

BRITISH NEUROPSYCHIATRY ASSOCIATION

ABSTRACTS FOR 2002 Meeting

Variants of human prion disease: old and new J Collinge, Institute of Neurology/MRC Prion Unit, London

Abstract not available

Neuropsychiatric Aspects of New Variant CJD E C Johnstone, University of Edinburgh

This paper consists of a clinical description of 10 cases of new variant CJD described at the National CJD Surveillance Unit in Edinburgh in 1996. I had the opportunity to peruse the case notes of all of these patients. Many of them were assessed by psychiatrists often early in their illness. The purpose of the paper is to provide a brief overview of the psychiatric features that they presented.

The rapid course of the illness in many of these cases is a striking feature and overall the picture presented would be unusual in psychiatric practice. Reasons for the psychiatric referral were explored – some cases could have been construed as depressive or other non-organic disorders for months before cognitive and neurological features became obvious, although others had organic features from early on. Taken as a whole, however, the clinical picture presented by these cases would not be one seen by psychiatrists until the 1990s. An exception to this general statement is presented.

Variant Creutzfeldt-Jakob Disease R G Will, The National CJD Surveillance Unit, Edinburgh

There is now compelling evidence that variant Creutzfeldt-Jakob disease (vCJD) is caused by the agent of bovine spongiform encephalopathy (BSE) and it is thought that transmission of this cattle disease to humans was through BSE infection in food. As of February 2002 one hundred and fourteen cases of vCJD had been identified in the UK and statistical analysis has shown that the numbers of cases are increasing with time. It is likely that there was extensive exposure to the BSE agent in the human food chain, but there is uncertainty about the total future number of cases of vCJD because of many unknowns, including the mean duration of the incubation period of BSE in humans.

Variant CJD is also a cause for concern in other European countries because of the occurrence of BSE in some countries and the recent identification of affected cattle in countries that were previously thought to be BSE free. A surveillance system for CJD of all types, funded by the European Union, was established in 1993 and now includes all member states together with other countries, including Canada, Australia, Norway, Iceland, Israel and Switzerland. Five cases of vCJD have been identified in France and one in the Republic of Ireland. The Irish case had lived in the UK during the 1980s when human exposure to BSE was likely to have been significant, but three of the French cases had never visited the UK, suggesting exposure to indigenous BSE or perhaps to BSE contaminated exports from the UK.

Apart from residence in the UK, the main risk factors for vCJD are a young age (the mean age at death is 29 years) and a particular genetic make-up, methionine homozygous at codon 129 of the prion protein gene. About 40% of the general population and all tested cases of vCJD have this genotype, which may represent a susceptibility factor. However it is possible that genetic variation may influence incubation period and cases with genotypes other than methionine homozygous may yet be identified.

Concern about the risks from vCJD has been increased by the possibility of transmission of infection from person to person through the use of blood or blood products, or from contaminated surgical instruments. Exclusion criteria for blood donors, based on residential history in the UK, have been introduced in some countries such as the USA and Canada. To date there is no evidence of transmission of vCJD through these routes, but with an incubation period potentially of many years, it will be some time before the risks of secondary transmission can be excluded.

Variant CJD represents the first known transmission of an animal prion disease to humans and this has had profound economic and political implications. Human prion diseases continue to be very rare in comparison to

many other neurological disorders, but the full implications of the transmission of BSE to humans will not be known for many years.

Distinct qualitative neuropsychological features in Creutzfeldt-Jakob disease
J S Snowden, D Neary, Greater Manchester Neuroscience Centre

Aims: To determine whether classical Creutzfeldt-Jakob disease (CJD) gives rise to a characteristic pattern of mental change.

Methods: Six patients with suspected CJD underwent neuropsychological evaluation at the time of their initial diagnostic clinical investigations, an average of 6 months after onset of symptoms. The diagnosis of CJD has subsequently been confirmed in 5 patients.

Results: Consistent with previous reports mental symptoms were highly variable. One patient presented with visual disturbance, two with impairments in language, two with impairments in concentration and memory and one with behavioural change. Despite these differences there were qualitative features common to all patients. All showed during testing momentary episodes of unresponsiveness, during which information processing continued to take place. This distinctive feature is not seen in other dementias. Moreover, patients showed marked perseverative tendencies and interference from irrelevant auditory and visual environmental stimuli.

