INTERFACE BETWEEN NEUROLOGY AND PSYCHIATRY IN CHILDHOOD

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In the post war years of the 20th century, the divide between neurology and psychiatry seemed nearly complete. Such a separation between the “organic” biologically based disorders with florid neurological physical signs, and the “functional” mentally ill behaviourally, affectively or psychotically disturbed with minimal physical neurological abnormalities on examination would have seemed extraordinary a couple of centuries earlier. Freud himself was an expert in cerebral palsy and the minutiae of its description. For paediatric neurologists it has been the rare psychiatrist who has been a regular participant in their meetings and whose writings have proved educational and inspirational. Similarly, it is rare for neurologists to be involved in teaching child psychiatrists and few have had training in the psychosocial aspects of patient management. It is to be hoped that in the present century paediatric neurology and child and adolescent psychiatry will come even closer with a new generation of neuropsychiatrists.¹ Training in paediatric neurology and paediatric neurodisability currently reflects this with a requirement for psychiatry modules and placement.

BIOLOGICAL BASIS OF BEHAVIOUR DISORDERS

Neurobiology, genetic research, and particularly modern imaging technology have prompted re-evaluation of disorders of behaviour assumed to have little biological basis. Several major mental illnesses would now be thought of as having a significant biological basis—for example, obsessive compulsive disorder (OCD), schizophrenia, autism, and addiction. Attention deficit hyperactivity disorder (ADHD), dyslexia, and OCD are examples where functional neuroimaging of subjects compared with controls have shown consistent differences. In OCD, pre- and post-treatment paradigms demonstrate attenuation of hypermetabolism in orbitofrontal cortex, caudate nucleus, and anterior cingulate cortex, with reduction of OCD symptoms, as a consequence of effective treatment, irrespective of whether the treatment modality was behaviour therapy or medication.

It is often commented in jest that psychiatry is one of the medical disciplines that is striving towards its own extinction, through systematic biologic research of “functional” disorders. Genetic research in many behavioural disorders has shown the sophistication of approach needed to investigate the genetic predisposition and environmental interactive influence that contribute to the variable phenotypes. A recent study has for the first time demonstrated a clear environmentally mediated genetic effect on behaviour.²

This review is not intended just to emphasise the biological basis to many behavioural syndromes currently classified as psychiatric disorders in the *International classification of diseases*, 10th revision (ICD-10) and the *Diagnostic and statistical manual*, fourth revision (DSM-4), but seeks to emphasise the importance of understanding the behaviour of children and their parents in a variety of predicaments where psychiatry has much to offer and where such understanding should inform all medical practice.

There are many clinical situations in which the overlap between neurology/psychiatry is significant:

- ▶ “Organic” disorders presenting as “functional” disorders—for example, Creutzfeld-Jakob disease (CJD) presenting as a depressive disorder
- ▶ “Functional” disorders presenting as “organic” disorders—for example, non-epileptic seizure disorder, hysterical blindness/deafness
- ▶ Co-occurrence of both “organic” and “functional” disorders—for example, seizure disorder with non-epileptic seizure disorder
- ▶ Psychological factors worsening organic symptoms—for example, depression worsening pain
- ▶ Organic factors worsening/inducing functional symptoms—for example, brain injury worsening pre-existing personality traits
- ▶ Environmental factors inducing “organic” brain changes—for example, post-traumatic stress disorder
- ▶ “Organic” and “functional” factors contributing to disorder—for example, premenstrual dysphoria, chronic fatigue syndrome or myalgic encephalitis

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- ▶ Organic contributions to the basis of “functional disorders”—for example, schizophrenia, bipolar illness, depression
- ▶ Organic basis of neurodevelopmental disorders—for example, Tourette’s syndrome, autism, ADHD
- ▶ Impact of “organic” or “functional” illness on family—for example, depression in family arising from burden of disorder.

