT and CGRP-LI was observed to be co-localized in the individual granules of most paraneurons. Some paraneurons contained 5HT-LI only and associated nerve profiles contained CGRP-LI only. In Bronchopulmonary paraneurons there exists the possibility of co-release of 5HT and CGRP suggesting a self-regulating mechanism whereby the paraneurons in addition to receiving efferent input also possess intrinsic mechanisms to regulate its own activities and output through the neuroactive substances that it contains.

Estimating the Future Position of a Moving Target

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Predicting the future of a moving object is a common task as we move around, cross roads or play sport. Paradigms investigating the mechanisms of successful position prediction frequently involve presenting a target which moves across a screen and disappears, and asking subjects to estimate when the target would have passed a marked point, had it continued on its original path. To date, experiments have lacked adequate control of cues which might influence performance, and conclusions have been drawn from ambiguous results. In this study three experiments were conducted
under controlled conditions to clarify the mechanisms of such estimation. By controlling fixation, the first experiment demonstrated that contrary to previous suggestions, eye movements are not necessary for successful position prediction. Also, differences in performance with different target velocities were due to temporal differences in the stimulus and not differences in velocity per se, as previously reported. In the second experiment, the intervals over which the target was seen and over which the prediction had to be made were systematically varied. Temporal differences in the latter, but not the former, significantly affected performance. In the final experiment the target was presented either continuously or intermittently. Eliminating direct velocity cues through intermittent presentation did not degrade performance, suggesting that temporal and spatial cues alone are adequate for successful position prediction.

The Effect of Peripheral Nerve Section on Lectin Binding in the Dorsal Horn of the Rat Spinal Cord

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The extralysosomal enzyme, Fluoride Resistant Acid Phosphatase (FRAP) and the peptide, substance P (SP) have been located in the somata of unmyelinated primary sensory neurones and their terminals in the superficial dorsal horn of the spinal cord. Following section of the peripheral processes of these neurons both FRAP and SP are lost from their central terminals. Recently we have shown the plant lectin Soybean Agglutinin (SBA) to be a marker for the central terminals of unmyelinated primary sensory neurones (Plenderleith et al., Neuroscience, in press). In this study we have examined the effect of peripheral nerve section on the binding of SBA in the rat. Four, 15 and 43 days following unilateral sciatic nerve section, FRAP and SP-like immunoreactivity (-LI) were found to be depleted from the medial half of the superficial dorsal horn of the fourth lumbar segment of the spinal cord. No effect on the pattern or intensity of SBA binding was apparent at these survival times. However, 90 days following sciatic nerve section SBA binding was found to be depleted from the superficial dorsal horn. This depletion was topographically identical to that observed for FRAP and SP. These results indicate that, like FRAP and SP, SBA binding to unmyelinated primary sensory neurones is affected by a peripheral nerve lesion. However the onset latency of this effect is much greater for the lectin than it is for FRAP or SP.

Supported by the N.H. & M.R.C.
The Affective-Motivational Aspect of the Pain Experience and the Cerebral Cortex

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The experience of intense, chronic pain has two dimensions: (a) the sensory-discriminative aspect that permits localization and specification of stimulus energy and (b) the affective-motivational aspect that elicits from the sufferer adjectives such as terrifying, dreadful or killing (Willis, The Pain System, 1985). This latter aspect is relieved by opiates or prefrontal lobotomy. Because of the independence of the affective-motivational dimension of the pain experience from sensory discrimination, we might expect that the cortical neurons responsible for its elaboration will respond to the activation of a variety of nociceptors from wide areas of the body. In this study we have found such responses in 25 neurons close to the apex of the preoreus gyrus of the prefrontal cortex of 5 cats, deeply anaesthetized with 1 to 3% halothane. Effective stimuli included a gall bladder distension (1M of H₂O), heating the skin (55°C), joint deformation and intense pinching of the skin. To be effective, stimuli had to be maintained for 10 to 20 seconds but neurons sometimes continued responding for up to 4 minutes. Five cells gave excitatory responses and 20 were inhibited. This work supports the suggestions of Craig, Wiegand and Price (Journal of Comparative Neurology, 1982, 206, 28-48) that the part of the preoreus gyrus known as VLO-alpha which receives projections from the dorsal part of N. Sub medius of the thalamus might be responsible for the truly adverisive aspect of chronic pain.

An Investigation of a Diencephalic-Septal-Hippocampal Pathway

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Electrical stimulation of the dorsomedial-posterior hypothalamic region (DMPH) in urethane-anesthetized rats produced theta activity in the hippocampal formation (HF). Furthermore, there was a linear relationship between the increasing levels of stimulation of the DMPH and the increasing frequency of HF theta. The effects of DMPH stimulation on the HF were mediated by the medial septal/diagonal band (MSDB) region, since microinfusion (0.1 g/ml) of procaine hydrochloride into the MSDB produced a reversible blockade of the DMPH stimulation effects. Microinfusion (50 μg/μl) of atropine sulfate into the HF also abolished both spontaneously-occurring and DMPH-induced HF theta demonstrating that this theta was mediated by muscarinic receptors. Direct microinfusion (10 μg/μl) of carbamylcholine chloride into the HF resulted in theta activity with a mean frequency of 5Hz and stimulation of the DMPH could not alter this frequency. Thus, direct cholinergic activation of HF theta appeared to functionally deafferentate the DMPH-MSDB-HF pathway.
The Epidemiology of Panic and Agoraphobia

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Since 1980 when panic disorder was separated from other anxiety disorders in the American Psychiatric Association's Diagnostic and Statistical Manual (third edition), this disorder has been the subject of considerable clinical, neurobiological and epidemiologic research. Concurrent with this interest there has been the suggestion that agoraphobia usually arises secondary to the experiencing of panic attacks. Epidemiologic studies before 1980 reported that the prevalence of anxiety disorders was between 2 and 5%. Studies completed in the last decade applying DSM-III criteria have consistently reported a six month prevalence of panic disorder between 0.5 and 1.5%, and a lifetime prevalence of 1.0 to 2.2%. Contrary to increased clinical findings that agoraphobia seldom developed in the absence of panic attacks, the NIMH epidemiologic catchment study reported that agoraphobia could develop in the absence of either panic attacks or major depression, although the data from Christchurch suggested this only occurred if the agoraphobic avoidance was very circumscribed. Recent findings suggest that comorbidity of other disorders with panic disorder is more the rule than the exception, and that there is considerable overlap with affective disorders. Neurobiological, family and pharmacological studies suggest much overlap between panic disorder and major depression. Why only some people with panic attacks develop agoraphobic avoidance is unclear, although there is some evidence that agoraphobic avoidance is familial and that those who develop agoraphobic avoidance may have had more depressive, anxiety and conduct disorder symptoms as children and have grown up in a more adverse family environment.