Conclusion: Patients with CJD, who have different focal cortical deficits, show common distinctive qualitative performance characteristics. The alterations in responsiveness suggest impaired activation of cortex from subcortical structures and are keeping with a putative role of the thalamus in giving rise to symptoms of CJD.

Neural representation of voices “outside the head”

M D Hunter, T D Griffiths, T F D Farrow, Y Zheng, I D Wilkinson, W Woods, S A Spence and P W R Woodruff, University of Sheffield,

Aims: We aimed, using fMRI, to test the hypothesis that the perception of auditory verbal hallucination-like (AVH-like) speech as located outside the head is subserved by the planum temporale.

Methods: 12 healthy right-handed male subjects participated. fMRI was performed on a 1.5T system at Sheffield University. We used AVH-like stimuli (spoken commands; 3-4 words; 1-2 seconds duration) prepared in order to achieve lateralisation towards right or left when presented via headphones. “Inside head” stimuli were created by adjusting the inter-aural amplitude ratio. “Outside head” stimuli were produced by convolution with a generic head-related transfer function. In 3 separate experiments, with different proportions of right- and left-sided stimuli, we used an A/B boxcar design to compare “inside head” and “outside head” AVH-like stimuli. Images were analysed using SPM99.

Results: In all experiments, contrasting “outside head” with “inside head” stimuli produced activation in the left planum temporale solely ($p < 0.001$ for height and extent, uncorrected).

Conclusions: The left planum temporale may have a critical role in the perception of AVH-like speech as originating outside the head. Further work with our paradigm may lead to a better understanding of the neural basis of the spatial phenomenology of AVHs in patients.

Is auditory cortex used to process a signed language?

M MacSweeney, R Campbell, B Woll, P K McGuire, A S David, GA Calvert, V Giampietro and M J Brammer, Institute of Child Health, University College London

Aims: To explore the cortical networks involved in sign language processing.

Methods: Profoundly congenitally deaf native signers, hearing native signers and hearing non-signers were tested. Functional magnetic resonance images were acquired while signing participants performed a British Sign Language (BSL) sentence acceptability task. Hearing non-signers performed the same task in response to audio-visual English sentences. Performance was compared to a non-linguistic, target detection task.

Results: Regions activated by both BSL and spoken English included inferior prefrontal regions (including Broca's area) and superior temporal regions (including Wernicke's area). This activation was predominantly left lateralised for both languages. Input modality differences were also observed. Audiovisual speech generated greater activation in auditory cortices than BSL, while BSL generated greater activation in posterior occipito-temporal regions including visual movement cortex (MT). A comparison of deaf and hearing signers demonstrated greater activation in left superior temporal regions in deaf signers than hearing signers.

Conclusions: These data support the argument that there is a common pattern of localisation for language, independent of modality. The difference between deaf and hearing signers suggests that access to left-temporal language sites may be privileged for processing heard speech. When hearing is absent, these regions may be colonised for sign language.

Auditory recognition memory in Schizophrenia using the remember/know paradigm

J L Drakeford, N M J Edelstyn, S Srivastava, and F Oyebode, The Queen Elizabeth Psychiatric Hospital, Birmingham

Aims: Auditory recognition memory was investigated in Schizophrenia in terms of remember (i.e. specific recollection) and know (i.e. familiarity without specific recollection) judgements.

Methods: Three groups were investigated: normal controls (N=21) and patients diagnosed with Schizophrenia (N=10) and Major Depressive Disorder, Recurrent (N=10) according to DSM IV criteria. Participants were required to discriminate between previously heard sentences (targets) and novel sentences (distracters).

Results: Results were analysed in terms of hit-rate frequency (number of correct targets), false-alarm rate frequency (number of false alarms), and signal-detection measures of A' (ability to discriminate between targets and distracters), and B''_D (response bias i.e. probability of accepting a stimulus as a target when uncertain). Non-parametric tests showed no significant differences for hit-rate frequency, false-alarm rate frequency, A' , and B''_D . However, significant differences in remember ($P<0.001$) and know ($P<0.05$) were found. Patients with Schizophrenia made significantly more know judgements relative to normal controls ($P<0.01$) and significantly fewer remember judgements relative to normal controls ($P<0.001$) and patients with Major Depressive Disorder, Recurrent ($P<0.01$).