Very often the presentations involve more than one of the interactions mentioned above. Acuteness of onset of symptoms in general signals a search for some underlying organic basis for a change in behaviour. However, this is not always necessarily the case because acute onset of symptoms can occur following an acute stressor—for example, acute mutism/perplexity following abuse.

Delirium

Delirium is defined as a fluctuant impaired consciousness with fluctuant impairment of cognitive function affecting memory, environmental orientation, attention, planning, and mood. Rapidity of onset distinguishes delirium from dementia. Illusions, perplexity, delusions, and hallucinations are common. Fluctuating consciousness distinguishes delirium from other acute impairments of cognitive function such as psychosis. Important causes are:

- ▶ drug induced: anticholinergic drugs, anticonvulsants, steroids, alcohol and other illicit drugs.
- ▶ metabolic causes: renal or hepatic failure, inborn metabolic disorders
- ▶ infections: general or cerebral
- ▶ head injury
- ▶ epilepsy: ictal, interictal, post-ictal
- ▶ other cerebral causes: cardiovascular/neoplastic.

Treatment is by recognising the state, removing/treating the underlying cause, and symptomatic treatment if necessary with a short course of antipsychotics or benzodiazepines.

Degenerative disorders

Sub-acute symptom onset is common. The need for both psychiatrist and neurologist to work together and the overlap of symptom presentation in an undoubted organic disorder is exemplified in the presentation of the variant Creutzfeldt-Jakob degenerative neurological disease (vCJD). A recent study demonstrates this clearly, with six of 100 patients reviewed being under 16 years at onset, and the median age of the group being 26 years, with 63% presenting with psychiatric symptoms, 22% presenting with a mixture of psychiatric and neurological symptoms, and only 15% presenting with pure neurological symptoms.³ The typical psychiatric symptoms included dysphoria, withdrawal, anxiety, insomnia, and loss of interest. In just over half, a neurological symptom appeared within two months which most commonly was pain.³ Other degenerative neurological diseases in children are reviewed elsewhere.

Behavioural aspects of epilepsy

There is a high correlation of behaviour problems and school based problems of learning and achievement in children with epilepsy. Disentangling the contributing factors can be difficult. In 1970, Rutter and colleagues first described the range of associated behavioural features with epilepsy.⁴ Many studies have since confirmed the association. Co-morbidity adds to the diagnostic complexity and increases difficulties from the child and family’s perspective. This highlights the need for multidisciplinary teams managing the most complex

Behavioural presentations in epilepsy

- (1) Caused by epilepsy
  - ▶ pre and peri-ictal—prodromal/aura/automatisms
  - ▶ post-ictal, especially frontal disinhibition
  - ▶ caused by focal discharges—for example, left temporal/aggression, frontal lobe behaviour, transient cognitive impairments, localised hemispheric behaviour improved by hemispherectomy, frequent absences leading to confusional states/withdrawal/attention problems, electrical status epilepticus in sleep (ESES) in Llandau-Kleffner syndrome, language regression and autistic features
- (2) Caused by antiepileptic drugs (AEDs) (see below)
- (3) Caused by underlying brain dysfunction causing both problems in behaviour and epilepsy
- (4) Personal/parental reaction/response to having epilepsy
- (5) Idiopathic

Mechanisms of behavioural side effects of AEDs

- ▶ Dose/pharmacologically related in central nervous system (CNS) or outside CNS. This includes making seizures worse—for example, carbamazepine and absences
- ▶ Idiosyncratic response
- ▶ Caused by drug interactions, especially those metabolised in the liver
- ▶ Teratogenic effects on fetal neural development

cases and from the clinician’s point of view the necessity of considering co-morbid diagnosis rather than just the primary presenting conditions, since successful outcome will depend upon paying attention to each symptom. For example, a child with epilepsy who appears to have the epilepsy well controlled but is still failing socially and academically needs a more comprehensive history and examination to exclude general or specific learning problems, specific attentional problems or specific social impairments. A recent study emphasised the need also to look at pre-epilepsy behaviour when trying to explain the impaired performance on attention tasks requiring combined speed and accuracy in children with idiopathic epilepsy. Surgery has an important place to play in the management of severe epilepsy; the positive effects are frequently those on behaviour as shown by quality of life measures following surgery in temporal lobe seizures, in Llandau-Kleffner syndrome, and following hemispherectomy in hemiplegia with severe epilepsy.⁵

