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122 Chapter 4 Neuropsychiatry A brief history of neuropsychiatry ' . . . from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations . . . And by the same organ we become mad and delirious, and fears and terrors assail us . . . ' From 'On the Sacred Disease' Hippocrates (c.400 BC) Wilhelm Griesinger (1817–1868) is often referred to as the 'founding father of neuropsychiatry' (perhaps more accurately the first 'biological psych iatrist'). It is to him that the (apocryphal) quotation has been attributed that all mental diseases are just diseases of the brain.1 Griesinger was a phys ician (the concept of psychiatrist did not exist at the time), and there is no doubt that his textbook Pathologie und Therapie der Psychischen Krankheiten [Textbook of Mental Pathology and Therapeutics] (1845) was hugely influen tial. He established the journal Archiv für Psychiatrie und Nervenkrankheiten [Archives of Psychiatry and Nervous Diseases], which, in the hands of Meyer and Wetsphal, became the leading research journal in psychiatry internationally. The philosophical roots of modern neuropsychiatry are to be found in the earlier new materialism of the nineteenth century. Étienne-Jean George2 (1795–1828), a disciple of Pinel and Esquirol, emphasized the organic aeti ology of mental disorder. Antoine Laurent Bayle (1799–1858) challenged the dualist view of the time with a unitary view of general paralysis—that dementia and mental disorder are both features of the same disease. However, it was Griesinger's works that had the greatest influence on many European neuropsychiatrists, including Meyer, Meynert, Liepmann, Pick, Oppenheim, Charcot, Korsakoff, von Monakow, Babinski, Janet, Freud, Jackson, Bleuler, Kraepelin, Bonhoeffer, and Alzheimer. In the UK, the most important psychiatrist at the time Henry Maudsley (1835–1918) had views very close to those of Griesinger.3 It was Meynert's disciple Karl Wernicke (1848–1905)4 who further advanced Griesinger's ideas, proposing: a model to encompass all brain-related diseases

(whether so-called psychiatric or neurological); the development of a pathophysio logical model to mediate between the brain and behaviour; and the 1 Griesinger's ideas were a reaction to gross German materialism. He was keen on emerging physio logical ideas of the time, and it was in this new ambiguous space that he located mental disorders (i.e. not neuroanatomically). His related view that many psychological events occur in non-conscious spaces has led some to consider him a 'pioneer' of psychodynamic psychiatry. 2 Georget introduced the still popular 'technology alibi' that, although all mental disorders are caused by changes in the brain, in some cases, we cannot yet demonstrate this due to a lack of appropriate technology. (Caveat lector: this is not a scientific hypothesis, but rather a hypothetical syllogism based upon a foundational claim that the mind is represented in the brain). 3 In The Physiology and Pathology of Mind (1867), Maudsley states: 'Mental disorders are neither more nor less than nervous diseases in which mental symptoms predominate'. 4 Wernicke is one of the most important psychiatrists of the late nineteenth century, and had he not died young, psychiatry might now be a 'Wernickian world', as his views on classification, mental symptoms, and the relationship between brain and behaviour could have superseded Kraepelin's.

A brief history of neuropsychiatry introduction of the first 'neuropsychological approach' to mental symp toms. Other important figures include Jackson (1834–1911), von Monakow (1853–1930), Goldstein (1878–1965), and Guiraud (1882–1974). In the early 1900s, neuropsychiatry was an emerging discipline in the German- and French-speaking world, and to an extent in the USA. All was to change when the rise of psychodynamic thinking led many psychiatrists to embrace a new 'mentalistic' approach, and a separ ation from neurology began. There was resistance. Notably, Sir Charles Symonds (1890–1978), the doyen of British neurologists, fought to prevent psychiatry's drift away from neurology and neuroscience.5 However, after World War II, the division between neurology and psychiatry widened, symbolized by The Archives of Neurology and Psychiatry (first published in 1919) separating into two journals. In many countries, separate depart ments of neurology and psychiatry were formed, with separate training programmes. However, from the mid-twentieth century onwards, developments in neuropsychopharmacology led to the emergence of what has been called the 'second biological psychiatry'. There was a real explosion of research in neurosciences, a 'remedicalization' of psychiatry, and a decline in the dom inance of psychodynamism. By the 1980s, even the nosology of psychiatry was changing, with the publication of ICD-9 (1978) and DSM-III (1980), when the neuroses were rejected in favour of a biological medical model. With the development of functional imaging techniques, including CT, MRI, and PET/SPECT, and rapid advances in molecular genetics, research of neurologists, psychiatrists, psychologists, and cognitive neuroscientists in creasingly overlapped. In the UK, the British Neuropsychiatry Association (BNPA) was founded in October 1987, chaired by Professor Lishman,6 and all clinical neuroscience professionals were welcome to join. In the USA, the American Neuropsychiatric Association (ANPA) was founded in 1988 and the first joint meeting with the BNPA was in 1991. At the turn of the millennium, there were calls for a rapprochement of neurology and psychiatry.7 The Royal College of Psychiatrists established a Special Interest Group in Neuropsychiatry in 2001, and this led to a Section of Neuropsychiatry in 2008 and a Faculty of Neuropsychiatry in 2014, with emphasis on training, standards, service development, and academic/re search links. It is likely that over the next decade, we will see the disciplines of neurology and psychiatry becoming closer still. Early signs are in pro posals for ICD-11 where 'Dissociative neurological symptom (previously conversion) disorders' may be listed with other 'Diseases of the nervous system'.8 5 Lishman WA (1992) What is neuropsychiatry? J Neurol

Neurosurg Psychiatry 55:983–5. 6 There is no doubt that WA Lishman (1931–) has been a major influence in the field of neuropsych iatry, both as a teacher and trainer of generations of neuropsychiatrists at the Institute of Psychiatry/ Maudsley and through his textbook Organic Psychiatry: The Psychological Consequences of Cerebral Disorder' (1978, 1987, 1997, and multi-author 2012). 7 Martin JB (2002) The integration of neurology, psychiatry, and neuroscience in the 21st century. Am J Psychiatry 159:695–704. 8 Stone J, Hallett M, Carson A, Bergen D, Shakir R (2014) Functional disorders in the Neurology section of ICD-11. A landmark opportunity. Neurology 83:2299–301.

124 Chapter 4 Neuropsychiatry What is neuropsychiatry? 'Psychiatry is a protean discipline and neuropsychiatry is one of its incarnations.' Berrios and Markova (2002)9 To many psychiatrists, neuropsychiatry is synonymous with psychiatry as both are concerned with 'the functional or organic disturbances of the central nervous system that give rise to, contribute to, or are associated with mental and emotional disorders.'10 The history of (neuro)psychiatry (E A brief his tory of neuropsychiatry, p. 122) is populated by figures like Emil Kraepelin (1856–1926) and Alois Alzheimer (1864–1915) who practised psychiatry but hoped to discover the basis of psychiatric diseases through histological and neuropathological research. These days, the term neuropsychiatry can be applied in many ways. In the scientific field, neuropsychiatry may refer broadly to any endeavour by a scientist, educator, clinician, policymaker, or individual who seeks to advance our understanding of the neurological basis of psychiatric disorders, the psychiatric manifestations of neurological dis orders, and the evaluation and care of those with neurologically based be havioural disturbances. When referring specifically to a medical subspecialty, it may mean one or the other of two parallel, but historically distinct, clinical disciplines: behavioural neurology and neuropsychiatry. Behavioural neurology (also known as behavioural neuroscience and brain sciences) is essentially a branch of neurology that links normal and abnormal behaviours to functioning of specific areas or functional networks of the brain. The origins of this approach arise in research and early localiza tion theories of Franz Gall (1758 –1828),11 followed in the mid-nineteenth century by neuroanatomical lesion studies in aphasias by Paul Broca (1824– 1880) and Carl Wernicke (1848–1905). Research in this area peaked in the late nineteenth and early twentieth centuries, with work extending into the clinical descriptions of dementias by Alzheimer and Arnold Pick (1851– 1924). It was not until 1972 that the 'father of behavioural neurology' Norman Geschwind (1926–1984) coined the name at a meeting of the American Academy of Neurology, and in 1982, the Behavioural Neurology Society was founded (now the Society for Behaviour and Cognitive Neurology).12 In the USA, Geschwind and colleagues were responsible for a renaissance of behavioural neuroscience, not only because of their work on disconnection syndromes, aphasia, and behavioural syndromes of limbic epilepsy (the eponymous Geschwind syndrome), but also the legacy of training generations of behavioural neurologists (including such luminaries 9 Berrios GE, Markova IS (2002) The concept of neuropsychiatry: a historical overview. J Psychosom Res 53:629–38. 10 'Neuropsychiatry', as defined in Campbell's Psychiatric Dictionary, 9th edn (2009), Oxford University Press. 11 Claimed as the founder of phrenology, Gall's ideas that a person's personality could be deter mined from the shape of their skull, although controversial and repeatedly disproven, did promote the idea of functional localization within the brain—an idea originally put forward by French naturalist and philosopher Charles Bonnet (1720–1793) over 60 years earlier. 12 Society for Behavioral and Cognitive Neurology. M http://the-sbcn.org/ [accessed 30 May 2018].