Psychiatric Disorder in Urban and Rural New Zealand Women

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A random community survey into psychiatric disorder in urban and rural New Zealand women is described. The measures for psychiatric disorder were the GHQ-28 (n = 1516) and the short PSE (n = 314). The urban sample was drawn from Dunedin city electoral roll, the rural from the surrounding Otago area. A large number of socio-demographic variables were studied. Certain demographic differences were found between the two samples; urban women were more often at age extremes, not married, better educated, had better household and child care facilities, and had better access to neighbours, shops and family doctor, but drove a car less often. There were no overall urban-rural differences in psychiatric morbidity on either measure. Multiple regression found the same three factors accounted for most of the explained variance in both the urban and the rural total PSE scores. These were the quality of social networks, difficulties with alcohol and the past experience of childhood sexual abuse. Low socio-economic status, poor physical health, adult experiences of sexual and physical abuse were correlated with increased psychiatric morbidity for both
These results suggest that urban-rural residence in and of itself does not influence the prevalence of anxiety and depressive syndromes. In contrast to previous studies, married and widowed women and mothers showed lower rates than the never married and childless women. A plausible explanation is provided by available analysis of New Zealand gender roles. Such an explanation would reconfirm the importance of socio-cultural factors in community psychiatric disorder.

Separate Reticular System Influences on Hippocampal EEG in CA1 and Dentate Gyrus

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Previous studies have shown that repetitive stimulation in a number of brainstem and midbrain reticular sites significantly affects the pattern of electrical activity recorded in the hippocampus. In particular, it has been shown that stimulation in some areas of the reticular formation elicits hippocampal rhythmic slow activity (RSA), while stimulation of other reticular areas elicits a pattern of fast, irregular activity at the same recording location. The amplitude of hippocampal RSA is maximal in the stratum oriens of area CA1 and in the stratum moleculare of the dentate gyrus. Most studies of reticular influence on hippocampal EEG have been made with recording electrodes in one or other of these locations. It is of interest therefore, to discover if stimulation at particular reticular sites has the same (or similar) effects on EEG throughout the hippocampus. In the study to be reported here, recording electrodes were placed in CA1 and in the dentate gyrus at one septo-temporal hippocampal level, and also in either CA1 or dentate at a more temporal level. The response to reticular stimulation was recorded simultaneously at these three electrodes. It was found that stimulation at some midbrain reticular loci elicits RSA in area CA1 with little change in EEG in the dentate. Conversely, there are other reticular loci, stimulation at which elicits RSA in the dentate with little or no change in EEG in area CA1.

The Epidemiology of Generalized Anxiety Disorder: Data from a New Zealand Urban Community

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Generalized Anxiety Disorder (GAD) is included within the diagnostic category of Anxiety Disorder in both DSM-III and DSM-IIIR, though information about the nature of the disorder is limited. There have now been a number of epidemiological studies which have provided data on the epidemiology of all the DSM-III Anxiety
Disorders except GAD, yet it is suspected that GAD is the most common anxiety disorder in the community. This paper presents data from a New Zealand urban community on the prevalence, course, comorbidity and associated health service utilisation of GAD. The disorder is shown to be common, persistent and to be associated with increased health service utilisation. Persons with GAD have an increased likelihood of also having another anxiety disorder, major depression or a substance use disorder.

Evolution and Anxiety

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Emotions in general, and anxiety in particular, have components which are phylogenetically old. The ease with which we use specific words to refer to specific emotions is likely to owe more to regularities in the environment than to unity of underlying mechanisms and processes. A review of the way in which components of emotion could evolve suggests such unity is unlikely. In the study of anxiety it is particularly important to associate the term with a recurring set of correlated adaptive pressures as opposed to some unitary internal control system. It will be argued that anxiety refers to a set of behavioural and physiological reactions to the anticipation of threat. Anticipation must be contrasted with actuality and threat must be distinguished from mere aversiveness. This account is more comprehensive than conventional accounts of anxiety based on, for example, the distinction between conditioned and unconditioned aversive stimuli. Experiments with opiate antagonists show that, consistent with an evolutionary approach, anxious responses depend on at least two separate 'rule of thumb' control systems.

The Effects of d- and l-Fenfluramine and d-Amphetamine and Their Combination on Food Intake and Feeding Behaviour in Normal Male Subjects

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Serotonin (5-HT), noradrenaline (NA) and possibly dopamine (DA) have been implicated in the regulation of food intake. Both fenfluramine (an indirect 5-HT agonist) and amphetamine (an indirect NA and DA agonist) suppress hunger and reduce food intake. The present trial was undertaken to compare the effect of the isomers, d- and l-fenfluramine, and d-amphetamine on a number of feeding related parameters. Using visual analogue scales, a 10-channel automated food dispenser and a computerised observational technique, we have examined the effects on food consumption of single oral doses of d-fenfluramine (d-FF) 30 mg, l-fenfluramine (l-FF) 30 mg, d-amphetamine (d-Amp) 15 mg, the combination of d-Amp with d-FF or l-FF, and placebo in 12 fasting healthy male subjects. The study was double-blind...
with treatments given at least one week apart in randomised order. Total energy intake was reduced significantly compared to placebo by d-FF and d-Amp, but not by l-FF. The combination of d-Amp and d-FF had a greater effect than either drug alone. The consumption of non-sweet food was reduced by all three drugs, whereas that of sweet food was lowered significantly only by the combination of d-FF and d-AMP. Protein intake was not affected by d-FF but was altered by d-AMP. The finding that l-FF, which is a weaker 5-HT agonist than d-FF, lowered intake of non-sweet food, whereas d-FF also affected total intake, suggests that the interaction between taste and consumption involves more than one central neurotransmitter pathway. The regulation of sweet food intake in humans appears to involve 5-HT, thus confirming our previous findings (Goodall and Silverstone, *Appetite*, 1988, 11, 215–228).