Antiepileptic drugs (AEDs) both old and new have all been reported to result in treatment emergent psychiatric disorders, although the issue regarding causation is complicated by the increased incidence of psychiatric disorders in those with epilepsy. Behavioural difficulties are increased in the presence of learning difficulties (both specific and general), and where the epilepsy is refractory to treatment. Phenobarbitone, carbamazepine, valproate, and the newer AEDs, vigabatrin, lamotrigine, and topiramate have all been implicated. For many AEDs the therapeutic window is very close to the levels that induce side effects such as affecting general cognitive function or their specific neurotransmitter action affects behaviour.

DEVELOPMENTAL DISORDERS

The overlap of psychiatry and neurology in developmental disorders was first highlighted in the classic Isle of Wight

Considerations in treating psychiatric disorders with pharmacological approaches in the presence of epilepsy

- (1) If related to epilepsy—needs epilepsy controlled
- (2) If related to AEDs—change drug. Vigabatrin's action of blockade of GABA breakdown may precipitate psychosis in predisposed individuals
- (3) Use appropriate medication based on symptoms and knowledge of drug mechanism
  - ▶ Psychosis: drugs acting on reducing D2 activation may help
  - ▶ Depression: selective serotonin reuptake inhibitors (SSRIs) for depression may have a pro- or antiepileptic effect depending on individual seizure type
  - ▶ Bipolar disorder: AEDs that work through blockade of voltage activated sodium channels—for example, valproate, carbamazepine, and lamotrigine are useful
  - ▶ ADHD: stimulants may precipitate an epileptic fit, but rarely
  - ▶ Acute aggression: benzodiazepines are useful general tranquillisers that are also antiepileptic

study.⁴ The presence of a developmental disorder is now regarded as a key “risk factor” for the development of a psychiatric disorder; whether associated or consequent is still the subject of research. The rate of psychopathology in different developmental disorders is shown in table 1.

Autism and autistic spectrum disorders (ASD)

Autism is now conceived as a dimensional rather than a categorical disorder, with a prevalence rate of 6 per 1000 children from recent studies in the UK and USA. Autism was originally thought to have a basis in parental behaviour—“refrigerator mothers”. The occurrence of epilepsy in a third of children with autism over time was one of the first indications that this disorder had a neurobiological basis to it. Genetic studies in twins and subsequent family studies have confirmed the high heritability of autism and a broader phenotype family developmental pattern in which either communication or socialisation skills were affected. Current research is focused on trying to find genes responsible with high LOD scores currently found on 2Q, 7Q, 16P and 17P. Magnetic resonance spectroscopy and event related potentials (ERPs) and other neuroimaging techniques suggest abnormal functioning in the superior temporal sulcus, the fusiform sulcus (responsible for face encoding), the amygdala (responsible for emotional recognition and arousal memory), and the ventromedial pre-frontal cortex (responsible for social cognition and emotional regulation) occurs in autism. Recent rates of increased diagnosis have particularly been in the high functioning mainstream schoolchildren and this is largely responsible for the current sex ratio of 8:2 male to female. This is also responsible for the fact that many children currently diagnosed as being in the autistic spectrum have an IQ in the normal range. A number of specific chromosome abnormalities, noticeably on chromosome 15, are found in association with autism and importantly autism can occur as a co-morbidity in other chromosome disorders such as Down's syndrome.