What is neuropsychiatry? as Kenneth Heilman13 and Antonio Damasio14). With the advent of in vivo neuroimaging from the 1980s onwards, the cognitive neurosciences have capitalized on having new tools to explore lesion, structural, and functional correlations with behavioural dysfunction in living people. The interwoven history of neuropsychiatry is outlined briefly on E pp. 122–123. It is worth noting that historically neuropsychiatry is a dis tinct discipline from biological psychiatry, which emerged along with bio logical treatments of psychiatric disorders in the late 1930s to early 1950s. The term biological psychiatry was coined in 1946 after a meeting on 'the biological basis of behaviour', organized by Johannes M Nielsen (1890–1969), Professor of Neurology at the University of Southern California, and George N Thompson (1909–), Chief Psychiatrist at the Los Angeles General Hospital. From this meeting arose the Society of Biological Psychiatry, the membership of which comprised many of the elite of the American neuroscience estab lishment. Neilsen and Thompson published the first textbook of biological psychiatry The Engrammes of Psychiatry in 1947. Biological psychiatry devel oped to encompass the expanding fields of brain biochemistry, neuroendo crinology, cellular and molecular medicine, and genetics, as they applied to mental disorders. Due to the cross-fertilization of the neurosciences over the last 70 years, it has become increasingly difficult to distinguish biological psychiatry from other clinical and academic neurosciences. Indeed the term is sometimes used in a pejorative way to suggest overly reductive thinking. The same allegations have been levelled at neuropsychiatry. Developments in our understanding of the interaction between genes and the environment, together with the rise of biological psychology, neuropsychology, and more recently cognitive neuropsychiatry,15 also mean that if we are ever to have a more complete understanding of how the brain functions in health and dis ease, then further integration is vital. In clinical practice, ignoring psychological and social aspects is at best inconsiderate and at worst negligent. The current practice of both neuropsychiatry and behavioural neurology is focused on better understanding the links between neuroscience and behaviour, with an emphasis on the care of individuals with neurologically based behavioural disturbances. Whether trained primarily in psychiatry, neurology, or both, practitioners require specific experience in the evalu ation, differential diagnosis, prognosis, pharmacological treatment, psy chosocial management, and neurorehabilitation of persons with complex neuropsychiatric and neurobehavioural conditions. 13 Professor of Neurology and Health Psychology, Director of University of Florida Memory Disorders Clinic, Center for Neuropsychological Studies, and the Behavioral Neurology- Neuropsychiatry Fellowship Program. M http://neurology.ufl.edu/divisions-2/memory-and- cognitive-disorders/memory-and-cognitive-faculty/kenneth-heilman-m-d/ [accessed 30 May 2018]. 14 Professor of Neuroscience and Director of the Brain and Creativity Institute at the University of Southern California and an Adjunct Professor at the Salk Institute. He has written a number of books, including Descartes' Error: Emotion, Reason and the Human Brain (1994), which is regarded as one of the most influential popular science books of the twentieth century. M https://dornsife.usc.edu/cf/ faculty-and-staff/faculty.cfm?pid=1008328 [accessed 30 May 2018]. 15 First proposed in 1993 by Anthony S David, now Professor of Cognitive Neuropsychiatry at King's College London (David AS (1993) Cognitive neuropsychiatry? Psychol Med 23:1–5) as 'a sys tematic and theoretically driven approach to explain clinical psychopathologies in terms of deficits to normal cognitive mechanisms'. (For an overview, see: Halligan PW, David AS (2001) Cognitive neuropsychiatry: towards a scientific psychopathology. Nature Rev Neurosci 2:209–15). M http://psych.cf.ac.uk/home2/halligan/halligan_david%202001.pdf [accessed 30 May 2018].)

126 Chapter 4 Neuropsychiatry Psychiatric presentations of organic illness All psychiatric illnesses are, by their nature, organic, i.e. they involve abnor malities of normal brain structure or function. The term ‘organic illness’ in modern psychiatric classification, however, refers to those conditions with demonstrable aetiology in central nervous system (CNS) pathology. Organic disorders related to substance misuse are dealt with in E Chapter 14. This chapter deals with those disorders that are caused by degenerative, trau matic, inflammatory, infective, autoimmune, and metabolic conditions. Organic illnesses are included in the lists of differential diagnoses for most psychiatric syndromes. For this reason, most patients presenting with psy chiatric symptomatology merit a thorough physical examination (including neurological examination and, in some cases, special investigations) before a diagnosis of primary psychiatric illness is made. While psychiatrists do not have to be expert neurologists, a sound knowledge of those conditions that bridge neurology and psychiatry is essential. Listed here are common organic causes of psychiatric syndromes (de lirium, dementia, and amnestic disorders are discussed later). Organic causes of psychosis • Neurological [encephalitis, e.g. herpes simplex virus (HSV); epilepsy; dementia; brain injury; brain tumour; HIV; neurosyphilis; intracerebral abscess; stroke). • Endocrine (hyper-/hypothyroidism; Cushing’s; hyperparathyroidism; Addison’s disease). • Metabolic (uraemia; sodium imbalance; porphyria). • Autoimmune (systemic lupus erythematosus (SLE) (‘lupus psychosis’); autoimmune encephalitis). • Medications [steroids; levodopa (L-dopa); isoniazid; anticholinergics; antihypertensives; anticonvulsants; methylphenidate]. • Drugs of abuse [novel psychoactive substances (NPS); amphetamines; cocaine; LSD; cannabis; phencyclidine (PCP); opioids]. • Toxins. Organic causes of depression • Neurological [stroke; epilepsy; Parkinson’s disease; brain tumour; dementia; multiple sclerosis (MS); Huntington’s disease; brain injury]. Cerebellar disease is associated with a cognitive-affective syndrome with depressed mood or labile affect. • Infectious [HIV; Epstein–Barr virus (EBV)/infectious mononucleosis; brucellosis). • Endocrine and metabolic [hypothyroidism; Cushing’s; Addison’s disease; parathyroid disease; vitamin deficiency (B12 and folate); porphyria]. • Cardiac disease [myocardial infarction (MI); congestive cardiac failure (CCF)]. • SLE. • Rheumatoid arthritis. • Cancer.

Psychiatric presentations of organic illness • Medications [analgesics; antihypertensives; levodopa; anticonvulsants; antibiotics; steroids; combined oral contraceptive (OCP); cytotoxics; cimetidine; salbutamol). • Drugs of abuse [alcohol; benzodiazepines (BDZs); cannabis; cocaine; opioids]. • Toxins. Organic causes of mania • Neurological (stroke; epilepsy; brain tumour; brain injury; MS). • Endocrine (hyperthyroidism). • Medications (steroids; antidepressants; mefloquine; interferon, isoniazid; cytotoxics). • Drugs of abuse (cannabis; cocaine; amphetamines). • Toxins. Organic causes of anxiety • Neurological (TLE; dementia; brain injury; stroke; brain tumour; MS; Parkinson’s disease]. • Pulmonary [chronic obstructive airways disease (COAD)]. • Cardiac (arrhythmias; CCF; angina; mitral valve prolapse). • Endocrine (hyperthyroidism; phaeochromocytoma). • Medications (antidepressants; antihypertensives; flumazenil; yohimbine; fenfluramine). • Drugs of abuse [alcohol (withdrawal); BDZs (withdrawal); caffeine; cannabis; cocaine; LSD; MDMA (ecstasy); amphetamines, NPS].

128 Chapter 4 Neuropsychiatry Neurological examination in psychiatry A neurological examination should ideally be performed in all patients pre senting with psychiatric symptoms—urgently where there is suspicion of an ‘organic’ disorder. With practice, the feeling of ‘normal’ (tone, reflexes, optic discs, tandem gait) becomes more firmly established and it becomes possible to pick up minor abnormalities which may be diagnostically helpful. Examination routine • General

observation—of the patient walking into the examination room (or lying in bed) gives an impression of the conscious level, demeanour, mood, gait, and the presence of movement disorders (E Movement disorders in psychiatry, p. 132). • Gait Ask the patient to walk to the end of the room and turn round. • Tandem gait—ask the patient to walk heel-to-toe across the room. • Romberg's sign—with the examiner's hands on either side and ready to support the patient, should they lose balance, ask the patient to stand with their feet together and eyes closed. The test is positive, suggesting impaired proprioception, if the patient loses balance. • Cranial nerves—with the patient seated on a chair or an examination couch, cranial nerves I–XII may be quickly assessed using this routine: • I: not routinely clinically tested, but ask about the sense of smell— often lost (anosmia) after brain injury and in Parkinson's disease. • II: test visual acuity using the Snellen chart; visual fields with a 'wiggling finger' or a red pin; and optic discs via fundoscopy. Test pupillary reactions to light and accommodation. • III, IV, and VI: test eye movements and observe any ptosis. • V: test facial sensation in all three branches of the trigeminal nerve, using cotton wool. Test jaw clench. • VII: test facial movements, asking the patient to copy the examiner— raise the eyebrows, close the eyes, and bare the teeth. • VIII: test hearing by whispering in each ear. • IX: gag reflex—not routinely tested. • X: ask the patient to swallow and cough. • XI: ask the patient to elevate their shoulders and to turn their head left and right against resistance. • XII: ask the patient to stick out their tongue. • Muscle tone—with the patient seated or reclined on the examination couch, test muscle tone in upper and lower limbs. If i tone is suspected, test for ankle clonus by rapidly dorsiflexing the foot at the ankle. • Muscle power—test power in upper and lower limbs. • Reflexes—test deep tendon reflexes at the knees, ankles, and elbows. The plantar reflex (Babinski) rewards the inconvenience of removing shoes with the reassurance that there is no significant upper motor neuron lesion. • Sensation—finally, an attempt at sensory examination may be made using cotton wool (light touch), a tuning fork (temperature and vibration), and proprietary sensory-testing sharps (e.g. 'Neurotip™'); note that sensory testing relies entirely on the patient's subjective report.

