the same neurobiological process. Recent examples of the success of a cytogenetic approach to studying mood disorders include the identification of an interstitial duplication of chromosome 15q associated with panic and phobic disorders in a family (Gratacos et al. 2001 *Cell;106:367*) and the analysis of a balanced reciprocal translocation in a large Scottish family that has identified two genes implicated in major psychiatric disorder, directly disrupted at the breakpoint on chromosome 1 (Millar et al. 2000 *Hum Mol Genet;9:1415*). This chromosome translocation segregates in a single large family with a phenotype that includes unipolar and bipolar affective disorder and schizophrenia (Blackwood et al.2001. *Am J Hum Genet 69:428*). Analyses of families with chromosome rearrangements segregating with major mental illness are likely to implicate further genes whose disruption leads to mood disorders and the phenotypes associated with these rearrangements may help to clarify or redefine diagnostic categories.

S18. Gene–environment interplay

Chairs: P. McGuffin (GB), H. Ewald (DK)

S18.1

Genes and environment in ADHD

A. Thapar*. *Child & Adolescent Psychiatry Section, Department of Psychological Medicine, University of Wales College of Medicine, UK*

There is now considerable evidence that Attention deficit hyperactivity disorder (ADHD) is strongly influenced by genetic factors. There have been a wealth of family, twin and adoption studies and now there is considerable international effort directed towards identifying susceptibility genes for ADHD. Early results look promising. Nevertheless the role of environmental factors and the question of how ADHD is best defined remain important issues. There is also increasing interest in the application of genetic findings in clinical settings with pharmacogenetic research aimed at examining what genetic factors influence treatment response. Recent and emerging research on the genetics of ADHD will be reviewed.

S18.2

The role of personality in influencing genetic and environmental risk factors for major depression

A. Farmer*. *SGDPRC Institute of Psychiatry, Denmark Hill, Camberwell, London, UK*

Personality factors such as extraversion or neuroticism could influence the way individuals respond to environmental adversity that could lead, in turn, to the development of an episode of depression. For example, subjects with high rates of neuroticism, may view the world as particularly threatening and hostile, and consequently may be unable to satisfactorily resolve the problems caused by an adverse life event. Alternatively, an extravert individual may indulge in risky activities, which have an attendant high risk of excess adverse events occurring, and who could be considered as leading "hazard-prone" life styles.

The role of personality will be considered in relation to the genetic vulnerability to depression in a sib-pair design. Depressed probands, their nearest aged siblings, healthy control probands and their nearest aged siblings were compared for the rates of depression in the 2 groups of siblings, and the number of different types of life events experienced in a 12 month period by all four groups of subjects. In addition, the relationship between various measures of current mood, personality and life events will be discussed.

S18.3

Genetic influences on autism

M. Rutter. *Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK*

Twin and family studies over the last quarter of a century have consistently pointed to a strong genetic influence on the liability to autism – a liability that extends beyond the traditional diagnosis of a seriously handicapping disorder, and which probably involves a relatively small number of susceptibility genes. During the last decade, several large-scale collaborative molecular genetic studies of autism have been established, with some partially replicated findings of gene loci. The paper will provide an update on the state of genetic knowledge and will consider the implications for our understanding of this multifactorial psychiatric disorder.

S18.4

What do comorbidity studies with somatic disorders tell us about the etiology of schizophrenia?

O. Mors*. *Institute for Basic Psychiatric Research, Risskov, Denmark*

It has proven very difficult to progress from evidence confirming a genetic contribution to the etiology of schizophrenia to evidence implicating the specific genes in the disease. At the same time the environmental risk factors have eluded us their discovery. The study of possible associations between somatic disorders and schizophrenia may generate hypotheses about the role of both genetic and non-genetic factors in etiology of schizophrenia: candidate chromosomal regions for schizophrenia may be identified, gene-environment interactions suggested and sources of natural selection in man illustrated. Comorbidity studies have usually been register based, since large data sets is needed to generate sufficient power to demonstrate significant, moderate increased or decreased relative risks. Results from on ongoing study in Denmark of associations between schizophrenia and other complex disorders such as autoimmune diseases (e.g. rheumatoid arthritis and type I diabetes) and also appendicitis will be presented. Methodological pitfalls such as selection bias will be discussed.

S18.5

Genetic and non-genetic factors in bipolar affective disorder

H. Ewald. *Institute for Basic Psychiatric Research, Risskov, Denmark*

Developments in diagnostic instruments and criteria, molecular genetics, computer programs and statistics have helped to identify more than 10 candidate chromosome regions potentially containing genes which increase susceptibility to bipolar affective disorder. A number of research groups are now attempting to identify the specific risk genes in the most promising chromosome regions including chromosome 4p, 12q, 18 and 21. Increased knowledge of the neurobiology of the brain has also resulted in new candidate genes. Though no DNA sequence variation of relevance has yet been reported the draft sequence of the human genome and recent developments for high-throughput genotypings and other molecular genetic methods will facilitate this. Genetic mapping studies

have suggested that a combination of susceptibility and possibly protective alleles at a number of loci determines the genetic risk of developing bipolar affective disorder in the individual. Some of the risk genes are possibly also involved in the etiology of schizophrenia.