Epilepsy is common, occurring in 17% of persons with autism over their lifetime, with a higher rate in those with additional severe learning problems (onset is often in late childhood and adolescence). There is a particular association of autism with tuberous sclerosis and especially when hamartomas are in the temporal region. Early diagnosis of autism by

the age of 2 or 3 years is now being shown to be reliable. Epidemiological studies do not support an association of autism with MMR (measles-mumps-rubella) immunisation. Despite medication having an impact on symptomatic management of ASD, no specific effects have been shown on the core autistic features. The mainstay of treatment remains an educational teaching/learning approach.

Attention deficit hyperactivity disorder (ADHD)

ADHD is a collection of behavioural symptoms in which there is impulsivity, inattention and hyperactivity, fidgetiness, and motor restlessness. Depending on definition, prevalence is 1–5% of the school age population, with the more severe hyperkinetic disorder occurring in approximately 1% of the population. High rates of oppositional defiant disorder, conduct disorder, mood disorder, and specific learning difficulties frequently coexist with ADHD. Like ASD, ADHD is also diagnosed more frequently now. A genetic basis to ADHD emerges from twin studies. Functional imaging confirms differences in the right pre-frontal cortex as well as in the caudate nucleus. This circuit is hypothesised to be involved in normal suppression of impulsive behavioural responses to unwanted events. Castellanos and colleagues have recently demonstrated that children with ADHD have smaller brain volume with approximately a 3% reduction.⁶ Their longitudinal study failed to pick up any negative effect of psychostimulants on brain development. Psychostimulant medications have been shown to be effective in improving the core symptoms of hyperactivity, impulsivity, and inattention in over 90% of subjects if used appropriately.^{7,8} The long term changes on academic performance and reduction in co-morbid behaviours are less clear.

Developmental speech and language disorders

Speech and language disorders are the most common of the developmental delays seen by most paediatricians. Definition and “caseness” of what represents significant delay in speech and language continues to be the subject of research discussion and contributes to the variable prevalence rates of 6–15% in pre-school children. For those with a very severe delay in either receptive or expressive speech there is a strong likelihood of continued difficulties, but even those with milder but definite problems at the age of 4–5 years who appear to catch up by the age of 8 can still be shown to have impairments in language and literacy skills, particularly comprehension of reading at the age of 16. Studies of language delays in 3 year olds have shown that 58% had a behaviour problem compared with the base rate of 14%. Long term outcome studies of severe language impairment when receptive/comprehension skills are involved suggest a significant continuing morbidity and level of social impairment with psychopathology. A failure to have an adequate communication system in a number of developmental disorders—for example, autism, severe cerebral palsy—contributes not only to the child's frustrated behaviour but also to the burden of parental care and the child's vulnerability.

Developmental coordination disorder (DCD)

This disorder is defined on the basis of a failure of acquisition of skills in both gross and fine movements which is not explicable on the basis of impaired general learning. This is a frequently overlooked developmental problem which can have considerable impact on children's lives as they struggle to plan, organise, and execute what is effortless for so many of their peers. Often associated with soft neurological signs and subdivided into difficulties with motor planning, learning

Table 1 Psychiatric disorder in developmental disability

Diagnostic group/cohort	Rate	Type of problem encountered	Reference
General population			
Rural	7%	CD, ED	Rutter <i>et al</i> 1970
Urban	18%	All types	Gillberg 1995
Mixed UK 5–15 years	8%	All types	Emerson 2002
Intellectual disabilities (mental retardation)			
All levels	39%	9.5% ED, 25% CD	Emerson 2002
	40%	All types	Einfeld and Tonge 2000
Mild	12%	Autism spectrum	Nordin and Gillberg 1996
Severe	64%	All types	Gillberg <i>et al</i> 1986
	30%	Autism spectrum	Nordin and Gillberg 1996
Cerebral palsy	24%	All types	Rutter <i>et al</i> 1970
With mental retardation	11%	Autism spectrum	Nordin and Gillberg 1996
Hemiplegia	61%	All types ED 25%, CD 34% ASD 3%	Goodman 1998
Speech language disorders	50%	All types, CD	Cantwell and Baker 1985
Epilepsy	29–58%	All types	Rutter <i>et al</i> 1970
With mental retardation	44%	Autism spectrum	Steffenburg 1996
	12%	ADHD	Steffenburg 1996
Deficits in attention motor control and perception (DAMP)	69%	All types	Gillberg and Rasmussen

ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; ED, emotional disorder.

sequences of movement or executing movements, when all three are involved the term dyspraxia is frequently used. Developmental coordination disorder (DCD) and speech/language disorders show overlap with expressive/speech problems, especially those that have an oro-motor component to the speech problem.