Neurological examination in psychiatry Examination findings in neuropsychiatric conditions Some or all of the following signs may be observed or elicited on examin ation, aiding diagnosis. • Vascular neurocognitive disorder (vascular dementia)—pyramidal weakness with i tone and brisk reflexes, dysphasia, hurried shuffling gait (marche à petit pas). • Parkinson's disease—shuffling gait with stooped posture, bradykinesia, asymmetrical pill-rolling tremor, cogwheel rigidity, dysdiadochokinesia, positive glabellar tap test. • Drug-induced Parkinsonism—similar to Parkinson's disease, but posture less stooped and rigidity and tremor are symmetrical. • Functional neurological disorders—Hoover's sign, intermittent 'give way' weakness, tight-roping (excessive, successfully corrected overbalancing) on tandem gait, non-anatomical sensory loss, tubular visual field defect, tremor 'entrains' to rhythm of repeated voluntary movements in another limb. • Raised intracranial pressure—papilloedema, drowsiness. There may be signs of a localizing lesion (e.g. hemiparesis or aphasia due to tumour). Idiopathic intracranial hypertension is associated with papilloedema and most common in obese young women. • Normal pressure hydrocephalus (NPH)—hypokinetic gait—the patient looks 'glued to the floor'. Ataxia. • Advanced dementia—long tract signs, including brisk reflexes and upgoing plantars, may be present. Primitive reflexes are less specific. • Amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)—muscle wasting, fasciculation, dysarthria. • Progressive supranuclear palsy—characteristic loss of downgaze, followed by loss of upgaze. Unsteady gait, dysarthria. • Creutzfeldt–Jakob disease (CJD)—ataxia, myoclonus, visual impairment (blurred vision, visual agnosia, or cortical blindness). • Wilson's

disease—Kayser–Fleischer rings, ataxia, masked facial appearance, dysarthria, late dystonia, rigidity, spasticity, and flexion contractures. • Subacute combined degeneration of the cord—(caused by B12 deficiency and associated with a dementia syndrome) Spasticity in the legs with extensor plantars, but hyporeflexia at the knees and ankles. Peripheral sensory loss (especially to pain and temperature) and optic atrophy (pale discs). • Neurosyphilis—ataxia, signs of stroke, reduced visual acuity, optic atrophy, Argyll Robertson pupils (small; accommodate but do not react), hearing loss, hypotonia and hyporeflexia, loss of proprioception and vibration sense, positive Romberg's test.

130 Chapter 4 Neuropsychiatry Neurological investigations in psychiatry Basic observations and blood tests to exclude reversible causes or comorbid physical illness should be routinely performed in all new presentations of psychiatric illness. Standard blood tests in psychiatric practice • FBC, U&Es, LFTs [including gamma glutamyl transferase (GGT) which is sensitive to alcohol excess], inflammatory marker [C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)], thyroid function, bone profile (calcium, phosphate). • B12 and folate. • Tests for relevant infections: HIV (+ viral hepatitis) where risk factors; HIV and syphilis in subacute dementia. • Blood or urine toxicology. In certain circumstances, more invasive and/or expensive investigations may be useful, as follows. Additional blood tests • Autoimmune encephalitis antibodies —aypical psychosis (e.g. with alteration of consciousness or cognition, seizures, or movement disorder). • Genetic tests for specific mutations—consider where history of early- onset and strong family history of dementia, e.g. dementia of the Alzheimer type (DAT) (E Alzheimer's disease 1, p. 156), fronto- temporal disease (FTD) (E Fronto-temporal dementia, p. 160). Note ethical issues in testing for Huntington's disease, which has implications for other family members (E Huntington's disease, p. 166). Imaging • CT brain—is usually performed in the investigation of cognitive impairment, in order to exclude tumour/space-occupying lesion (SOL) or NPH and to assess the extent of cerebrovascular disease and global and focal areas of atrophy. • MRI brain—may be suggested to allow abnormalities on CT to be assessed in higher resolution or where the CT scan appears normal, but abnormalities are suspected. Changes after brain injury, in encephalitis, and after stroke may be evident on MRI, but not CT. Pacemakers and other metal implants are contraindications to MRI. • PET/SPECT/dopamine active transporter (DAT)—radioisotope scans can be used to assess function. SPECT is helpful in discriminating DAT from FTD, and DAT can help with early diagnosis of Parkinson's disease and Lewy body dementia.

Neurological investigations in psychiatry Electroencephalography16 • Interictal EEG—in general, has a limited role in the differential diagnosis of epilepsy. A normal EEG does not exclude epilepsy, and epileptiform discharges are found in 1% of the general population and between 10% and 30% of people with other cerebral pathology or on psychotropic medication. In conditions other than epilepsy, the EEG is often non-specific—showing similar patterns in most types of encephalopathy. However, there are notable exceptions where the EEG is distinctive: non-convulsive status epilepticus, CJD, and subacute sclerosing panencephalitis (SSPE). EEG can be useful in distinguishing functional/psychogenic coma from organic causes of unconsciousness. • Video EEG/video telemetry—can aid the diagnosis of epilepsy and dissociative (non-epileptic) seizures by recording a typical event, but only if an event is captured during recording. Cerebrospinal fluid sampling (lumbar puncture) • LP and analysis of cerebrospinal fluid (CSF) for protein, blood, and cytology should be considered where encephalitis (infective or autoimmune) is suspected. • Oligoclonal bands in CSF which are not matched in the plasma (unpaired oligoclonal bands)

suggest CNS inflammation. • Test for CSF 14-3-3 protein in suspected CJD. 16 Smith SJM (2005) EEG in neurological conditions other than epilepsy: when does it help, what does it add? J Neurol Neurosurg Psychiatry 76(Suppl 2):ii8–12.

132 Chapter 4 Neuropsychiatry Movement disorders in psychiatry Movement disorders occur in three contexts within psych iatry: neurodegenerative disorders with psychiatric symptoms (e.g. Parkinson's disease), psychiatric disorders with abnormal movements (stereotypies, tics), and medication-induced movement disorders (e.g. EPSEs). Pathophysiology Movement disorders commonly involve a disequilibrium of neurotransmit ters, such as dopamine (DA), acetylcholine (ACh), and gamma-aminobutyric acid (GABA), within the circuits of the basal ganglia. Levels of DA and ACh tend to be inversely related. For example, in Parkinsonism, there is dDA with iACh; conversely, chorea is characterized by iDA and dACh. Parkinsonism A syndrome characterized by four core symptoms: slow, 'pill-rolling' tremor (4Hz); rigidity; bradykinesia; and postural abnormalities. Aetiology • Degenerative diseases—idiopathic Parkinson's disease (85% cases) and Lewy body dementia; progressive supranuclear palsy (PSNP); multisystem atrophy (MSA); corticobasal degeneration (CBD). • Medication—antipsychotics; metoclopramide; domperidone. • Toxins—cobalt; manganese; magnesium; organophosphates. • Infections—encephalitis lethargica (post-influenza); CJD. • Miscellaneous—cerebrovascular disease involving the basal ganglia; trauma of the basal ganglia; NPH; neoplasia of the basal ganglia; dementia pugilistica (punch-drunk syndrome). Tic disorders Tics are spontaneous, repetitive, rhythmic movements that can be motor or vocal and usually involve iDA in the basal ganglia. They are semi-voluntary and can only be resisted for a short time with difficulty. Tics are classified as primary or secondary and occur in: • Tourette's syndrome—multiple motor, and at least one vocal, tics many times per day for >1yr (E Tic disorders, p. 676). • Chronic tic disorder—motor or vocal tics, but not both. • Provisional tic disorder—childhood tics present for <1yr. • Infection—CJD; Sydenham's chorea; encephalitis. • Drugs—levodopa; methylphenidate; cocaine; amphetamines. • Other—carbon monoxide (CO) poisoning; stroke/trauma (rare). Tremor • Exaggerated physiological tremor—(8–12Hz); occurs at rest and with action; causes: stress, anxiety, caffeine, medications. • Essential tremor—(6–12Hz); at rest, with action and postural; most noticeable symmetrically in upper limbs. • Extra-pyramidal—(4Hz); resting tremor; e.g. Parkinsonism. • Cerebellar, midbrain, or red nucleus—(4–6Hz); intention tremor; causes: trauma, vascular, MS, tumour.