**Modulatory Effect of Endogenous Opioid Peptides on Morphine Withdrawal Behaviour**

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There are indications that increased activity of the endogenous opioid peptides, might have a significant inhibitory effect on opiate withdrawal behaviour (Pinsky, C. et al., *Brain Research*, 1982, 243, 301; Dzoljic, M.R., et al., *Archives of International Pharmacodynamic Therapy*, 1986, 283, 222). In this study we examined the effect of three modulators of the endogenous opioid system on morphine withdrawal syndrome in rats: 1. guanidinoethylmercaptosuccinic acid (GEMSA) – an inhibitor of enkephalin convertase which converts enkephalin precursor into enkephalins; 2. Actinonin – an inhibitor of enzymes involved in the biodegradation of enkephalin and 3. SCH 34826 – an enkephalinase inhibitor with potent oral antinociceptive activity. This drug penetrates the blood brain barrier and it was administered intraperitoneally, while GEMSA and actinonin were injected intracerebroventricularly. Chronic opiate dependence was induced by implantation of morphine (75 mg) pellets and the withdrawal syndrome was precipitated by naloxone (5 mg/kg, intraperitoneally) 72 hours after implantation. We have demonstrated that actinonin (50–200 µg) and SCH 34826 (15–60 mg/kg) attenuate, while GEMSA (3–12 µg) aggravates the majority of naloxone-precipitated withdrawal signs. It has been concluded that saturation of central opioid receptors by endogenous opioid peptides significantly affects the severity of opiate withdrawal syndrome. In this respect, the orally active inhibitors of brain enkephalinase, such as SCH 34826, might be of potential clinical interest.
Anxiety and the Septo-Hippocampal System

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Hippocampal Rhythmic Slow Activity (RSA) can be elicited by either septal or reticular stimulation. The two types of elicitation demonstrate neurophysiologically and pharmacologically separate aspects of the control of RSA. All anxiolytic drugs, including buspirone which does not interact with GABA systems, have common effects on both types of task. No non-anxiolytic drug has yet been shown to do this. The behavioural effects of the anxiolytic drugs in animals can all at present be attributed to an action on the septo-hippocampal system via either the 'septal' or the 'reticular' route. The implied connection between anxiolysis and hippocampal 'amnesic' effects has been confirmed in a test of the effects of a benzodiazepine, chlor-diazepoxide, in the Morris Water Maze – a critical test of hippocampal damage in rats.

Rotational Seizures in Tuberous Sclerosis: the Role of Subependymal Nodules

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Five cases of tuberous sclerosis with rotational or backward or forward falling attacks following psychomotor seizures were studied. All had subependymal nodules on the thalamostriate sulcus and most cases (4/5) suffered from West syndrome in their infancy. Some causative relationships existed between the side of nodule and the direction of attack. Three girls with unilateral nodules rotated to the side contralateral to the nodule, two boys with bilateral nodules fell backwards or forward. Pharmacobiological observation and polysomnography (PSG) were conducted to elucidate the pathophysiology of these phenomena. PSG findings for one case revealed a pattern of dopaminergic hyperactivity. Small doses of L-dopa worsened her rotational attacks and induced right-left asymmetry in the incidence of twitch movement (TM) of the limbs on PSG, whereas pimozide alleviated rotational attacks and asymmetric TM. These results suggest that the observed rotational or falling attacks in tuberous sclerosis are mostly caused by dopaminergic hyperactivity, the direction of rotation depending on the location of the nodule.
In 1988 a comprehensive neuropsychological and psychosocial assessment was carried out on all the available survivors (N = 16) from a population identified in the year 1983 in an epidemiological study of the incidence of primary subarachnoid haemorrhage (SAH) in Auckland, New Zealand. Ten subjects (‘aneurysm’ group) had had a ruptured aneurysm clipped, and six subjects (‘no aneurysm’ group) had no identifiable aneurysm, and therefore had not had surgery. In 1988, all subjects were rated as having a ‘good’ neurological outcome by a neurosurgeon, yet the psychological test results showed that degrees of cognitive and psychosocial impairment ranging from mild to severe were present in all subjects. The Botterell score at the time of admission to hospital following the SAH was found to be a significant predictor of the number of cognitive dysfunctions five years post-SAH, but did not predict psychosocial impairment. No significant difference was demonstrated between the ‘aneurysm’ and ‘no aneurysm’ groups on overall cognitive functioning, although a trend was noted in the direction of greater difficulty with cognitive flexibility and concept formation in the ‘aneurysm’ group. Significant differences between the ‘aneurysm’ and ‘no aneurysm’ groups were found in areas of psychosocial functioning, with the ‘no aneurysm’ group reporting a greater reduction in their capacity to work and in their leisure activities, and greater feelings of fatigue. The implications of these findings will be discussed.

Updating Visuo-spatial Errors During Discrete Aiming Movements

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A series of experiments is reported concerning the double-step analysis of discrete aiming movements. A second target (i.e. an artificially induced movement error signal) was presented during the trajectory of the response to an initial step. In this way overshoot and undershoot errors, deliberate and random errors could be investigated. Response parameters were considered as a function of the interstep interval which was randomly varied across trials. Data are reported in terms of movement times, standard deviations and a constant amendments score of double-step trials. Subjects could respond more appropriately and effectively to a deliberate rather than a random error, and an undershoot error rather than an overshoot error. Furthermore, a quadratic function relating the variability of movement endpoints to the
interstep interval argued against an error averaging model of visuo-spatial error updating in the manual aiming situation. These results are discussed in terms of a mixed-mode of visuo-spatial error updating and related to the generalized motor programme hypothesis.

Does Increased Inertia Influence Neuromotor Reaction Time?

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When the moment of inertia of a limb or limb-segment is increased simple reaction time (SRT) which measures the speed of initiation of a rapid movement, is lengthened (Anson, 1989, Journal of Motor Behavior, 21, 60-71). Within the SRT interval the premotor time (PMT) remains unchanged but the motor time (MOT) increases apparently as a function of the greater moment of inertia. This effect has been described in two experiments involving index finger extension and forearm flexion respectively but between-experiment differences in instrumentation, location, and procedure diminished the degree to which comparison of the results could be made. For example, if inertia affects just MOT then PMT should be similar across limb segments as well as within segments given small differences in neural impulse conduction time to the respective muscles. This experiment compared finger extension (weighted and unweighted) to forearm flexion (weighted and unweighted). Each subject received 40 trials per condition. SRT, PMT, and MOT were measured. Initial results generally confirm the effects described earlier. SRT, PMT, and MOT were altered minimally in the weighted forearm flexion condition, but SRT and MOT increased appreciably for weighted finger extension. For comparison, data from an accelerometer mounted on the limb-segment provided a second measure of SRT. Preliminary results indicate that the accelerometer is much more sensitive as an 'SRT switch' and is capable of detecting movement onset earlier. Previous interpretations of peripheral effects on SRT may require revision in light of these data.