Specific learning difficulties in literacy (and numeracy)

This group of disorders occurs as specific skills deficits in otherwise intellectually normal children. Current imaging techniques support the idea of specific areas of neurological difference within the brain in dyslexia associated with the phonological processing, which is thought to be important in most cases of specific reading difficulty linked to sound symbol correspondence. Reading impairments are also associated with impairments in writing, spelling, speech, higher order language competence, motor skills, and mathematical skill deficit, all in varying degrees.

CO-MORBIDITY

All of the above developmental disorders are more frequently found in children with a range of behaviour and psychiatric disorders compared with those who do not, and vice versa. Taking a symptom approach (where criteria for a full co-morbid diagnosis are not necessarily met), hyperactivity, inattentiveness, labile mood, anxiety, aggression, sleep problems, eating problems, and elimination disorders are all much more common in children with developmental disorders.

- Developmental disorders themselves frequently co-occur, thus supporting a hypothesis of multiple primary neurological deficits rather than single localised lesions. In a study of 7 year olds with ADHD, only 13% of the ADHD group had the pure syndrome, 87% were co-morbid with oppositional defiant disorder (ODD) (53%), reading disorder, writing disorder (40%), tics and Tourette's syndrome

(33%), and Asperger's syndrome (7%). Other studies have shown that 50% of children with ADHD have DCD. In special schools for dyslexia 30–40% have developmental coordination disorder.

- Since many of the developmental disorders have a significant genetic component this presents a problem for genetic studies. Rather than conceptualisation of a single gene having a single phenotypic outcome, the probability is that each gene has several effects and that the strength of the effect varies.

MENTAL RETARDATION

As the addition of significant mental retardation increases the psychiatric co-morbidity, measurement of IQ and learning abilities needs to be part of a comprehensive assessment—for example, in ASD and learning disability.⁹

- Likelihood of ASD rises with falling IQ
- Male: female ratio falls with falling IQ
- ASD diagnosis is less likely to be made in profound mental retardation and presence of physical disability
- 12% ASD found in mild/moderate learning disability
- 30% ASD found in severe learning disability
- The addition of epilepsy increases the likelihood of autism symptoms in learning disability
- Prevalence of autism in learning disability plus active epilepsy is 27% and the prevalence of an autistic-like condition is 11%
- High co-morbidity with self injurious behaviour.

Symptoms of conduct disorder and emotional disorders, ADHD, and ASD are all increased in mental retardation and most notably in severe mental retardation.

NEUROIMAGING AND SPECIFIC PSYCHOPATHOLOGY

Neuroimaging research of psychiatric disorders has increased exponentially in the last decade. The current information

Table 2 Hypothesised brain regions involved in childhood psychopathology

	Frontal	Parieto-occipital	Temporal	Caudate	Putamen	Limbic	Corpus callosum	Cerebellum	Altered laterality
ADHD	Probable	Possible	Possible	Probable	Likely		Likely	Possible	Possible
Autism	Possible	Possible	Probable	Possible	Probable	Probable		Likely	
Tourette's	Probable			Possible	Probable	Possible			Likely
OCD	Probable			Probable				Likely	Likely
Schizophrenia	Possible		Probable			Possible	Likely	Likely	Possible
Mania	Possible								
Depression	Possible					Possible			
Dyslexia	Possible	Probable	Probable			Possible			Possible
Phonological processing			Left perisylvian region – probable						
Executive function	Probable								
Spatial cognition/maths/handwriting		Posterior right hemisphere – possible							

ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder.