Movement disorders in psychiatry Catatonia (E The catatonic patient, p. 1054) • A motor syndrome with several causes, diagnosed (DSM-5) by the presence of three or more of the following: • Stupor (no psychomotor activity). • Catalepsy (passive induction of a posture held against gravity). • 'Waxy flexibility'. • Mutism. • Negativism (opposition/no response to instructions or stimuli). • Posturing (active maintenance of postures against gravity). • Mannerism. • Stereotypy. • Agitation (motor excitement not influenced by external stimuli). • Echolalia and echopraxia. • Treatment—BDZs, ECT. Chorea Brief, irregular, 'dance'-like, unpredictable movements, which, in mild cases, may appear voluntary. There are many causes, including preg nancy, Sydenham's chorea, drugs (antipsychotics, levodopa, OCP), and Huntington's disease. Treatment—antipsychotics, BDZs, or tetrabenazine have been tried. Hemiballismus A rare and dramatic movement disorder. An extreme version of chorea in which a structural lesion or metabolic damage to the subthalamic nu cleus causes involuntary flailing, ballistic movements of the limbs. Causes— include stroke and non-ketotic hyperglycaemia. Treatment—antipsychotics or tetrabenazine may help. Alien hand syndrome A complex movement disorder associated with a

sense of loss of limb ownership. The patient's hand performs complex, meaningful move ments without being guided by the intention of the patient, who is unable to stop the hand from grasping objects. It occurs in 60% of patients with corticobasal degeneration17 and has also been described after stroke. Encephalitis lethargica Roughly 20yrs after the great influenza epidemic of the 1920s, large numbers of patients who had suffered from influenza encephalitis during the epidemic developed this disorder (also called post-encephalitic Parkinsonism), now thought to be an autoimmune condition. Clinical findings—Parkinsonism; oculogyric crises; pupillary abnormalities; psychosis. The disorder was the subject of the book (and film) by Oliver Sacks, entitled Awakenings. 17 Belfor N, Amici S, Boxer AL, et al. (2006) Clinical and neuropsychological features of corticobasal degeneration. Mech Ageing Dev 127:203–7.

134 Chapter 4 Neuropsychiatry Functional neurological symptoms Epidemiology Functional neurological symptoms (also historically called hysterical, con version, psychogenic, or medically unexplained) account, in whole or part, for up to 30% of presentations to neurology outpatient clinics.18 Patients experience similar levels of disability to those with conditions such as MS, but greater levels of psychiatric comorbidity and emotional distress; up to 70% have depression or anxiety disorders. Rates of misdiagnosis are low19 (see also E Medically unexplained symptoms 1: introduction, p. 858; E Medically unexplained symptoms 2: clinical presentations, p. 860; E Medically unexplained symptoms 3: management principles, p. 862). Clinical features Symptoms often have a sudden onset, which may or may not follow a recent traumatic event, injury, illness (migraine is a common trigger), medical inter vention, or anaesthetic. Symptoms may closely mimic those of neurological disease: weakness, sensory loss, dysphonia or dysarthria, muscle jerks, or seizures. Diagnosis requires positive clinical features of functional disorder (see Box 4.1). Aetiology is unclear; current research suggests that abnormal attentional focus may generate symptoms, and functional MRI (fMRI) studies show abnormal activation of the prefrontal cortex during attempted move ment; dissociative seizures may relate to panic (although most patients do not experience typical anxiety symptoms). A history of prior trauma is no longer required for diagnosis (DSM-5); recent reviews suggest many, but importantly not all, patients have a history of stressful life events. 18 Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M (2000) Do medically unex plained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. J Neurol Neurosurg Psychiatry 68:207–10. 19 Stone J, Sharpe M, Rothwell PM, Warlow CP (2003) The 12 year prognosis of unilateral func tional weakness and sensory disturbance. J Neurol Neurosurg Psychiatry 74:591–6. Box 4.1 Positive clinical features of functional neurological disorder • Leg weakness and gait disturbance—Hoover's sign, marked inconsistency on examination (e.g. able to walk but unable to move the leg during examination). • Tremor—'entrains' to a rhythm tapped with the opposite hand or with the foot; disappears when distracted. • Sensory symptoms—sharply demarcated and non-anatomical distribution of sensory loss, e.g. with a sharp midline boundary. Tubular visual field defect. • Dissociative seizures—long duration, fluctuating course, asynchronous movements, side-to-side head and body movements, eyes closed, and ictal crying. • Cognitive symptoms—detailed recall of 'forgetting' events; gross inconsistency in test performance vs observed or reported level of function; attending clinic alone.

Functional neurological symptoms Prognostic factors Symptoms with a short history and acute onset often get better within days or weeks; however, commonly, symptoms run a chronic course, with high levels of disability and distress ongoing after many years. Perpetuating fac tors may include: fear of neurological disease, avoidance of movement and normal activity, secondary

anxiety or depression, and social adversity. As with most psychiatric and neurological conditions, litigation is the strongest predictor of poor outcome. Investigations Even in the presence of positive clinical evidence of a functional disorder, it is generally sensible to perform relevant investigations—CT head, CT spine, neurophysiology—to be sure no organic pathology has been missed and to reassure the patient that their concerns have been taken seriously. Where it is not possible to witness or obtain a good witness account of dissociative seizures, video EEG can be extremely helpful. Management • Explanation: where the diagnosis is clear, it can and should be confidently explained that this is a positive diagnosis, and not one of exclusion, and that the condition is familiar, common in neurology clinics, and not a 'medical mystery'. • The condition may be described as a disturbance of function, but not structure; some use the basic analogy of a 'software', rather than 'hardware', problem; other patients may be able to engage with an explanation of abnormal attentional focus disturbing processes which are usually automatic. • If present, positive clinical signs, such as the Hoover's sign or entrainment of tremor, can be positively used to demonstrate to the patient the unhelpful role of attention and therefore potential for recovery.20 • For patients who do not improve after a clear explanation of diagnosis, physiotherapy (ideally from a therapist with interest or experience in functional disorders),21 or CBT may be effective. Treat comorbid depression or anxiety. • Follow-up for those with widespread symptoms may help to prevent iatrogenic harm from over-investigation or from treatments that are likely to be unhelpful. BDZs and opiates, in particular, can worsen symptoms of dissociation and fatigue. 20 Stone J, Edwards M (2012) Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 79:282–4. 21 Nielsen G, Stone J, Matthews A, et al. (2015) Physiotherapy for functional motor disorders: a consensus recommendation. J Neurol Neurosurg Psychiatry 86:1113–19.

136 Chapter 4 Neuropsychiatry Neurodevelopmental disorders in adulthood As the rates of diagnosis of neurodevelopmental disorders in children have i in recent years, there is increasing recognition of the lifelong impact of neurodevelopmental disorders (E Attention-deficit/hyperactivity dis order, pp. 668-672). Individuals, often without a previous diagnosis, may present complaining of difficulties associated with core symptoms of these disorders or due to associated psychopathology and social difficulties. Parents may recognize their own symptoms and seek diagnosis following the diagnosis in a child. Attention-deficit/hyperactivity disorder Epidemiology The estimated prevalence of ADHD in adults in the USA is 4.4%, and in the UK 2.3%. ♂:♀ 2:1. Some symptoms of childhood ADHD persist in adult hood in 50–65%, with the full syndrome persisting in 15%. Clinical features Social problems as a result of inattentive and impulsive behaviours include: • Difficulty maintaining relationships and employment. • Poor engagement with medical care. • Criminal behaviours. ADHD is common in prisons and young offender institutions. • Substance misuse and addiction, particularly with stimulants, reflecting a combination of social disadvantage and self-medication. It may be difficult to disentangle symptoms of ADHD from symptoms of intoxication, withdrawal, or complications such as drug-induced psychosis. Diagnosis Symptoms of inattention and/or hyperactivity-impulsivity: • Impaired function. • Present in different settings (e.g. home and work). • Present from childhood, evidenced by collateral history from parent ± school reports. • Must not be explained by another mental disorder, although the presence of secondary mood, anxiety, or substance misuse disorders may make this difficult to establish. Treatment (See NICE guidelines, 2008.)22 • Atomoxetine, methylphenidate, or dexamfetamine. • Full medical examination and history, including assessment of cardiac risk factors prior to treatment. 22 Kendall T, Taylor E, Perez A, Taylor C (2008)

Guidelines: diagnosis and management of attention- deficit/hyperactivity disorder in children, young people, and adults: summary of NICE guidance. BMJ 337:751–3.