Conclusions: Evidence suggests that amongst the reported cohort of patients with Schizophrenia; remember judgements play a significantly reduced contribution to auditory recognition memory compared to normal controls and patients with Major Depressive Disorder, Recurrent.

How does the brain process complex sound? Current controversies
R J Zatorre, Montreal Neurological Institute, McGill University, Canada

The human auditory cortex has evolved specialized mechanisms for processing the information contained in our acoustic environment. Among the more complex of these signals are speech sounds and musical patterns. I shall present data bearing on the organization of the human auditory cortices as it pertains to the processing of these types of sounds using functional neuroimaging techniques as well as behavioral-lesion studies. In particular, I will argue that studying musical processes offers insights into aspects of perception, thought, and emotion which add to our understanding of how the nervous system underlies cognition. First I will discuss studies examining functional differences between the auditory regions of the two hemispheres, and how these differences may relate to higher-order processing of music and speech. Second, studies examining the processing of imagined musical sounds will be discussed. These studies demonstrate that auditory cortical areas are recruited during the experience of imagined sound, even in the absence of real sound, hence demonstrating that auditory cortex is recruited not only by external stimulation but also by endogenous processes. Finally, recent studies bearing on affective reactions to musical stimuli will be presented. The data suggest that neural circuitry related to motivation and reward systems can be recruited by the abstract sound patterns of music when they are perceived as highly pleasant, raising novel questions about the interaction between cognition and emotion.

The neural basis for auditory musical hallucinations
T D Griffiths, Newcastle University

Musical hallucinations most commonly occur in subjects with acquired deafness, and are a difficult treatment problem when they occur. A model for the production of musical hallucinations in this group is based on detailed prospective examination of the phenomenology in a typical group of patients. The model is based on spontaneous activity within a cognitive system for the normal perception and imagery of patterned segmented sound. As such, I argue that musical hallucinations represent amplification of an imagery process that occurs in normal hearing subjects; 'tunes in the head' that are a common (possibly universal) experience. Evidence from functional imaging of normal subjects suggests that normal perception and imagery are instantiated in cortical networks distinct from the primary auditory cortex. Specifically, right-dominant processing in the planum temporale and frontal operculum are involved. A direct test of the model for musical hallucinations was carried out by using functional imaging to seek areas where regional brain activity increases as a function of the strength of the hallucination. This showed a network of activity similar to that demonstrated during the normal perception and imagery of music. These results are consistent with hierarchical brain processing mechanisms for music beyond the primary auditory cortex.

An update on auditory hallucinations
P McGuire, Section of Neuroimaging, Institute of Psychiatry & GKT School of Medicine, London

Functional neuroimaging (PET and functional MRI) has been used to examine the neural correlates of cognitive processes putatively relevant to auditory hallucinations, and of auditory hallucinations themselves. The former approach involves studying patients with schizophrenia who have a history of frequent hallucinations, comparing them with patients with no history of hallucinations and with healthy volunteers. This approach has been complemented by the comparison of regional activity in patients when they are and are not experiencing auditory hallucinations. Much of the research in this area has involved cognitive tasks that entail the processing of inner speech, and many of these paradigms have also been studied at the psychological level. Overall, the data are consistent with the notion that hallucinations represent inner speech which has been misidentified as 'alien' due to defective verbal self-monitoring. However, they also indicate that this is not the sole factor underlying auditory hallucinations in schizophrenia. Recently, findings from research on hallucinations have informed the development of new psychological and biological treatments for hallucinations, and these are currently under evaluation.

Deafness and mental health
P Hindley, St George's Hospital, London

The interaction between deafness and mental health sheds light on a range of psychiatric processes.. This paper presents background factors relating to deafness and uses clinical examples from two specific disorders, autism and bi-polar affective disorder, to illustrate the interaction.

Early onset, severe to profound deafness affects approximately 1/1000 children. 95% of these children are born into hearing families with no previous experience of deafness. The majority of these children, especially those with profound deafness will grow up to use British Sign Language but parental and family use of BSL is very variable. The majority of deaf children attend mainstream schools where the quality of communication, particularly informal communication is very variable. Thus many deaf children grow up experiencing some degree of linguistic and experiential deprivation. BSL is the naturally occurring language of the British Deaf community. Its lexicon and grammar are wholly different from English although language mixing occurs when deaf and hearing people work alongside each other. Key features of BSL include: the use of space and movement in space as grammatical concepts; hand shapes or morphemes as equivalents to morphemes; the interaction between facial expression, eye gaze, body posture and movement to create semantic, syntactic and prosodic features in BSL.