Table 3 Drug action sought in managing psychopathology

Symptom	Neurotransmitter action sought	Example of drug
Obsession, compulsions	Increase serotonin	SSRIs, e.g. fluoxetine, sertraline
Hyperactivity, inattention	Increase dopamine and noradrenaline	Stimulants, e.g. methylphenidate
Impulsivity	Increase serotonin	SSRIs
Tics	Decrease dopamine	Atypical antipsychotics, e.g. risperidone
Mood lability, explosive rage	Modulate GABA	Sodium valproate
Low mood	Increase serotonin and noradrenaline	SSRIs

GABA, γ aminobutyric acid; SSRIs, selective serotonin reuptake inhibitors.

available from research indicates that diffuse networks are involved in most neuro-cognitive tasks, which are impaired in many developmental disorders. A summary of the current neuroimaging findings in these disorders is presented in table 2. Abnormal functioning of the pre-frontal cortex is common to a number of developmental disorders. Increasingly, the role of the cerebellum in developmental disorders is being recognised—for example, in coordination of cognitive processes. Right cerebellar lesions give rise to problems with organising language and sequential symbolic functions, sequential auditory memory, and left frontal lobe impairments. Left cerebellar lesions give rise to visuo-sequential deficits, problems with visuo-spatial configuration, and right frontal lobe dysfunction.

A SYMPTOM BASED APPROACH TO MANAGEMENT OF DEVELOPMENTAL PSYCHOPATHOLOGY

Many of the behaviours associated with psychiatric disorder are thought to have their basis in neurotransmitter function and this has led to an approach to treatment based on altering levels of specific neurotransmitters that might be implicated—for example, the obsessive compulsive symptoms of OCD when combined with anxiety are thought to have a serotonergic basis which can logically be altered using serotonin reuptake inhibitors. Table 3 outlines this approach. There are limitations to this simplistic approach that assumes that symptoms have single causes. Despite the theoretical suggestion that self injurious behaviour may be connected to opioid increase, naltrexone has not been very effective. Drugs may cause unwanted as well as wanted effects and may interact. Metabolism in children may be different from adults and altered by developmental disorder. Long term side effects remain unknown in many medications.

FUTURE DIRECTIONS

There will be an increasing need for child psychiatrists and paediatric neurologists to work closer together in order to integrate and offer optimal services for children with

Framework for assessment

- ▶ Developmental history, including pregnancy and birth using semi-structured interviews
- ▶ History of onset/timing/relation to events including medications
- ▶ Communication, speech, and language—including eye gaze and use, non-verbal communicative behaviours of coordinated gestures, facial expression, comprehension, expressive skills, content, pragmatics in conversation and articulation
- ▶ Learning—abilities, attainments, style, and problem solving
- ▶ Risk assessment in those with co-morbid conditions
- ▶ Obtain information and note behavioural observations of attention, activity levels, quality of movements, social behaviour, greeting, responsiveness, insight, and empathy
- ▶ Family history of neuropsychiatric problems
- ▶ Reaction of family and child to stress of illness
- ▶ Neurodevelopmental/neuropsychiatric examination to include mental state (consciousness level, orientation, memory, speech and language, emotional state, mood, thoughts, perception, insight)
- ▶ Physical examination to include height, weight, blood pressure, pulse, head circumference, soft neurological signs, dysmorphic features, and a thorough neurological examination
- ▶ Systematic quantitative symptom evaluation in order to monitor response
- ▶ Regular side effect check at each visit, and re-evaluate the need to continue medication

neurodevelopmental disorders. Training in child and adolescent psychiatry will need to be modified to enhance neurodevelopmental assessment skills, and training in developmental paediatrics may need to enhance the understanding of psychiatric aspects of and environmental impact on these disorders. The holistic “bio-psycho-social” approach will need to become the mainstay of management in both settings. Investigation of the impact of early identification and treatment of developmental disorders needs to occur in order to identify whether it can enhance developmental progression and/or protect children through high risk periods. Dimensional as opposed to categorical approaches in understanding and managing developmental psychopathology will increase in the future. More research will need to focus on associations between symptom dimensions and biological markers such as neuroimaging, neurocognitive deficits, neuroimmunology, molecular genetics, and pharmacogenetics. It is hoped that in the future diagnosis of neurodevelopmental disorders will take into account information regarding symptoms, biological markers, environmental adversity, and medication response to obtain more homogeneous groups which will help in prognostication.