Neurodevelopmental disorders in adulthood • Atomoxetine may cause agitation, suicidality, and idiosyncratic liver reactions but is safest if there is a risk of diversion or misuse and is less likely to cause psychosis. • Monitor weight (risk of weight loss), blood pressure (BP), and pulse on all stimulants. • Offer CBT to those unable or unwilling to take medication. Autism spectrum disorders (See also E Pervasive developmental disorders, p. 820; E Autism spec trum disorders, p. 674.) Clinical features The core features are: • Deficits in reciprocal social interaction. • Restricted and repetitive behaviours and interests. • Communication impairments. In adolescence and adulthood, communication skills often improve, but so cial deficits can be more problematic, perhaps reflecting the more complex demands of adult relationships.23 Adults without a prior diagnosis of ASD may present with secondary anxiety or mood disorders. Diagnosis Requires collateral history or supporting information (e.g. school reports) evidencing that deficits have been present since early childhood. The Autism Spectrum Quotient (AQ) questionnaire can be helpful as a screening tool. Treatment Supportive, including direction to available support agencies. Secondary mood disorders or anxiety disorders should be treated as for those without mood or anxiety disorders, including with psychological treatment where available. 23 Seltzer MM, Krauss MW, Shattuck PT, Orsmond G, Swe A, Lord C (2003) The symptoms of autism spectrum disorders in adolescence and adulthood. J Autism Dev Disord 33:565–81.

138 Chapter 4 Neuropsychiatry Psychiatric aspects of epilepsy 1 An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disease of the brain, characterized by an enduring predispos ition to epileptic seizures. The prevalence of active epilepsy in the UK is estimated to be 5–10/1000. The clinical manifestation of a seizure depends on: the cause of epilepsy, the location of the epileptic focus, and the spread of the epileptic discharge within the brain. Seizures are broadly classified as generalized when arising in diffuse bilateral networks or focal when arising from specific areas of the brain. Epilepsy carries significant disease burden and is associated with an i risk of psychiatric disorders, the most common being depression and anxiety which affect up to 30% of people with epilepsy. Psychological consequences of diagnosis People with epilepsy have a significantly poorer health-related quality of life, when compared with the general population, associated with frequent seiz ures, medication side effects, social disability, and stigma, as well as cognitive and mood problems. Neuropsychiatric effects of treatment All antiepileptic drugs can induce psychiatric symptoms in people with epi lepsy. Mood disorders are the most prevalent, followed by behavioural disturbances and, rarely, psychosis. Patients with a previous psychiatric his tory are at higher risk of developing these side effects. Specifically, pheno barbital, vigabatrin, tiagabine, topiramate, levetiracetam and zonisamide have been reported to trigger symptoms of depression, and vigabatrin, tiagabine, topiramate, and levetiracetam have been associated with psych osis. Aggressive behaviour and irritability have also been reported as a side effect of some antiepileptic drugs, particularly levetiracetam, perampanel, and topiramate. Cognitive problems Cognitive problems are common with multifactorial aetiology, depending on the underlying epilepsy-causing pathology, the frequency and localization of the seizures, the effects of medication, and psychiatric comorbidity. Early onset of seizures, long duration of epilepsy, and high frequency of seizures are associated with poorer cognitive outcome. Clinically, the most common presentation is of memory problems—in general, the result of sedation and slower processing speed secondary to medication.

However, in TLE, there is a primary problem of encoding and consolidating information due to brain pathology. Psychiatric disorders directly attributed to epilepsy— independent of seizures Interictal depression Depression is the most common psychiatric comorbidity in people with epilepsy. Prevalence ranges from 10% in people with well-controlled epi lepsy to 50% for those with refractory epilepsy and symptomatic focal

Psychiatric aspects of epilepsy 1 epilepsy (TLE). There is a bi-directional relationship between depression and epilepsy—people with a history of depression have a 7-times risk of developing epilepsy, suggesting a possible common pathogenic mechanism. Diagnosis—depression in people with epilepsy is often under-recognized; atypical depressive symptoms are sometimes attributed to 'interictal dys phoric disorder', and typical symptoms of depression, including fatigue, weight changes, sleep difficulties, and poor concentration, overlap with common side effects of antiepileptic drugs and/or the consequences of recurrent seizures. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)24 is a self-rated six-item questionnaire which has been validated to screen for depression in patients with epilepsy. Suicide rates in people with epilepsy are three times that of the general population, and suicide is the cause of up to 5% of all epilepsy deaths. Newly diagnosed pa tients are at higher risk of suicide. Treatment—there is some evidence that CBT is helpful. Antidepressants, usually SSRIs (E Prescribing for patients with epilepsy, p. 1038), may also be effective. Interical anxiety The prevalence of anxiety in people with epilepsy is higher than in the gen eral population, with a significantly elevated risk of social phobias, general ized anxiety disorder (GAD), and agoraphobia. Anxiety is more common in people with focal epilepsy. Interictal psychosis The prevalence of psychosis among people with epilepsy is between 7% and 10%—6–10 times that of the general population. Risk factors include family history of psychosis, earlier age at onset of epilepsy, and low intel lectual ability. A schizophrenia-like syndrome, characterized by an absence of negative symptoms and little deterioration of personality, has been de scribed. More recent studies have found no differences in psychotic symp toms between patients with schizophrenia with or those without epilepsy, although there is evidence that people with epilepsy may have a less severe course and a better response to antipsychotics. Treatment—antipsychotic medication, usually haloperidol or sulpiride (E Prescribing for patients with epilepsy, p. 1038). There is little evidence for superiority of any particular medication, and choice represents a balance between effective treatment of psychosis and the risk of lowering the seizure threshold. In general, the chosen antipsychotic should be titrated slowly to the lowest effective dose. Most antipsychotics can cause non-specific changes on the EEG in patients with or without epilepsy. Clozapine can produce epileptiform discharges on the EEG, but this does not predict the occurrence of seizures. Forced normalization or alternating psychosis A relatively rare situation in which the patient's presentation alternates be tween periods of frequent seizures with a normal mental state and periods of improved seizure control and normalization of the EEG, but with the emergence of psychotic symptoms. This phenomenon has been observed following the introduction of anticonvulsants. 24 Gilliam FG, Barry JJ, Hermann BP, et al. (2006) Rapid detection of major depression in epilepsy: a multicentre study. Lancet Neurol 5:399–405.

140 Chapter 4 Neuropsychiatry Psychiatric aspects of epilepsy 2 Psychiatric disorders directly attributed to epilepsy— dependent on seizures Pre-ictal symptoms People with epilepsy may experience mood changes during the days and hours leading up to the seizure. These include symptoms of irritability, emo tional lability, depression, anxiety, or (rarely) aggression, all of which subside after the seizure. Ictal symptoms Changes in mental state as a direct expression of the

seizure activity begin abruptly, are short-lasting and stereotyped, and are often accompanied by other ictal symptoms like motor automatisms. Ictal fear and anxiety are a common experience, particularly in patients with TLE. Psychotic-like symp toms include brief experiences of visual, auditory, or gustatory hallucin ations, usually with preserved insight. In non-convulsive status epilepticus, these psychotic-like symptoms can persist and can be distinguished from a primary psychiatric disorder by the presence of confusion and other ictal features. Ictal aggression is very rare. Post-ictal symptoms Post-ictal confusion Characterized by an altered state of consciousness following a seizure, resulting in agitated and confused behaviour, lasting between minutes to an hour. Aggressive behaviour may be a feature; however, it is often non- directed, unintentional, and brief. Post–ictal depression The most commonly reported mood disturbance following a seizure. Depressive symptoms range from mild to moderate and are often accom panied by symptoms of anxiety. Some patients, particularly if they have a history of mental illness, will experience suicidal ideation. Post-ictal depres sion symptoms often resolve within 24hrs, although they can at times last for several days after the seizure. Post-ictal psychosis This affects 7–10% of people with epilepsy. Risk factors include a >10yr history of seizures, bilateral ictal foci, structural brain abnormalities, and a previous history of psychiatric disorders. Episodes are often triggered by a cluster of, or a marked increase in, generalized seizures, followed by a 24–72hr period of normal mental state, after which psychotic symptoms develop. Psychotic symptoms include delusions (paranoid, persecutory, re ligious) and visual and auditory hallucinations. There is frequently a marked affective component and a degree of confusion or delirium. Symptoms resolve spontaneously within days or weeks, but during the acute phase, BZDs or antipsychotics may be required. In the long term, improving seizure control will reduce the chances of further episodes (see Box 4.2).