Effects of Focal Brain Lesions on Visuo-spatial Problem-Solving Abilities

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Thirty-nine patients with unilateral brain lesions and sixteen normal control subjects performed a set of Matchstick Problems, similar to those described by Guilford (1967) as a measure of adaptive flexibility. For each item in the set, the subject was told to demonstrate as many ways as possible of removing a particular number of sticks (e.g., two) from a two-dimensional geometric figure, in order to arrive at a specified resultant shape (e.g., three squares). Answers were classified as either ‘Shifts’ (i.e., changes in solution strategy) or ‘Alternatives’ (i.e., permutations of the same solution strategy on different sides of the figure). Patients with right parietal-lobe lesions
showed a general visuo-spatial dysfunction, in that they had difficulty in finding both Shift and Alternative solutions. In contrast, a selective impairment in the ability to shift strategy was seen after right frontal-lobe damage. A parallel is drawn between this finding and the deficit seen in patients with left frontal-lobe lesions on the Wisconsin Card Sorting Test. The results are interpreted as consistent with Ungerleider and Mishkin's (1982) proposal of a dorsal visual pathway in primates for the processing of spatial information, and they provide further evidence that in humans, the right hemisphere is more important than the left for this type of processing.

Dental Surgery as a Model for the Evaluation of Anxiety and Anxiolytic Drug Response

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The rationale for testing anxiolytic drugs in normal volunteers subjected to 'stressful' laboratory tests, is that the response of the volunteers allows for prediction of the therapeutic efficacy of the drug. However, the ecological validity of these studies may be questioned, in that the degree and type of stress, which may ethically be induced in a laboratory, is limited. The absence of emotional and cognitive connotations surrounding experimentally-induced 'anxiety', further limits the generalizability of findings obtained with such techniques. Increasingly, psychopharmacologists are advocating the use of naturalistic settings to evaluate psychotropic drug response. Dental surgery is an ideal situation for such research. Advantages of this model include, naturally occurring anxiety, and the availability of a young healthy sample. Furthermore, the nature of dental surgery provides a 'semi-laboratory' setting, allowing for rigorous experimental control of many environmental variables. This paper considers theoretical aspects of dental anxiety, and reviews recent research concerning anxiolytic drug response. It is concluded that dental surgery provides an excellent model for the investigation of the neuro- and psychopharmacological aspects of human anxiety.

Naloxone Does, but Atrial Natriuretic Peptide (ANP) Does Not Reduce Post-Deprivation Water Drinking of Rats With Lesions of the Subfornical Organ (SFO)

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In rats drinking after water deprivation is much reduced by prior IVT injection of naloxone or ANP (Siviy, Bermudez-Rattoni, Dargie & Reid, Pharmacology Biochemistry & Behavior, 1981, 15, 257; Masotto & Negri-Vilar, Brain Research Bulletin, 1986, 15, 23). The effects of ANP may be mediated by neurons in the SFP (Buranarugsa & Hubbard, Brain Research Bulletin, 1988, 20, 627). We prepared 14 rats with cannulae in their lateral ventricles; 7/14 were also given radiofrequency lesions shown
later to destroy the SFO. For each test the rats were without water for 16 hours overnight and then given access to water via a sipper tube attached to a calibrated water filled burette. Access was either 5 min after the IVT injection of ANP (5 nM in 4 μl) or normal saline (4 μl) or 15 min after injection of naloxone (100 μg in 2 μl) or immediate (on injection). The rats with or without lesions drank significantly less water \( (p = .05) \) at 15, 30 and 60 min after injection of naloxone than they did after injections of normal saline or after no injection. The rats with SFO lesions drank amounts of water after ANP injection or no injection which were not significantly different. We conclude that the antidipsogenic effect of ANP depends on the SFO but the antidipsogenic effect of naloxone does not.

**5HT1A Receptors may Mediate the Effects of Buspirone on Hippocampal Rhythmic Slow Activity**

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Buspirone is clinically effective at reducing anxiety, without the concomitant side effects of muscle relaxation, sedation or anticonvulsant action demonstrated by classical anxiolytics. How buspirone acts in the central nervous system to achieve its behavioural effects is unknown. Unlike benzodiazepines or barbiturates, buspirone does not interact with the GABA-BDZ chloride ionophore complex. Classical anxiolytics all decrease the frequency of hippocampal rhythmic slow activity (RSA) produced by reticular stimulation – as does buspirone. Methysergide, a 5HT antagonist which is most effective at 5HT2 sites; GR38032F, a 5HT3 antagonist, and pindolol, which is an effective 5HT1A antagonist, were used to investigate the possibility that buspirone affects some aspect of serotonergic neurotransmission to achieve anxiolysis. Neither methysergide nor GR38032F reduced the effect of buspirone on RSA. Pindolol at a dose of 0.2 mg/kg partially blocked the frequency-reducing effect of buspirone, but not that of chlordiazepoxide. In the present test, therefore, the common effect of buspirone and at least one classical anxiolytic are being achieved through different mechanisms. The effect of buspirone on frequency of RSA could be mediated by 5HT1 as opposed to 5HT3 receptors.

**Topographic EEG Findings of Parkinsonism**

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Thirty-nine topographic EEG was obtained from 31 Parkinsonians to define EEG characteristics of Parkinsonism. There were 10 males and 21 females. Mean age at onset was 51.7 years, at examination 60.5 years and mean duration of illness was 8.6 years. Fourteen recordings were made after thalamotomy, and 25 either before or
without thalamotomy. The majority of recordings were made under the influence of L-DOPA. In all cases significant increase of slow waves was noted. Dominance of slow wave was lateralized to the left in 21 recordings, to the right in 7 and not lateralized in 11. Various clinical parameters which might be attributable to this slow wave asymmetry were examined. These parameters included thalamotomy, influence of L-DOPA treatment, laterality of symptom at onset and at EEG examination, age at onset, duration of illness and WAIS. There seem to be marginal clinical features in the group with left side dominant slow wave i.e., somewhat older age at EEG examination, longer duration of illness and higher verbal IQ (or conversely, lower performance IQ) than groups with right sided slow wave dominance and without slow wave lateralization. The total IQ itself is relatively high in this group. Besides, in a group with right sided dominant slow wave, somatic lateralization of symptoms and slow wave lateralization seems to be well correlated. This left sided dominance of slow waves in Parkinsonians as noted by topographic EEG study was thought to be more than incidental. Possible underlying biochemical and physiological mechanisms for this phenomenon will be discussed.