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REFERENCES AND FURTHER READING

- 1 Price BH, Adams RD, Coyle JT. Neurology and psychiatry closing the great divide. *Neurology* 2000;**54**:8–14.
- 2 Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. *Science* 2002;**297**:752.
- 3 Spencer MD, Knight RSG, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. *BMJ* 2002;**324**:1479–82.
- 4 Rutter M, Graham P, Yule W. A neuropsychiatric study in childhood. *Clinics in developmental medicine*, Nos 35/36. London: SIMP, Heinemann Medical Books, 1970.
- 5 Weibe S, Blume W, Girvin J, et al for the Effectiveness of Surgery for Temporal Lobe Epilepsy Group. A randomized controlled trial of surgery for temporal lobe epilepsy. *N Engl J Med* 2001;**345**:311–31.
- 6 Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with ADHD. *JAMA* 2002;**288**:1740–8.
- 7 MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1073–86.
- 8 MTA Cooperative Group. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1088–96.
- 9 Steffenberg S, Gillberg C. Autism and autistic-like conditions in Swedish rural and urban areas: a population study. *Br J Psychiatry* 1986;**149**:1–7.
- 10 Gillberg C. *Clinical child neuropsychology*. Cambridge: Cambridge University Press, 1995.
- 11 Goodman R. Congenital hemiplegia. In: Neville B, Goodman R. *Clinics in Developmental Medicine* No 150. Mac Keith Press. Cambridge University Press, 2000.
- 12 Cantwell DP, Baker L. Association between ADHD and learning disorders. *J Learn Disabil* 1991;**24**:88–95.
- 13 Fonagy P, Target M, Cotrell D, et al. A review of the outcomes of all treatments of psychiatric disorder in childhood MCH 17-33. Final report to Mental Health Executive, 2000.
- 14 Kaplan B, Dewey D, Crawford S, et al. The term comorbidity is of questionable value in reference to developmental disorders: data and theory. *J Learn Disabil* 2001;**34**:555–65.
- 15 Oostrem KJ, Schouten A, Kruitwagen CL, et al for the Dutch Study of Epilepsy in Childhood. Attention deficits are not characteristic of school children with newly diagnosed idiopathic or cryptogenic epilepsy. *Epilepsia* 2002;**43**:301–10.
- 16 Emerson E. The prevalence of psychiatric disorders in children and adolescents with and without intellectual disabilities. *Journal of Mental Deficiency Research* (in press).
- 17 Taylor DC. The components of sickness: diseases, illnesses and predicaments. In: Apley J, Ounsted C, eds. *One child. Clinics in Developmental Medicine* No 80. London: SIMP with Heinemann Medical; Philadelphia: JB Lipincott, 1982:1–13.
- 18 Tonge B. Psychopathology of children with developmental disabilities. In: Bouras N, ed. *Psychiatric and behavioural disorders in developmental disabilities and mental retardation*. Cambridge: Cambridge University Press, 1999.
- 19 Nordin V, Gillberg C. Autism spectrum disorder in children with physical or mental disability or both. Part I: clinical and epidemiological aspects. *Dev Med Child Neurol* 1996;**38**:197–313.
- 20 Gillberg C, Rasmussen P, Carlström G, et al. Perceptual motor and attentional deficits in six year old children: epidemiological aspects. *J Clin Psychol Psychiatry* 1982;**33**:131–44.