Deaf children appear to be more vulnerable to mental health problems and the presentation of mental health problems in deaf children is influenced by BSL and visual communication. However this increased vulnerability is not present across the full range of mental health problems. Emotional and behavioural problems appear more common. Autism and related disorders appears to be more common. Psychotic disorders such as schizophrenia and bi-polar affective disorder are not more common but the presentation of thought disorder and abnormal experiences such as hallucinations are profoundly affected.

The epidemiology and presentation of autism in deaf children will be used to explore links between linguistic and experiential deprivation and mental health problems in deaf children. The presentation of bipolar affective disorder in a deaf child and a deaf adult will be used to explore the relationship between BSL and thought disorder.

How the brain processes emotional and social stimuli
R Adolphs, University of Iowa, USA

The neural mechanisms by which we process emotionally and socially relevant stimuli have been explored most in relation to a particular class of stimuli: emotional facial expressions. Investigations using functional imaging, lesion methods, and single-neuron recordings have elucidated several components of a neural system that links perception of such stimuli to the modulation of social behavior. The components include the amygdala, the orbitofrontal cortex, the cingulate cortex, and somatosensory-related cortices. My lecture will review some of these findings, discuss their relevance to a model of social cognition, and discuss their implications for our understanding of social behavior in general.

Is autism an extreme of the male brain?
S Baron-Cohen, University of Cambridge, Autism Research Centre

Autism affects males far more often than females. This is especially true for the related condition of Asperger Syndrome (AS) where the sex ratio may be at least 10:1 (male:female), if not a lot higher. Why might this be? One possibility is that autism is an extreme form of the male brain. This theory was first proposed by Hans Asperger, but our recent work puts it to the test. First we define what we mean by the male and female brain. This is discussed in terms of two processes, empathising and systemising. We look at evidence for sex differences in these processes. Then we look at whether autism involves deficits in empathising together with talents in systemising. Some of the biological mechanisms underlying this are also tested and discussed.

Autism and developmental receptive language disorder – a follow-up comparison in early adult life. Social, behavioural, and psychiatric outcomes
P Howlin, St George's Medical School, London

In this study we compared adult outcome in a group of young men with autism and a group with developmental receptive language disorders. The two groups were first assessed in early childhood, when aged 7 to 8 years of age. Although matched at that time for non-verbal IQ (mean 92-93) and expressive language ability the Autism group was significantly more impaired on most measures of social and communication skills and stereotyped behaviours. A later follow-up, in mid childhood, suggested that although the groups were still quite distinct, social and behavioural problems had become more apparent in the Language group.

The current study was completed when the participants were aged, on average, 23 to 24 years. The findings indicated that verbal IQ and receptive language scores had improved significantly more in the Autism group than in the Language group over time. Moreover, although the Language group was less severely impaired in their social use of language, many showed a number of abnormal features in this domain. There were no differences between the groups on tests of reading or spelling.

Similarly, although the Autism group continued to show significantly more impairments in terms of stereotyped behaviour patterns, social relationships, jobs and independence, problems in all these areas were also common in the Language group. Many still lived with their parents, few had close friends or permanent jobs and ratings of social interaction indicated abnormalities in a number of different areas. On a composite measure of social competence only 10% of the Language group was assessed as having severe social difficulties compared to 74% of the Autism group. Nevertheless, 65% were rated as having moderate social problems and only 25% were rated as being of near/normal social functioning. Two individuals in the Language group, but none in the Autism group, had also developed a florid paranoid psychosis in late adolescence.

Discriminant Function analysis, which had clearly distinguished between the groups as children now showed much greater overlap between them. Regression analysis indicated that although early language ability appeared to be related to outcome in the Autism group, in the Language group there was little association between measures of childhood functioning and later progress.

Theoretically, these findings have implications for our understanding of the nature of autism and other pervasive language disorders, and of the relationship between them. Practically, they demonstrate the very persistent problems experienced by individuals with developmental language disorders, and their need for much greater help and support than is presently available.