Lap-Top Personal Computer Data Acquisition and Processing System for Long-term Evaluation of Parkinsonism

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As a part of a computerized data acquisition and processing system for stereotaxic functional neurosurgery, which is now being developed in our department, a lap-top personal computer system for outpatient clinic use is presented. This personal computer system has dual functions: One as a pre- and post-operative data acquisition terminal to the host system; and as an independent system exclusively for storage and processing of long-term follow-up data in the clinic. Data obtained in the clinic include scores on physical examination, functional disability and complication scale, psychometric tests and reaction time, and medication records. In addition, by simply adding new data files, it can handle virtually all clinical data obtained in the clinic and therefore the accumulation will make a huge clinical data library covering all aspects of disease processes which are subject to the functional neurosurgery. By processing the stored data, the system can automatically display chronological review of clinical data of particular interest which usually ranges for many years. These data, which can be retrieved almost instantaneously, are of great value as an outpatient clinic support system. Some of the results obtained by this system, including long-term evolution of physical examination, functional disability scores and psychometric test (WAIS) in relation to age at onset, duration of illness, thalamotomies and chronological changes in treatment strategy in our clinic, are presented. It is hoped that further accumulation of data and more sophisticated analysis by this system will define long-term natural history and its modification by various treatment modalities, and may help selecting the best long-term treatment schedule for individual patients.
The anxiolytic action of the benzodiazepine drugs may be related at least in part to enhancement of the inhibitory action of the neurotransmitter GABA on GABA-A receptors in the central nervous system. We and others have shown that the properties of GABA-A receptors may be altered by a variety of stressors, e.g. a 3 minute warm swim stress in mice results in an apparent 70% increase in the availability of GABA-A binding sites in the forebrain. Such rapid changes in the GABA-A receptors induced by environmental factors are considered to be mediated via endogenous modulators called GABARINS (GABA Receptor Inhibitors)—these modulators include various peptides, phospholipids, purines and steroids which are thought to be normally associated with GABA-A receptors regulating their activity and availability. Rapid changes in the properties of GABA receptors may be achieved by changes in these modulating agents rather than changes in receptor synthesis. The most important of the GABARINS in the present context may well be the steroids since it has been shown that cortisol and cortisone have very potent modulating actions on certain GABA-A receptors. They act at concentrations as low as 10–12 M and at such low concentrations cortisol and cortisone have opposing actions, cortisol enhancing and cortisone blocking the inhibitory action of GABA. These modulatory actions are not mediated through the classical glucocorticoid genomic receptors but are considered to involve receptors on the extracellular surface of neuronal membranes. Such receptors can be rapidly activated in order to modulate associated GABA-A receptors and are not directly related to benzodiazepine receptors. Given the involvement of cortisol in many responses to stress it seems likely that the modulatory actions of cortisol, and also cortisone, on GABA-A receptors play important roles in anxiety mechanisms. Furthermore the high potency of cortisol and cortisone gives important structural clues for the design and development of new anxiolytic agents based on steroid and related structures.

Organic Psychosis Following a Second Course of Diethylproprion: Case Report: Model and Mechanism Proposed

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This paper is a case report of a previously healthy, 46 year old woman with no past psychiatric or medical history. Two years previously she had taken Diethylproprion 75 mg, an amphetamine-like anorexiant, each day for 12 weeks. As no adverse effects were experienced, she again took the same drug in the same dose. This time she developed side effects gradually developing over 10 days, including marked insomnia, sweating and a fearful sense of foreboding. She stopped the medication. Five days later she was admitted to our Psychiatric Unit with increasing episodic agitation characterised by terror, grunting, impaired contact with reality, perseveration and echolalia. This organic psychosis settled, and she was discharged 14 days after
cessation of the named drug, and remains well. Investigations of alternative medical, psychiatric or psychological explanations were non-contributory. Current understanding of drug-induced reactions cannot account for this sequence of events. However, psychoses have been reported following chronic drug administration (amphetamine) and following a second drug course (steroids). It is suggested that these are analogous models for this phenomenon. Animal studies using indirect catecholamine agonists (amphetamine, methylphenindate, cocaine) have been linked to pharmacological kindling and sensitisation. It is proposed these mechanisms describe the clinical phenomenon outlined in this case and suggest possible management rationales. It is not clear which is the more adequate explanation. Kindling and sensitisation have been implicated in at least one major psychiatric disorder, bipolar affective disorder. Psychoses induced after repeated administration of psychomotor stimulants, or appearing only during a subsequent course may well provide a further clinical example.

Behavioural Assay of Motor System Function in Chronic Spinal Chicken Embryos and the Emergent Dysfunction of Brachially Innervated Hindlimbs

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Chicken embryo hindlimb buds transplanted in place of forelimb buds on the third day of incubation (E3) develop into grossly normal hindlimbs. It has previously been shown that such ectopic hindlimbs become innervated by the same number of motoneurons as the contralateral wing, and anecdotal data indicate that grafted hindlimbs exhibit normal motility. However, unlike results obtained from Uredeles, the grafted hindlimbs of chicken embryos become profoundly dysfunctional before hatching, despite an apparently normal motor and sensory innervation of muscle and normal motoneuron ultrastructure. To quantify the behavioural effects of transplantation, grafted hindlimb movements made in a ten minute period were compared with forelimb movements of normal and chronic spinal embryos. The total number and temporal distribution of movements were computed. While there was no difference between the number of movements made by normal and chronic spinal embryos at any stage examined (from E8 to E18), significantly fewer movements were made by grafted hindlimbs from E12 onwards. There was also a significantly smaller proportion of small intervals between movements, indicating less discrete phases of limb activity. In contrast, chronic spinal embryo forelimb movements exhibited a greater than normal proportion of smaller intervals from E10 onwards, indicating a greater tendency for movements to occur in clusters. The different behavioural abnormalities imply that the emergence of grafted hindlimb dysfunction is not due simply to an absence of interaction with the supra-spinal nervous system.
Serotonin And Obsessive Compulsive Disorder

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The serotonin hypothesis of obsessive compulsive disorder (OCD) was formulated to explain the effectiveness of clomipramine in the treatment of OCD. The evidence for the hypothesis comes from three areas: Baseline serotonin studies, pharmacological challenge studies and the response of sufferers to serotonin re-uptake inhibitors of which clomipramine is one. This paper critically examines the evidence from the three areas. Though there is no dispute regarding the effectiveness of clomipramine in some OCD sufferers, the evidence for the serotonin hypothesis from baseline and challenge studies is tenuous at best.