Psychiatric aspects of epilepsy 2 The ecstatic seizures of Prince Myshkin He was thinking, incidentally, that there was a moment or two in his epi leptic condition almost before the fit itself (if it occurred in waking hours) when suddenly amid the sadness, spiritual darkness, and depression, his brain seemed to catch fire at brief moments . . . His sensation of being alive and his awareness increased tenfold at those moments which flashed by like lightning. His mind and heart were flooded by a dazzling light. All his agita tion, doubts, and worries seemed composed in a twinkling, culminating in a great calm, full of understanding . . . but these moments, these glimmerings were still but a premonition of that final second (never more than a second) with which the seizure itself began. That second was, of course, unbearable. Dostoyevsky: The Idiot M http://www.gutenberg.org/ebooks/2638 Box 4.2 Post-ictal psychosis diagnostic criteria • Episode of psychosis (often with confusion and delirium), developing within 1wk of a seizure or cluster of seizures. • Psychosis lasting at least 15hrs and <2mths. • Mental state characterized by delirium or delusions (e.g. paranoid, non-paranoid, delusional, misidentifications) or hallucinations (e.g. auditory, visual, somatosensory, olfactory) in clear consciousness. • No evidence of: • A history of treatment with antipsychotic medications or psychosis within the past 3mths. • Antiepileptic drug toxicity. • An EEG demonstrating non-convulsive status. • A recent history of head trauma or alcohol/drug intoxication or withdrawal (other than BZDs used for epilepsy). Reprinted from Logsdail SJ, Toone BK. Post-ictal psychoses. A clinical and phenomeno-logical description. Br J Psychiatry 1988;152 with permission from Cambridge University Press.

142 Chapter 4 Neuropsychiatry Parkinson’s disease and related syndromes Parkinson’s disease results in progressive impairment of voluntary initiation of movement, associated with dementia of

variable severity, as well as psy chiatric morbidity. It is caused by a gradual loss of dopaminergic neurons in the substantia nigra (pars compacta). This results in dDA and iACh in the basal ganglia. The remaining cells of the substantia nigra contain Lewy bodies. Epidemiology Occurs in 20/100,000 people; typically has its onset in the 50s and peaks during the 70s; ♂:♀ = 3:2; 5% of cases are familial; 25% of patients are dis abled or die within 5yrs and 760% within 10yrs; rare survival 720yrs. Symptoms and signs of Parkinson's disease • Tremor—resting, 'pill-rolling' tremor of 4Hz; this is an early sign that may start unilaterally and may be asymmetrical in intensity; tremor increases with excitement or fatigue and diminishes during sleep. • Rigidity—'lead-pipe' or 'cog-wheel' rigidity, especially in flexor muscles. • Bradykinesia—slowness; difficulty initiating movement; reduced facial expression and blinking; 'mask facies'; reduced arm swing; 'festinating gait'; reduced voluntary speech; micrographia; 'freezing' episodes. • Postural abnormalities—flexed posture; postural instability, with frequent falls. • Autonomic instability—postural hypotension; constipation; urinary retention; sweaty, greasy, seborrhoeic skin; hypersalivation with drooling. • Positive glabellar tap. Differential diagnoses • MSA—Parkinsonism; ataxia; vertical gaze palsies; pyramidal signs; autonomic abnormalities. • PSNP—also known as Steele–Richardson–Olszewski syndrome; has its onset in the 50s and 60s and is characterized by a tetrad of: subcortical dementia, pseudobulbar palsy, supranuclear palsy, and dystonia (of the head and neck). • Dementia with Lewy bodies (DLB) (E Dementia with Lewy bodies, p. 162). Dementia in Parkinson's disease Fifty to 80% of patients develop dementia. Risk of dementia increases with increasing age, increasing severity of symptoms, and coexisting cardiovas cular disease. Patients who do not develop dementia may develop subtle cognitive deficits such as rigidity and difficulty sequencing multi-stage tasks. Clinical features Usually a subcortical dementia with slowing, im paired executive function, personality change, and memory impairment. Hallucinations and paranoia are common, and the later picture is as in DLB (E Dementia with Lewy bodies, p. 162). Pathology Indistinguishable from that of DLB.

Parkinson's disease and related syndromes Depression in Parkinson's disease Very common finding, with 40–70% of patients affected. While depres sion may arise in the context of adjustment to diagnosis and worsening Parkinson's disease symptoms, reduced levels of monoamines [DA, nor adrenaline (NA), 5-hydroxytryptamine (5-HT)]) and degeneration of subcortical pathways are likely to be important causative factors. Mood fluctuations are often noted in association with changes in plasma DA levels. Treatment SSRIs; ECT (improves the depressive illness but can precipitate delirium). Psychosis/delirium in Parkinson's disease Psychosis occurs in some cases and is commonly due to medications used in Parkinson's disease such as: • Anticholinergics—delirium, agitation, hallucinations, etc. • levodopa and DA agonists can cause psychiatric complications, including delirium, psychosis, mania, and impulse-control disorders (ICDs). Treatment Removal or dose adjustment of causative agents; occasionally, atypical antipsychotics with a lower risk of EPSEs may be used cautiously. Impulse-control disorders (E Impulse-control disorders 1, p. 422; E Impulse-control disorders 2, p. 424; E Impulse-control disorders 3, p. 428.) ICDs, in the form of pathological gambling, hypersexuality, compulsive eating, or compulsive shopping, are recognized complications of treatment with dopamine agonists and occur in 714% of patients with Parkinson's dis ease (also in patients receiving treatment with dopamine agonists for other conditions such as restless legs syndrome, MS, and PSNP). Treatment Patients must be warned of the risk of ICDs prior to com mencing treatment. Decrease or discontinue dopamine agonist if symptoms develop. Dopamine dysregulation syndrome Patients develop addictive behaviours towards prescribed dopamine agonist medication, taking doses in excess of those required to treat motor symptoms.

Resulting dopaminergic excess can cause ‘punding’ (repetitive, purposeless, complex motor behaviours such as collecting or rearranging objects), ICDs, and psychosis. Treatment Reduction and supervision of medication.

144 Chapter 4 Neuropsychiatry Neuropsychiatric aspects of central nervous system infections Viral encephalitis • Mumps, varicella-zoster, arbovirus, rubella—may cause encephalitis, resulting in behavioural problems, learning difficulties, and ADHD-like symptoms in children. • HSV 1—involves inferior frontal and anterior temporal lobes, resulting— in the acute phase—in delirium, hallucinations, and TLE. Chronic outcomes include an isolated amnestic syndrome, dementia, and Klüver–Bucy syndrome. EEG: slowing, with bursts of i slow wave in the temporal region. Treatment: early treatment with intravenous (IV) aciclovir (before diagnosis is confirmed) reduces long-term disability. • Measles—can cause both an acute viral encephalitis and rarely SSPE, a slow viral infection with onset of symptoms years after initial measles infection. Clinical features: behavioural problems, deteriorating intellectual function, movement disorders (ataxia, myoclonus), seizures, and, finally dementia and death. Pathology: white and grey matter changes to the occiput, cerebellum, and basal ganglia. EEG: periodic complexes. Tuberculosis • TB meningitis—in high-prevalence areas most common in children, and in low-prevalence areas more common in adults; caseating exudate covers the base of the skull, leading to vascular infarcts and hydrocephalus; cranial nerves may become involved. Psychiatric symptoms: apathy, withdrawal, insidious personality changes, delirium, hallucinations, chronic behavioural problems. • Tuberculoma—presents with focal signs, seizures, raised intracranial pressure (ICP). Neurosyphilis Historically known as general paresis of the insane (GPI) or Cupid’s disease, neurosyphilis is a chronic outcome of spirochaetal infection of the brain parenchyma. It manifests roughly 15–20yrs after infection. The spirochaetes have a predilection for frontal and parietal lobes, and the disease typically presents as a progressive frontal dementia. Classic symptoms Grandiosity, euphoria, and mania with mood-congruent delusions. Disinhibition, personality change, and memory impairment are also common. Neurological features Argyll Robertson pupils, ‘trombone tongue’, tremor, ataxia, dysarthria, myoclonus, hyperreflexia, spasticity, and extra-pyramidal signs. Megalomania in general paralysis Gentlemen,—You have before you today a merchant, aged forty-three, who sits down with a polite greeting, and answers questions fluently and easily . . . His illness began about two years ago. He became absent-minded and forgetful, to such an extent at last that he was dismissed by the firm for whom he had worked. Then, a year ago, he became excited, made

145 NEUROPSYCHIATRIC ASPECTS OF CNS INFECTIONS extensive purchases and plans, weeping now and then in the deepest des pair, so that he had to be taken into the hospital. On admission, he felt full of energy . . . and intended to write verses here, where he was particularly comfortable. He could write better than Goethe, Schiller, and Heine. The most fabulous megalomania quickly developed. He proposed to invent an enormous number of new machines, rebuild the hospital, build a cathedral higher than that at Cologne, and put a glass case over the asylum. He was a genius, spoke all the languages in the world, would cast a church of cast- steel, get us the highest order of merit from the Emperor, find a means of taming the madmen, and present the asylum library with 1000 volumes, principally philosophical works. He had quite godly thoughts . . . When at its height, the disease may present a great resemblance to maniacal states, but the physical examination and proof of the defective memory will save us from confusing it with them. So also will the senseless nature of the plans and the possibility of influencing them, and the feebleness and yielding character of the manifestations of the will, which are all greater in general paralysis.