Emotional memory in temporal lobectomy patients with unilateral or bilateral damage
B Brierley, P Shaw, A S David, Kings College, London

Aims: The amygdala is hypothesised to mediate enhancement of memory for emotional material. We studied patients with unilateral and bilateral amygdala lesions secondary to TLE on a standard test of emotional memory.

Methods: 12 left-sided, 15 right-sided and 3 post-operative temporal lobe patients with bilateral amygdala damage (confirmed by volumetric structural MRI) were matched for estimated IQ (NART) and sex to healthy and generalised epilepsy controls. The Heuer and Reisburg (1990) test of emotional memory, was administered. One week later, recall for the different sections of the story, was compared.

Results: Right-sided TLE patients, healthy and generalised epilepsy controls demonstrated superior recall for the central, arousing section of the story. Patients with left-sided amygdala damage failed to show emotional enhancement; patients with bilateral damage demonstrated a significant disadvantage in retrieval for details pertinent to the emotional section. Intact (un-operated) amygdala volume correlated significantly with an emotional index for recall in all TLE patients.

Conclusions: These results implicate the amygdala in the long term consolidation of emotional memories. The left amygdala appears to play a particular role, but patients with bilaterally acquired damage showed selective impairment in the retrieval of arousing material.

Psychosis following temporal lobectomy

P Shaw, J Mellers, M Henderson, B Brierley, C Polkey, A David and B Toone, Institute of Psychiatry

Aims: Patients who become psychotic following temporal lobectomies for medically intractable epilepsy can provide insights into the pathogenesis of other psychotic illnesses- particularly schizophrenia. We describe the phenomenology of such a group of patients and examine the relationship of their psychosis to both the operation and subsequent seizure activity. Using a retrospective case- control design, we also attempt to identify risk factors for the development of psychosis among surgically treated patients.

Method: Patients who developed psychosis were identified from a series of 360 patients who had temporal lobectomies. Each case was matched with the next three patients who did not become psychotic and case notes reviewed.

Results: 13 patients who developed psychosis post-operatively were identified and compared with 39 controls. The psychoses were diagnostically and phenomenologically varied but characterised chiefly by paranoid delusions with prominent affective symptoms and followed a chronic relapsing remitting course. Most psychoses started in the early post-operative period. No clear relationship between seizure activity and fluctuations in psychotic symptoms emerged. There was a trend for psychotic patients compared to controls to have more bilateral EEG abnormalities, pathology other than mesial temporal sclerosis and smaller anterior temporal lobes structures on post-operative MRI.

Conclusions: Temporal lobectomy for medically intractable epilepsy may precipitate a psychosis characterised by paranoid delusions and affective symptoms. Patients with bilateral damage may be at particular risk for the development of psychosis.

Rivastigmine is preferable to Olanzapine in the management of dementia with Lewy bodies (DLB)

G Elrington, J Ashton, Oaks Hospital, Colchester

Aims: To establish whether an atypical antipsychotic drug, or a cholinesterase inhibitor offer the best outcome for people with DLB.

Methods: Retrospective analysis of the notes of patients with Parkinson's disease (PD), under active supervision by a Parkinson's nurse

Results: Among 260 people with PD, 58 (22%) had DLB; 35 (60%) were given drug treatment for DLB.

24 were first given olanzapine. 8 (30%) had a good response, 6 (22%) withdrew treatment because of worsening PD. v

13 took rivastigmine. 8 (62%) had a good response, none suffered worsening of PD. Two of this group had previously tried olanzapine, one of whom had a satisfactory response to rivastigmine.

Conclusions: Rivastigmine appears about twice as likely to provide useful benefit, than olanzapine, with a greatly diminished risk of exacerbating PD.

Magnetisation transfer detects anterior cingulate abnormalities in Bipolar Disorder

S D Bruno, M S Bagary, M Symms, M A Ron, Institute of Neurology

Aims: The study aims at the investigation of possible brain abnormalities in patients with bipolar disorder (BD) using Magnetisation Transfer, a novel technique of structural MRI.

Methods: 39 patients with DSM-VI diagnosis of BD and 28 matched healthy controls were scanned on a 1.5 tesla scanner.

Results: A voxel-based analysis in SPM '96 and '99 showed significant decrease in magnetisation transfer ratio in the supracallosal anterior cingulate and surrounding periventricular regions, which indicates neuropathological changes in such regions.