Life-Events and Anxiety

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Negative and positive life-events and social conditions, and even more importantly chronic conditions and difficulties, especially in the areas of partner, relationship, work and household, play an important role in the course of Anxiety Disorders. Similar to Depressive Disorders two mechanisms seemed to be involved in this process: (i) specific single life-events, and (ii) ongoing social difficulties and situations in an overall ‘deviant’ life situation patterning. Whereas, the role of life-events seems to be well established as a provoking agent in the onset of Anxiety Disorders, there are a number of indicators that suggest that in the further long-term course of Anxiety Disorders (over more than 7 years) they do not play such a crucial role as in Depressive Disorders. The statistical relationship between life-event and psychopathology was found to be relatively weak for Anxiety Disorders if the data are controlled for the occurrence of a depressive episode. Nevertheless, for Agoraphobia and Panic Disorders, a statistically significant relationship was found with indices for an overall dynamic deviant structure of life-events and social conditions and difficulties which result in a change of the life-cycle of these patients. In these patients a worsening of the Anxiety Disorder was usually triggered by the occurrence of several chronic negative life conditions as well as life-events. The study suggests that life-events per se do not play a crucial role in the further course of Anxiety Disorders.
Burst-Type Firing of Hippocampal CA3 Pyramidal Cells Varies with Cell Position and Morphology

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A sub-population of pyramidal cells in region CA3 of the mammalian hippocampus generate bursts of action potentials when stimulated with an intracellular injection of depolarising current. It has been unclear if, or how, this burst-type firing is related to cell morphology or cell location, although one previous study has suggested that bursting cells are more likely to be located in subregion CA3a than CA3b. In the present study, intracellular recordings were made from a sample of pyramidal cells located in subregions CA3a, b and c of the guinea pig in vitro hippocampal slice. Of these cells 58% were subsequently filled with Lucifer Yellow, allowing correlation of gross morphology and cell location with electrophysiology. Of the total pool of cells, 48% produced burst-type firing to a depolarising current injection. Contrary to previous results, it was determined that the proportion of cells which generated bursts did not differ significantly across CA3 subregions. It was found, however, that cells with somata located close to the stratum pyramidale – stratum oriens border were twice as likely to generate burst-type responses than were cells located closer to stratum radiatum. One notable morphological feature of these cells was the greater length of the initial portion of their apical dendrite, as measured from soma to primary branching point. This observation is consistent with the hypothesis that burst-type responses are generated or modulated by dendritically, rather than somatically, located ion channels.

Panic Disorder: Some Historical Trends

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This paper provides an historical glimpse at research and theory on the precursors of what is today termed Panic Disorder (DSMIII-R, 1987). The paper focuses on the contributions provided by two main research streams, internal medicine and psychiatry/psychology, prior to 1960. Within each research stream, the syndrome underwent several name changes over the first half of this century, which ‘probably reflect more the special interests and theories of the various observers rather than a diversity of clinical disorders’ (Cohen and White, 1950). The history of panic disorder reveals a cyclical pattern in the dominance of biological and psychological perspectives. Reconciliation of these two perspectives may be enhanced by the recognition of parallels between past and present attempts to characterize the disorder.
It is proposed that acquired anxiety reactions are based upon a common appraisal process which generates anxiety via the activation of expectancy of harm. Appraisal is powerfully influenced by previous dealings with the stimuli in question, including direct experience with a stimulus and its consequences (conditioning), observation of the effect of a stimulus on others (modelling), and symbolically presented information concerning a stimulus (instruction). These routes also correspond to the major therapeutic strategies for reducing inappropriate anxiety reactions: exposure, modelling and cognitive restructuring. The hypothesis that all three routes operate via a common mechanism of threat appraisal is investigated by laboratory psychophysiological procedures involving aversive but harmless stimuli such as electric shock. Both conditioning and instructional procedures are employed to evaluate possible biases in threat appraisal in trait anxious subjects. In particular, the research highlights the distinction between uncertainty and ambiguity in threat appraisal.

An Investigation of Image Generation Using Spontaneous Drawing In Patients with Focal Brain Lesions

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The aim of this study was to investigate the 'Image generation' component of the visual imagery system and to determine the neural mechanisms that underlie it. Sixty patients with focal brain lesions and 30 hospitalised control subjects were asked to draw 14 common objects without being given any models. They were also required to copy four line drawings of objects. The drawings were scored in several ways by independent judges. Variables included recognisability, accuracy, drawing size, neglect and inability to visualise. Six patients had difficulty generating images of some objects, in spite of being able to answer informational questions about them and recognising drawings of them. These patients either failed to draw such objects at all, or reported trouble picturing the object and produced a drawing that was very poor in detail. They had no difficulty copying line drawings. Two other patients complained that they had previously noticed that they were unable to visualise common objects, although at the time of testing there was no evidence of a deficit on the tasks. No control subject had any such problems. Of the eight patients with visualisation difficulties, two had bilateral lesions involving parietal and occipital regions, three had left-sided lesions (two parietal and one frontal/parietal) and three had right-sided lesions (one temporal/parietal, one temporal/occipital and one frontal). Evidence for the bilateral representation of an image generation process is discussed.
Effect of Nifedipine, an Organic Calcium Channel Blocker, on Amygdala Kindling of Rats

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It is known that the entry of calcium ions into neurons represents an important mechanism underlying epileptogenesis. In the present study, we investigated the effect of an organic calcium channel blocker, nifedipine, on amygdala kindling seizure development of rats. Two different doses, 5 mg/kg and 50 mg/kg of nifedipine were injected 30 min. before each kindling stimulation. Nifedipine mildly suppressed motor seizure development especially in the last part of the kindling session and the latency of bilateral forearm clonus was increased in the high dose group. The high dose group, however, showed prolonged afterdischarge duration especially in the middle part of the session. The results suggest that, though nifedipine may suppress the seizure generalization process during kindling development, the drug prolongs epileptic afterdischarges of the amygdala. The mechanism underlying these effects is unclear.