Kraepelin E (1913) Lectures on Clinical Psychiatry, 3rd nglish edn. London: Baillière, Tindall and Cox

146 Chapter 4 Neuropsychiatry HIV/AIDS and psychiatry 1 Highly active antiretroviral rherapy (HAART) has, in many countries, re sulted in greatly i life expectancy for those living with HIV infection. Nevertheless, neuropsychiatric complications are not uncommon, particu larly in developing countries where rates of infection remain high, and in other circumstances where HIV/AIDS remains undiagnosed, where treat ment is unavailable, or where treatment is available but social or psycho logical factors prevent compliance with treatment. In addition, a diagnosis of HIV and associated morbidity and mortality may have major conse quences for the psychological and social functioning of individuals, fam ilies, and communities. People with HIV/AIDS are subject to prejudice and stigma as a result of the diagnosis, but also due to historical association with socially marginalized groups. Stigma contributes to the psychological burden of infected individuals and their families. The responsibility of carers working with patients with HIV/AIDS goes far beyond that of treating immediate physical problems. Holistic practice requires the healthcare professional to adopt a true biopsychosocial ap proach with appreciation of the emotional state of the patient, as well as the host of social, economic, spiritual, and ethical challenges accompanying the diagnosis with the disease. Contexts in which psychiatric problems may arise There are a number of contexts in which psychiatric problems may arise in relation to HIV/AIDS: • Health anxiety in non-infected individuals who may be concerned about being infected due to contact with HIV +ve individuals. • Pre-test anxiety. • Post-test stress may precipitate a psychiatric illness such as adjustment disorder, a major depressive episode, and suicidality. • Living with HIV/AIDS often results in stressful life events (e.g. losing a job, becoming economically disadvantaged, experiencing social alienation). • In some cases, individuals with psychiatric needs (e.g. victims of abuse, patients with learning disabilities) may be more vulnerable to becoming infected with the virus. • HIV can directly infect neurons in the brain, causing neuropsychiatric symptoms. • HIV +ve individuals are susceptible to secondary opportunistic infections and/or tumours of the CNS, which may manifest with neuropsychiatric symptoms. • Antiretroviral medications may cause psychiatric symptoms. Efavirenz can cause depression, anxiety, and suicidal ideation. Zidovudine (AZT [azidothymidine]) may precipitate both depression and mania, especially at high doses, while isoniazid prophylaxis has been known to precipitate a psychotic illness.

HIV/AIDS and psychiatry 1 Counselling HIV/AIDS patients • Pre-test counselling—consider: meaning of a +ve result; what actions the individual will take; confidentiality issues; fears of the individual; high-risk behaviours; reactions to stress; social and other implications of +ve result. • Post-test counselling—clarify distortions; assess emotions; decide who to tell; discuss the prevention of transmission; offer support to the individual and family. Ethical issues • HIV testing—issues of informed consent; only test without consent if a test result will significantly alter clinical management. • Confidentiality—encourage the individual to tell their sexual partner and other medical personnel; if the individual refuses, one may be obliged to inform without consent. • Resource allocation—e.g. availability of antiretroviral drugs.

148 Chapter 4 Neuropsychiatry HIV/AIDS and psychiatry 2: clinical presentations Depression At least 30–50% of individuals suffer a major depressive episode at some time following diagnosis, and depression can contribute to treatment non- adherence. Depression in HIV often has multiple causes. Depressive illness should be differentiated from the physical effects of HIV-related illness (e.g. weight loss, loss of energy) and from HIV-associated dementia. Treatment— is as for

individuals without HIV, although the choice of antidepressant may be influenced by HIV-related comorbidities. Suicide Although suicide rates have declined since the introduction of HAART, there is still a nine times i risk of suicide in individuals living with HIV/ AIDS. Risk factors include younger age, psychiatric illness, social isolation/ alienation, and exposure to efavirenz. Mania Manic symptoms may develop in the context of HIV psychosis or as a result of treatment with antiretroviral agents such as zidovudine (AZT). Treatment—lithium is preferable (beware risk of toxicity), since there is some evidence suggesting that sodium valproate may increase viral replication. Anxiety Infection with the virus is associated with an i risk of GAD, panic disorder, PTSD, and OCD. Chronic pain Up to 80% of patients experience chronic pain at some point, in particular chronic headache. This may lead some individuals to self-medicate, putting them at risk of substance dependence. Delirium Delirium occurs in up to 30% of patients with advanced illness (AIDS). It can be caused by direct infection of the brain by the virus, secondary infections and/or tumours, or substance withdrawal. Psychosis A psychotic illness characterized by fluctuating symptoms that may alter over hours to days may occur in the context of HIV infection. Atypical bizarre psychotic symptoms may give way to prominent mixed affective symptoms, which, in turn, may change to a withdrawn apathetic state. Aetiological factors Include the effects of stress, medications, and sec ondary infections/tumours, superimposed on the effects of direct infection of the brain by the virus. Psychosis is a common early manifestation of HIV-associated dementia, and it is likely that mild cognitive deficits coexist with the psychotic illness.

HIV/AIDS and psychiatry 2: clinical presentations Preferred treatment Low-dose haloperidol or an atypical antipsychotic (e.g. olanzapine, quetiapine) due to i sensitivity to EPSEs. Antiretroviral agents, such as zidovudine (AZT), may also reduce psychotic symptoms. HIV-associated neurocognitive disorder (HAND) HIV-associated dementia (HAD; previously termed AIDS dementia com plex) is relatively common in advanced HIV (AIDS), although the incidence has declined significantly with HAART. Epidemiology Ninety per cent of AIDS patients have CNS changes post-mortem; 70–80% develop a cognitive disorder; 30% develop HAD. Mean survival after diag nosis with HAD is 6mths. Pathology Direct central nervous system infection HIV is neurotropic, entering the brain through endothelial gaps; the virus attaches to group 120 on CD4 +ve sites of microglial cells; a cascade opens calcium channels, leading to excitotoxicity and causing neuronal death and i apoptosis in the basal ganglia and subcortical and limbic white matter. Opportunistic infections/tumours Toxoplasmosis, papovavirus, cytomegalovirus (CMV), HSV, non-Hodgkin’s lymphoma, and Kaposi’s sarcoma give rise to variable neuropathology, including encephalitis and focal necrosis. Clinical presentation Mild neurocognitive disorder Asymptomatic HIV +ve patients may have very early CNS infection that is often discounted as stress. Symptoms include cognitive slowing and memory deficits, as well as motor slowing and subtle incoordination. HIV-associated dementia With worsening of symptoms, the clinical picture constitutes a dementia syndrome and is an AIDS-defining disorder. Clinical features are classified as cognitive (subcortical dementia, focal cognitive deficits, amnesia, mutism), motor (movement disorders, e.g. tremor, ataxia, choreo-athetosis, spasti city, myoclonus), and affective (depression, apathy, agitation, disinhibition, mania). The HIV Dementia Scale (HDS)25 can be used to screen for HAD. Investigations—CT/MRI: atrophy, iT2 signal; CSF: opportunistic infection, cytology, enzyme-linked immunosorbent assay (ELISA) +ve; EEG: general ized slowing. Treatment—with HAART can slow progression. 25 Sacktor NC, Wong M, Nakasujia N, et al. (2005) The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS 19:1367–74.

150 Chapter 4 Neuropsychiatry Autoimmune and connective tissue disorders Autoimmune (limbic) encephalitis Over the last 10yrs, there has been a great increase in recognition, under standing, and detection of a range of neuropsychiatric conditions caused by auto-antibodies to brain substrates. A case series of patients with anti- N-methyl-D-aspartate (NMDA) encephalitis found that 4% of patients pre sented with isolated psychiatric symptoms, although most of these cases presented during a relapse and only a minority (0.8%) at disease onset. Clinical features Vary between conditions and patients. Typically subacute or acute onset of anxiety, psychosis, cognitive impairment, seizures, and sometimes movement disorder. Investigations Blood should be sent for testing in cases of acute/subacute cognitive impairment ± anxiety or psychosis, especially with a history of seizures where alternative causes are not clear. Some would suggest testing all new presentations of psychosis, although resources may prevent this. Clinical subtypes • Voltage-gated potassium channel (VGKC) antibodies—target the hippocampus, leading to pure amnestic deficit. Seizures are common, and neuromyotonia (writhing fasciculations), sleep disturbance, or autonomic disturbance may also be present. • NMDA receptor antibody encephalitis—is more common in young women and often associated with ovarian teratoma (removal of which is associated with good prognosis). Symptoms: fluctuating anxiety, global cognitive impairment, psychosis, seizures. • Paraneoplastic encephalitis—antibodies associated with small cell lung cancer (anti-Hu), testicular cancer (anti-Ma2), and thymoma (CRMPS) lead to varying patterns of neuropsychiatric symptoms. • Other antibodies—other antibodies recently associated with autoimmune encephalitis include those to the AMPA (α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid) receptor (limbic encephalitis), GABA B receptor (seizures and limbic encephalitis), and glutamic acid decarboxylase (GAD) (TLE with cognitive involvement).26 Systemic lupus erythematosus This multisystem autoimmune disorder is most common in women in their 30s. Neuropsychiatric symptoms are common and may be due to the ac tivity of auto-antibodies (30%), cerebral microvasculopathy and thrombosis, disease activity in other systems (uraemia, hypertension, inflammatory me diators), or side effects of medication (e.g. steroids, isoniazid, hydralazine). Seizures, cranial nerve palsies, peripheral neuropathy, ‘spinal stroke’, and other focal signs may occur, in addition to the common dermatological, rheumatological, haematological, and cardiovascular manifestations of the disorder. Psychiatric symptoms occur in 60% of cases, and syndromes include: 26 Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J (2013) Frequency and characteristics of iso lated psychiatric episodes in anti-NMDA receptor encephalitis. JAMA Neurol 70:1133–9.