Conclusions: Using more sensitive techniques than conventional MRI it is possible to detect neuropathological changes in the brain of patients with BD in areas that are known to be implicated in mood regulation.

Near-Death Experiences in Children During Meningococcal Disease
D Shears, M E Garralda, S Khan, Imperial College School Of Medicine, London

Aims: To describe the near-death experiences of 3 children with Meningococcal Disease and to explore associations with illness severity and type, developmental level, psychological adjustment and previous family experiences, in the context of sparse existing literature on the topic.

Methods: Review of the literature and description of the components of the near-death experience (NDE). Exploration of the possible influence of child's adjustment and development. A comparison of the similarities and differences in these children's NDE's, in the light of their psychiatric adjustment and family characteristics is made with reference to the current literature.

Results: Analysis of the results is being carried out at present.

Conclusions: As for results.

A Neuropsychiatry Outreach Clinic
F Leonard, Shahid Majid, Kandiah Sivakumar, Brian Toone, The Maudsley Hospital, London

Aims: The aim is to show how a service innovation in the form of an outreach clinic in Maidstone can increase access to specialist expertise and to examine the referral pattern to the clinic over the 4 years that it has been operating. The increased local awareness in Neuropsychiatry is reflected in the changed pattern of referral to the Maudsley Neuropsychiatry service from the Maidstone area compared with surrounding areas.

Methods: The Neuropsychiatry Outreach Clinic in Maidstone, West Kent is an example of collaboration between secondary and tertiary services and is in keeping with the 'hub and spoke' model of care. We review referrals to the clinic over the 4 years of the clinic's existence between June 1996 and June 2000. We compare the referral pattern prior to June 1996 with the last 4 years from the West Kent Health Authority and adjacent Health Authorities.

Results: There were a total of 49 new referrals to the Outreach clinic in Maidstone between June 1996 and June 2000. Only 12% of the referrals were for conditions of a purely psychological nature such as non epileptic seizures or abnormal illness behaviour and all referrals were from psychiatrists. 61% of referrals were for investigation of an organic cause of psychiatric illness.

The last four years have seen a large increase in the number of referrals from West Kent (87 to 225) unlike East Surrey (22 to 42) and East Sussex (28 to 24)

Conclusions: Psychiatrists tend to refer patients with an organic problem and are possibly not aware of the full range of services that Neuropsychiatry can offer. The large increase in the number of referrals from West Kent in the last 4 years has coincided with the outreach clinic's existence. 19% of the 225 referrals from West Kent were first assessed in the Outreach clinic (the remaining 81% being seen in the Maudsley Hospital or Kings College Hospital, London). This implies that the outreach clinic has not only provided a means of referral to Neuropsychiatry but has also served to raise general awareness of the speciality as a resource for West Kent patients.

It is likely that a similar collaboration between secondary and tertiary services in other areas would have the effect of increasing the use of the service in those areas also.

Deconstructing Serotonin.

B E Leonard, National University of Ireland, Galway.

The Deconstructionist school of philosophy largely stems from the ideas of the contemporary French philosopher Jacques Derrida. In summary, the Deconstructionists argue that linguistic meaning is “constructed” through contrasts between binary opposites, such as black/white, and that the choice of one of the terms as positive depends on the negation of the opposite term.

Applying this concept to serotonin, it can be reasoned that the positive aspect lies in its role as a neurotransmitter and neuromodulator with additional properties as a local hormone in the gastrointestinal tract. Indeed, over 800 million years ago, serotonin and its primordial receptor occurred in some of the first multicellular organisms. The success of this indoleamine as a neurotransmitter has largely overshadowed its other non-neurotransmitter roles due to the very success of the psychotropic drugs which have wide applications in both psychiatry and neurology.

In keeping with the philosophy of Deconstructionism, serotonin also has a neurotrophic and immunomodulatory role which has largely been overlooked (“oppressed” in Deconstructionist jargon). Thus recent evidence suggests that serotonin acts to enhance anti-inflammatory cytokine (mainly interleukin 4) function. As proinflammatory cytokines, such as interleukins 1,6 and tumour necrosis factor alpha, have been implicated as causal factors in a number of psychiatric and neurological disorders, such observations could be of potential therapeutic importance. In addition, in vitro data indicates that serotonin acts on astrocytes in culture to stimulate the synthesis of nerve growth factor, while in the rat striatum it enhances neuronal plasticity by increasing the release of a glial trophic factor thereby promoting neuronal development.