Defensive Style and Anxiety

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In classical psychoanalytic thought, the operation of specific defense mechanisms was held to be responsible for the transformation of unconscious internal conflict into conscious anxiety and attendant symptoms. This paper outlines our recent research on defenses and anxiety, using the Defense Style Questionnaire (DSQ), a 72 item questionnaire designed to measure the conscious representations of defense mechanisms. Patients with anxiety were studied in two ways. Firstly, the DSQ was administered to three groups of individuals: Normal population, family practice patients and anxiety disorder patients. Factor analysis identified mature defenses (sublimation, humor), intermediate defenses (undoing, reaction formation) and immature defenses (projection, acting out). In addition factor scores varied systematically with group membership and symptom measures. In a second study, the DSQ was administered to patients with either panic disorder, agoraphobia, social phobia or obsessive compulsive disorder. There was evidence that a specific pattern of defenses was associated with each disorder.
Neurosis, Personality and Cognitive Behaviour Therapy

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In a 15 year follow-up of 193 patients admitted to hospital for depression we showed, for neurotic depression and for other neuroses but not for endogenous depression, that personality as measured clinically and by EPI Neuroticism and by Cattell IPAT accounted for 20% of the variance in long-term outcome. In a 16 month longitudinal study of 446 volunteer twin pairs we showed that different neurotic diagnoses (using the DIS) were not independent; that some 75% of the variance incasedness could be predicted from personality vulnerability as measured from neuroticism, locus of control and ego defense style; and that the resemblance between co-twins was at the personality and not the illness level. Treatment for neurosis should therefore address the underlying personality vulnerabilities. In a 15 month follow-up of 50 patients with panic/agoraphobia we showed that 80 hours of cognitive behaviour therapy produced a 2 standard deviation (SD) improvement in panic and avoidance and at 6 months had produced a 1.25 SD improvement in neuroticism and locus of control; and that this improvement rather than the symptomatic improvement accounted for symptom status at one year. We present evidence from the literature that cognitive behaviour therapy is an effective method of modifying personality vulnerability to neurosis and discuss the evidence for the mechanisms likely to be involved.

The Ethopharmacology of Fear and Anxiety

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A FEAR/DEFENSE TEST BATTERY (FDTB) involving reactions of wild rats to approaching and (painless) contacting threat stimuli provides measures of flight, freezing and defensive threat and attack. Three benzodiazepines, two 5-HT agonists and ethanol have been tested in this battery. The resulting behaviour profiles showed good agreement within different categories of compounds and some (or considerable) differentiation among compounds. Specifically, the BZPs tended to reduce only defensive threat while the 5HT1A agonists (especially gepirone) reduced both defensive threat and attack, and ethanol at low doses potentiated defensive threat and attack, leaving other behaviours largely unchanged. In an ANXIETY/DEFENSE TEST BATTERY (ADTB) measuring risk assessment behaviours and interference with nondefensive behaviours in response to potential threat, diazepam showed an especially clear profile of appropriate changes in risk assessment, with little alteration of other aspects of defense. In contrast, gepirone and ethanol both showed broader patterns of change on the ADTB. Finally, on the ADTB in contrast to the FDTB, a pattern of sex differences was obtained, with females generally showing greater anxiety than males.
Anxiety is unquestionably the most common psychiatric complaint, but the anxiolytic drugs used in huge quantities to treat anxiety disorders are frequently ineffective and commonly engender dependence. These factors suggest a need for improved understanding of the behaviour patterns involved in fear and anxiety in order to create more rational models for evaluating anxiolytic drugs. Recent research suggests that natural defensive behaviours of nonhuman mammals are very different in situations involving potential danger as opposed to present danger, and that specific behaviours seen in the former situation may be especially relevant to an analysis of anxiety. These behaviours center around a 'risk assessment' pattern which includes approach and scanning of potentially dangerous stimuli or situations, accompanied by changes in posture and movement characteristics. In contrast, reactions to specific, present, threat stimuli involve flight, freezing, and defensive threat and attack. We suggest that risk assessment is the central component of an anxiety pattern, while the reactions to present threat are better characterized as indicating fear. This differentiation is congruent with the clinical definition of anxiety and the risk assessment pattern also shows latency and duration features more typical of anxiety than of fear.

Agoraphobia Without Panic Attacks

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Agoraphobia has always been thought to occur in association with panic attacks. Although there have been several epidemiological reports of agoraphobia without panic attacks, there are no reported clinical studies. In this study the authors conducted follow-up clinical interviews on 36 people assigned this diagnosis from data gathered in a prospective study of 924 volunteer twins. The twins were interviewed with the Composite International Diagnostic Interview by trained lay interviewers, and diagnoses were assigned at a criterion level equivalent to that used in the National Institute of Mental Health Epidemiologic Catchment Area Programme. The diagnosis was confirmed in three subjects, reassigned in others, and in six subjects the clinician felt there were insufficient symptoms to warrant any lifetime psychiatric diagnosis.
There is wide acceptance of the view that benzodiazepines are rapidly effective in the relief of the symptoms and signs of anxiety with minimal risk of mortality or tissue morbidity. The main adverse effects are sedation, amnesia and dependence. The first two of these are largely dose dependent and can be avoided with the use of one of the least sedative benzodiazepines (e.g. bromazepam) together with careful dose selection. Dependence risk can be reduced to a socially acceptable low level by careful selection of patients, use of the lowest effective dosage and short periods of treatment to reduce the distress of anxiety down to manageable levels. The long-term relief of anxiety also requires the use of other non-pharmacological forms of therapy to remove the prime cause or to encourage the patient to come to terms with their problems. The paper will submit that benzodiazepines, and particularly those with a moderate to long half-life and minimal sedative activity, still represent the drug group of first choice and that used appropriately, therapeutic benefits substantially outweigh the problems.

Neurotransmitter Receptors in Spiking and Non-spiking Regions of Human Epileptic Temporal Cortex

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Using quantitative receptor autoradiographic techniques we have found no differences in the binding or distribution of benzodiazepine-GABA receptors and excitatory amino acid receptors (glutamate, TCP, NMDA, glycine, quisqualate, kainate) in actively spiking versus non-spiking regions of human epileptic temporal cortex removed in the routine neurosurgical treatment of complex partial seizures. However, preliminary results suggest a loss of anticonvulsant adenosine A1 (but not A2) receptors in spiking versus non-spiking regions. Because endogenous adenosine res-
stricts seizure initiation and spread via activation of the A1 receptor (Progress in Neurobiology, 1988, 31, 85–108), these A1 receptor losses, if confirmed, may represent the primary neurochemical pathology of temporal lobe epilepsy. Alternatively, these losses may be a consequence of seizure activity.