Non-genetic risk factors have not been much studied. However, recently a few studies have suggested parental loss in childhood and possibly head trauma. Other non-genetic risk factors of importance in schizophrenia do not seem to influence risk in bipolar affective disorder.

Knowledge of specific risk factors will facilitate the identification of other risk factors.

The identification of risk factors involved in susceptibility to bipolar affective disorder will enable more specific knowledge on the etiology and development of the disorder. This may lead to improvement of treatment, treatment choice, diagnostic classification and perhaps even preventive measures.

S19. Severe OCD: recent advances in techniques for neurosurgical treatment

Chairs: P. Cosyns (B), S. Andréewitch (S)

S19.1

Neuroanatomy, neurophysiology and neuropathology of OCD

F. Hohagen*. *Universitätsklinikum Lübeck, Germany*

Research of the last decades has accumulated evidence that neurobiological factores play an essential role in the pathophysiology of obsessive–compulsive disorder (OCD). Clinical observations in neurological disorders with an underlying dysfunction of the basal ganglia system, e.g. Gilles de la Tourette-Syndrom or Sydenham's Chorea, have shown that patients exhibit significantly more often obsessive and compulsive symptoms in addition to the typical neurological symptoms. The most consistent finding from neuroimaging studies with Positron Emission Tomography (PET), Single Photon Emission Tomographie (SPECT) and functional Nuclear Magnetic Resonanz Tomography (fNMR) is that patients suffering from OCD show increased neuronal activities in the nucleus caudatus, orbitofrontal cortex and gyrus cinguli when compared to normal controls. Furthermore, confrontation with objects provoking obsessive–compulsive symptoms increase the activity of the fronto-striatal system, whereas successfull treatment with serotonin-reuptake-inhibitors or cognitive behavioural therapy decrease the activity of the frontostriatal loop. Thus, clinical observations and controlled studies using neuroimaging techniques provide evidence that dysfunction of the frontoorbitostriatal system may be crucial for the manifestation of the obsessive compulsive symptoms.

S19.2

Psychopharmacological treatment in severe and/or resistant OCD: augmentation strategies

E.-G. Hantouche*, J.F. Allilaire. *Mood Center, Pitié-Salpêtrière Hospital, Paris, France*

Despite significant progress in the pharmacotherapy of OCD, a large proportion of patients (30–40%) still resistant or respond poorly or partially to conventional treatments. The literature on the phenomenology and physiopathology of resistant OCD and on appropriate solutions still scare. Few strategies are successful and/or well documented by controlled or replicated studies. Moreover augmentation strategies proposed in refractory severe cases of depression are not always effective in severe resistant OCD. Promising data to augment the anti-OCD efficacy were obtained by using combinations of anti-OCD psychotropics (i.e. clomipramine plus SSRI), atypical neuroleptics plus SSRI (risperidone, olanzapine, pimozide), precursors of serotonine (i.e. tryptophan). Other probes acting on the 5HT transmission (such as buspirone, fenfluramine, lithium, clonazepam) or agents acting on impulsivity (such as antiandrogen drugs, valproate) were also tested. In the moment, the clinicians should be able to face complex and severe OCD without any rigid algorithm. A practical approach should include: 1) early screening of the illness in the primary care system (i.e. juvenile onset OCD); 2) maximizing the effectiveness of the first trials; 3) systematic searching for comorbidity (especially hidden soft bipolarity); 4) better understanding of OCD subtypes with regard to phenomenological clustering; 5) finally, better utilization of the available non-drug treatments (multimodal CBT, intensive individual and/or group therapy...).

S19.3

Capsulotomy, a valid treatment for extreme OCD?

S. Andréewitch*, C. Rück, K. Flyckt. *Karolinska Hospital, Department of Clinical Neurosciences, Stockholm, Sweden*

There is uncontrolled evidence to suggest that capsulotomy may benefit OCD-patients refractory to standard treatment. Since brain regions affected by surgery are assumed to be involved also in executive cognitive function, a crucial issue is whether there is a price, in terms of cognitive dysfunction, which the patient may have to pay for any symptom amelioration. Follow-up studies point to a highly significant symptom reduction in operated patients. Neuropsychological function seems to remain essentially intact over time. However, a subgroup of patients show more perseverative responses on the Wisconsin Card Sorting Test (WCST), indicating dysfunction in systems involving the frontal lobes. A recently completed follow-up study at our center, of patients with non-OCD anxiety, operated with thermo- capsulotomy between the years 1975–91, indicate a greater than expected incidence of cognitive side effects. Although a different diagnostic group, the neurosurgical intervention is identical to that performed on OCD-patients. A long term follow-up of OCD patients is currently under way. Issues of relevant follow-up evaluation and directions for further research will be discussed.

(1) Nyman H., Andréewitch S. Applied Neuropsychology, 8: 91–98, 2001
(2) Rück C, Andréewitch S. Poster, ANPA 2000

S19.4

Deep brain stimulation in severe treatment refractory OCD

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Stereotactic capsulotomy, making precisely aimed lesions in the anterior limbs of internal capsules, has been performed for years for severe, long-standing, treatment-refractory OCD. Both prospective and follow-up studies suggest that this last-resort therapeutic option may not be discarded. The complication rate is low. Symptoms improve substantially for +/- 40% to 60% of the carefully selected, refractory OCD patients.

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