The lecture will illustrate both the “positive” and “negative” aspects of serotonin and thereby illustrate how the contemporary philosophy of Deconstructionism is alive and well and contributing to the theoretical development of neuroscience.

Inhibiting Excitation and Exciting Inhibition

J G R Jefferys, University of Birmingham

Networks of excitatory neurons play a key role in the initiation and synchronisation of many (most?) epileptic seizures. These networks are essential for normal brain function, but they also present a risk of excessive neuronal recruitment due to their strength and divergent connectivity. The strength of these connections is amplified by the ability of cortical excitatory neurons to fire bursts of action potentials in response to brief inputs. Evidence is accumulating that many idiopathic, and some genetic, epilepsies are associated with prolonged action potentials that will tend to promote burst firing and/or strengthen synaptic transmission.

The risk of epileptic activity in these circuits normally is contained by inhibitory neurons. They need to sample the net level of excitation (“exciting inhibition”) and to control the level of excitation as required (“inhibiting excitation”). The synapses involved at both stages have complex properties and can be modulated in many ways both by endogenous neurochemicals and by drugs. One example of this is the recent discovery by Wallace et al (2001; *Nature Gen* 28: 49-52) of an epilepsy-related mutation in the diazepam modulation site of the inhibitory GABA_A receptor, which suggests that there must be an endogenous ligand for this site, and that it plays a role in controlling seizures.

Epilepsy is not the result of a simple summation of excitation and inhibition. Rather, it is a product of the complex dynamics of neuronal networks. For example, inhibitory neurons often inhibit one another. At first sight this should result in disinhibition, but in practice mutual inhibitory connections can result in coherent oscillations which promote synchronisation of the excitatory neurons. For instance, in the reticular nucleus of the thalamus such circuits play a role in the generation of absence seizures.

The topic of this session is “New Drugs for Neuropsychiatry”. Conventional anticonvulsant drugs act on mechanisms such as: the ability of voltage gated channels to sustain action potentials at high frequencies, and factors affecting the efficacy of inhibitory synapses. New drugs for epilepsy have had varying degrees of success. One promising approach was to use NMDA receptor antagonists to weaken excitatory synaptic transmission, but these unfortunately resulted in psychotic symptoms and other problems. Some of the better new anticonvulsant drugs have proved rather “dirty” at a cellular level; their multiple cellular actions may even contribute to their success. Anticonvulsant drugs have applications outside epilepsy. For instance, valproate, carbamazepine and lamotrigine have been used in treating bipolar disorder. Other anticonvulsants are under investigation in this context. Whether their mood stabiliser and anticonvulsant actions share the same mechanisms is an important question, which may help illuminate the underlying brain mechanisms for affective disorders. Unfortunately, the multiple cellular actions of most of the anticonvulsants make it difficult to find an answer.

Neurotrophins in Alzheimer's disease

G K Wilcock, University of Bristol

Nerve Growth Factor (NGF) was first identified by Levi-Montalcini nearly half a century ago, when it was reported that mouse sarcomas transplanted into chick embryos attracted sensory and sympathetic nerve fibre ingrowth from the embryonic developing nervous system. Our knowledge of neurotrophic factors has increased rapidly since then, and a number are now well characterised, including NGF, Brain Derived Neurotrophic Factor (BDNF), and Neurotrophin 3 (NT-3) etc.

NGF appears to be released from cells lying in a "target" area, whence it is taken up by the efferent projections of deeper lying sub-cortical structures such as the basal nucleus of Meynert (NBM), a major sub-cortical cholinergic site. That NGF has a protective effect on cholinergic cells is now well established from a wealth of animal studies, and the potential function of a whole family of neurotrophins is under extensive investigation in relation to neuro-protection in several neurodegenerative disorders, including Alzheimer's disease.