Anxiety, Perception and Respiration

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The experience of somatic symptoms, especially shortness of breath or smothering sensations are common with both generalized anxiety (GAD) and panic disorders. These lead to expectations of the anxious being unusually perceptually sensitive, as exemplified by the GAD category of ‘vigilance and scanning’ with feeling keyed up or on edge, having an exaggerated startle response and so forth. Assessments of respiratory perception, including the perception of different respiratory loads, were used as a model to assess perception in anxiety states. The expectation was that the anxious would be unusually sensitive in perceiving changes in inspiratory loads, but results showed the contrary. The anxious were significantly less sensitive than the non-anxious, in their perceptions of these loads. Pilot data suggests that asthma patients with anxiety are insensitive to changes in extrinsic load which may hinder their ability to assess their ease of breathing and their asthma control.

Biological Aspects of Panic

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There is accumulating evidence that it is those drugs which act on the neurotransmitter serotonin (5-HT) which are most effective in blocking panic attacks in those who suffer from panic disorder. The early studies of drug treatment of panic disorder were of compounds which are not specific in their action on 5-HT and which, although acting powerfully on 5-HT uptake also have some effect on other neurotransmitters. In the main the drugs studied for this purpose were the tricyclic antidepressant imipramine and the monoamine oxidase inhibitor phenelzine. More recently drugs which have more specific effects on the 5-HT systems have been developed and in early studies these have shown some promise in the treatment of panic disorder. This has engendered the argument that panic disorder occurs as the result of some disturbance of 5-HT which is known to control the locus coeruleus. This in turn, when released from 5-HT control is responsible for bursts of arousal which it is speculated take the form of panic attacks. However, to date, biochemical data to support the existence of such a disturbance have been equivocal. It is likely that the action of these 5-HT uptake inhibitors is more complex than previously imagined. An important aspect of the development of a panic attack appears to be the occurrence of negative cognitions, which when coupled with physiological arousal produces the panic. This paper suggests that rather than having an effect on physiological arousal, the 5-HT activity of the antidepressants mentioned is to produce a change in cognitive patterns.
Task Dynamic Control of a Rhythmical Elbow Movement

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Kay, Kelso, Saltzman, and Schoner (Journal of Experimental Psychology: Human Perception and Performance, 1987, 13, 178–192) modeled the kinematic behaviour of a single degree of freedom rhythmical wrist movement in terms of low dimensional dissipative dynamics ('The Hybrid Oscillator Model'). The purpose of this study was to investigate the generality of this motor control perspective. The experiment of Kay et al. was repeated for a different joint, the elbow, and with a greater range of pacing frequencies. A manipulandum was used to restrict movement to a single degree of freedom (elbow extension-flexion). Four subjects participated in four experimental sessions over two days. A session consisted of a preferred frequency trial, followed by twelve metronome paced trials (frequency range from 0.2 to 2.5 Hz, administered in random order). The kinematics of the manipulandum arm were obtained using the Flextrac/ExpertVision video motion analysis system. Cycle amplitude frequency, and peak velocity were calculated for each trial. The hybrid oscillator model predicts a stable and reproducible reciprocal relationship between cycling frequency and amplitude. Preliminary analysis of data indicates that such relationships are exhibited, but that they are discontinuous at certain critical frequencies. This phenomena of patterns which are stable within certain limits, but change to other stable patterns at critical points is a general feature of open, self organized systems. Study of the behaviour of the system near critical points and their relationship to optimal points of the system may provide valuable clues as to the specific control mechanisms underlying its behaviour.

Behavioural Therapy for Panic Disorder

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Fifty-six patients with chronic panic disorder received either Self Mastery Training (SMT) or a placebo treatment Imaginal Rehearsal in addition to 28 hours of therapist assisted in-vivo exposure. Behavioural, independent observer, and self report measures of panic avoidance and general psychological functioning were collected with a 3% and 14% attrition rate 1 and 5 years after treatment. SMT produced significantly greater reductions in anxiety, panic frequency, phobic avoidance, help seeking and drug usage, and significantly greater improvements in self control, general psychological functioning, work adjustment and assertion. A composite criterion of clinical improvement reflected this superiority in that 79% vs 54% of patients were improved at the 1 year follow-up and 84% vs 56% at the 5 year follow-up. Relapses of a month or more were experienced by 78% of exposure patients and 36% of SMT patients. The theoretical and treatment implications are discussed together with suggested improvements to treatment.
Psychological Factors Influencing the Response to Biological Challenge Procedures in Panic Disorder Patients

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Over the past eight to ten years there has been a growing interest in biological challenge procedures as a method for studying factors of importance in panic disorder. The majority of this research has focused on biochemical factors. Recently, it has been demonstrated that psychological factors can also influence the response to biological challenge in panic disorder patients. While this work is still in its infancy, there have now been enough studies to begin to suggest some of the important psychological factors. Four, not necessarily mutually exclusive, factors have been identified: Perception of threat, belief in the future occurrence of threat, personal control over threat, and external control over threat. This paper will review the evidence for each of these factors, discuss shortcomings of the research, and explore research directions.

Pharmacology of Clomipramine in Anxiety Disorders

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Earlier investigations of clomipramine (CI) in the treatment of obsessive-compulsive disorders (OCD) and panic disorders (PD) will be briefly reviewed. A double blind placebo controlled comparison of CI and imipramine (I) and an open long-term study of CI and PD are presented. In the controlled study the patients were treated with placebo (n = 7), I (n = 24) or CI (n = 21) for three months. The doses were gradually increased dependent upon therapeutic and side effects (max. 250 mg daily). Doses of I and CI were not significantly different at the end of the study. I and CI, but not placebo, reduced anxiety, measured by HARS and as number of panic attacks per week. At the end of the treatment the CI-group but not the I-group differed significantly from the placebo-group with respect to both assessments. In the long-term study 41 patients from the control study were treated with CI openly, recommended to slowly reduce the dose and to try cessation if, once on the low dose, they had been free from panic attacks for approximately 6 months. At the follow-up 21 months (median) later the median patient took 25 mg of CI daily. Of 10 patients who had stopped taking CI, 63% were free from panic attacks and 88% reported themselves much improved in global rating. The possibility that the effects of CI in depression, OCD and PD are dependent upon different pharmacodynamic principles will be discussed.