Most cholinergic cells are concentrated in discrete sub-cortical nuclei that form part of a continuous ribbon of cells in the basal forebrain, i.e. the medial septal nucleus, the nucleus of the diagonal band of Broca and the basal nucleus itself. We and others have shown these cells to be immunopositive for the NGF receptor, and that immunohistochemical staining for markers of cholinergic cells co-localises with those for NGF receptors in the basal forebrain. The basal forebrain, of course, is well known to be one of the more vulnerable sites of cellular damage and loss in Alzheimer's disease. Early studies underestimated the number of remaining neurones in the NBM in Alzheimer's disease, and it would appear that most of these neurones still express the low affinity NGF receptor. There is therefore a potential sub-cortical substrate upon which NGF, or NGF mimics, could exert a valuable therapeutic effect.

Animal models have confirmed the neuroprotective effect of NGF on the cholinergic neurones in the basal nucleus. Intraventricularly delivered mouse-derived NGF has been administered to three patients with Alzheimer's disease in Sweden. Although there was some evidence of a positive effect, the results were in general disappointing, and this will be discussed further, as will possible mechanisms of improving efficacy and minimising NGF's potential adverse event profile. Although there are a small number of reports suggesting alteration in the level of other neurotrophins in Alzheimer's disease, NGF appears to be the most significantly affected, and to offer most therapeutic potential. Alternative delivery systems are also being explored, as is the development of compounds that may have NGF-like activity.

Neuronal growth and synaptic plasticity: understanding antidepressant action

I C Reid, University of Dundee

Recent studies have demonstrated that the stress and antidepressant agents have reciprocal effects on neural connectivity and neurogenesis. A range of stressors have a profound and long-lasting impact on neural proliferation and neural communication in the hippocampus of a variety of species. These effects help us to understand the interaction of genetic and environmental factors in the development of depressive disorder, including the emotional and cognitive effects of the illness. Studies in rodents reveal that early maternal separation has the capacity to modify adult neural responses stress in a way that models the clinical impact of adverse early life experience on the genesis of depressive disorder. A wide range of different antidepressant treatments have the common property of interacting with these pathoplastic processes, providing a new perspective on the pathophysiology of affective disorder with the potential to generate novel antidepressant strategies.

Atypical atypical antipsychotics
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The purpose of this presentation will be to discuss the next generation of antipsychotics and potential therapeutic targets beyond the current wave of drugs designated as atypical antipsychotics. The term atypical is most easily understood as a phrase that describes agents which are free or relatively free of extrapyramidal and endocrine side effects. The current generation of atypical drugs still rely on a dopamine D2 receptor blocking action for their efficacy and the atypical profile is afforded either by regional selectivity at limbic dopamine receptors or additional activity at 5HT2 receptors. There is an immediate next generation of drugs whose mechanisms of action depart somewhat from this and further generations of drugs which may have radically different mechanisms of action. The immediate next wave of drugs include Aripiprazole, Iloperidone and Ziprasidone. Aripiprazole stands out as having the most novel mechanism of action. The drug is a potent partial agonist at D2 receptors that theoretically is able to stabilise both hypo and hyperactive dopamine systems. Iloperidone whilst being a standard D2/5HT2 blocker has an interesting additional ability to block alpha 2c receptors. This action has a stabilising effect on ascending dopaminergic systems. Ziprasidone has already received regulatory approval in several European countries and the United states. Again this is a standard D2/5HT2 blocker, but additional actions at 5HT1a receptors and SSRI activity may give it additional antidepressant activity and make the drug weight gain neutral. The next 5-10 years may herald the introduction of agents whose mechanism of action departs radically from actions at D2 and 5HT2 receptors. There are drugs in the pipeline which may work by acting at limbic selective members of the dopamine receptor family namely D3 and D4 receptors. In addition recent work suggests that D1 receptor agonists may also have therapeutic potential. Probably most work on nondopaminergic therapeutic actions has been done on glutamate receptor systems. Consensus is that there may be hypofunction of this system in schizophrenia. The NMDA receptor subtype has received most attention in this regard. Pharmacological manipulation of this receptor is difficult because of the potential proconvulsant actions of such drugs. Nevertheless some attempts have been made at manipulating the glycinergic allosteric regulatory site of this receptor. These studies seem to show a weak effect. The sigma receptor may also be a relevant target and there are a number of drugs in early phase clinical development which suggests there may be weak actions at negative symptoms.

In conclusion it seems that most next generation drugs will still rely on a dopaminergic mode of action. Radically novel mechanisms of action do not currently carry much promise of strong clinical effects.