Autoimmune and connective tissue disorders • Lupus psychosis—transient psychotic episodes with a recurrent and fluctuating course. Relapses are frequent, and symptoms are variable with auditory and visual hallucinations, as well as paranoia, affective instability, and disturbed sensorium, characteristic of the illness. Severe prolonged cerebral vasculitis may result in vascular dementia. • Depression—up to 30% of SLE patients experience clinically significant depressive illness. • Schizophrenia-like psychosis—a rare finding in SLE. Polyarteritis nodosa Most common in young men, polyarteritis nodosa (PAN) is an immune- mediated necrotizing vasculitis, characterized by saccular aneurysms and infarction. Neuropsychiatric findings include: stroke, focal signs, seizures, ‘spinal stroke’, delirium, and auditory and visual hallucinations. Neurosarcoid Sarcoidosis is a multisystem inflammatory disorder of unknown cause. Central or peripheral nerve involvement (neurosarcoid) is rare, but diffuse vasculopathy may cause delirium, dementia, or seizures, and granulomatous infiltration of the CNS may cause a range of neuropsychiatric symptoms.27,28 Investigations Lesions may be visible on MRI, and there may be elevated protein in the CSF.

Histological diagnosis of an accessible lesion (e.g. skin, lung) reveals caseating granulomata. Treatment Corticosteroids, methotrexate, or immunomodulators, e.g. infliximab. 27 Vincent A, Bien CG, Irani SR, Waters P (2011) Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 10:759–72. 28 Hoitsma E, Faber CG, Drent M, Sharma OP (2004) Neurosarcoidosis: a clinical dilemma. Lancet Neurol 3:397–407.

152 Chapter 4 Neuropsychiatry Dementia: general overview Essence Dementia is a syndrome characterized by progressive, irreversible global cognitive deficits. Different patterns of deficits occur, depending on the underlying pathology. For a diagnosis to be made, there must be significant impairment of functioning and other possible diagnoses should be excluded (E Reversible causes of cognitive impairment, p. 154). Causes • Parenchymal/degenerative—Alzheimer's disease (50–70%); Lewy body dementia (<5%) and dementia in Parkinson's disease; FTD (5–10%); MS; PSNP; corticobasal degeneration; MND; Huntington's disease; Wilson's disease. • Intracranial—vascular dementia (20–30%); NPH (reversible in some cases). • Infection—CJD (prion disease); neurosyphilis; HAND; TB; SSPE. • Toxins—prolonged alcohol misuse [alcohol-related brain damage (ARBD)]; heavy metal poisoning. Clinical features (See Box 4.3.) • Cognitive impairment—characteristic patterns of impairment occur in different types of dementia. Most typically, initial impairment of episodic (short-term) memory progresses to more extensive memory impairment, apraxia, agnosia, and dysphasia. • History of personality change—social withdrawal, disinhibition, diminished self-care, apathy, deteriorating executive function. • Hallucinations and delusions—often paranoid (20–40%) and poorly systematized. • Anxiety and/or depression—in 50%. • Neurological features—seizures, primitive reflexes, pseudobulbar palsy, long tract signs (e.g. hyperreflexia or upgoing plantars. • Emotional lability/pseudobulbar affect—(in stroke) (E Psychiatric sequelae of stroke, p. 176). • Sundowning syndrome—as evening approaches, confusion and restlessness increase. Differential diagnosis Delirium; depression (pseudodementia; E Pseudodementia, p. 552); other reversible causes of cognitive impairment (E Reversible causes of cog nitive impairment, p. 154); amnestic disorders (E Amnestic disorders, p. 170); intellectual disability (ID); psychotic disorders; normal ageing (E Normal ageing, p. 544). Investigations FBC; LFT; U&Es; glucose; ESR; thyroid-stimulating hormone (TSH); cal cium; phosphate; syphilis serology; HIV; vitamin B12 and folate; CRP; blood culture; LP; EEG; chest X-ray (CXR); ECG; CT; MRI; SPECT.

Dementia: general overview Principles of management • Assessment—diagnostic, functional, and social. • Cognitive enhancement—acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine); glutamate receptor antagonist (memantine). • Treat psychosis/agitation—consider antipsychotics. • Treat depression/insomnia—SSRIs; hypnotics. • Treat medical illness—avoid drugs which may worsen cognitive impairment (e.g. opiates, BZDs, anticholinergics). • Psychological support—to both patient and caregivers. • Functional management—maximize mobility; encourage independence with self-care, toilet, and feeding; aid communication. • Social management—accommodation; activities; financial matters; legal matters (power of attorney, wills, and curatorship). Box 4.3 Clinical syndromes of dementia Dementias may be classified in terms of the primary site of pathology. Since the site of pathology in the brain correlates with neuropsychiatric symptomatology, this is a useful system of classification. • Cortical dementias Primarily involve the cortex: • bvFTD/PPA (E Fronto-temporal dementia, p. 160). Characterized in the frontal (behavioural) variant by prominent personality change, including either disinhibition and social indiscretion or profound apathy, and in temporal lobe variants by language impairments.

A common cause of early-onset dementia, it is often undiagnosed or mistaken for psychiatric illness. CT and MRI show fronto- temporal atrophy; SPECT shows fronto-temporal hypoperfusion, and FDG-PET shows reduced fronto-temporal glucose metabolism. • Posterior–parietal, e.g. Alzheimer's disease (E Alzheimer's disease 1, p. 156). Characterized by early memory loss and focal cognitive deficits. Personality changes are later manifestations. Language impairments involve problems with word-finding (lexical anomia). CT shows thinning (<12mm) of the cortex of the medial temporal lobe. • Subcortical dementias Parkinson's disease (E Parkinson's disease and related syndromes, p. 142); Huntington's disease (E Huntington's disease, p. 166); Wilson's disease (E Wilson's disease, p. 166); Binswanger encephalopathy (E Vascular dementia (vascular neurocognitive disorder), p. 164); PSNP (E Progressive supranuclear palsy, p. 142); HIV-associated dementia (E HIV-associated neurocognitive disorder (HAND), p. 149); NPH (E Normal pressure hydrocephalus, p. 154). Clinical features: gross psychomotor slowing, depressed mood, movement disorders, mild amnesia, and personality changes. • Cortical–subcortical dementias, e.g. Lewy body dementia (E Dementia with Lewy bodies, p. 162). Clinical features: cortical and subcortical symptoms. • Multifocal dementias, e.g. CJD and other prion diseases (E Prion diseases, p. 168). Clinical features: rapid onset and course; involves the cerebellum and subcortical structures.

154 Chapter 4 Neuropsychiatry Reversible causes of cognitive impairment An important aim of the assessment of a patient with suspected dementia is to exclude and treat any reversible causes of cognitive impairment. The dis orders listed below may be produced by a dementia-like syndrome, which, in many cases, can be reversed with treatment. Causes • Intracranial—NPH; chronic subdural haematoma (SDH); posterior reversible encephalopathy syndrome; autoimmune encephalitis (E Autoimmune (limbic) encephalitis, p. 150). • Psychiatric/functional—depression ('pseudodementia'); psychosis; functional or anxiety-related cognitive impairment. • Infection—HSV encephalitis; neurosyphilis; HAND (E HIV-associated neurocognitive disorder (HAND), p. 149); TB. • Endocrine—hypothyroidism; hyperparathyroidism; Cushing's and Addison's disease. • Metabolic—uraemia; hepatic encephalopathy; hypoglycaemia; calcium imbalance; magnesium imbalance; electrolyte imbalance. • Vitamin deficiency—B12; folate; pellagra (niacin); thiamine. • Drugs/medications—BZDs, opiates, and anticholinergic medications, in particular, cause a degree of cognitive impairment, which may be clinically significant in vulnerable individuals or those with comorbid dementia or brain injury. • Toxins—prolonged alcohol misuse; heavy metal poisoning; CO poisoning. Normal pressure hydrocephalus A syndrome where there is dilatation of cerebral ventricles (especially third ventricle), but normal CSF pressure at LP. It typically presents with the triad of dementia, gait disorder, and urinary incontinence. Importantly, the de mentia is potentially reversible if NPH is treated promptly. Aetiology Fifty per cent of cases are idiopathic; 50% are secondary to mechanical obstruction of CSF flow across the meninges (e.g. meningitis, subarachnoid haemorrhage, trauma; radiotherapy). Clinical features There is progressive slowing of cognitive and motor func tioning, consistent with a pattern of subcortical dementia. Gait is broad- based, bradykinetic, and shuffling. Urinary incontinence is a late symptom. Investigations CT scan shows isize of the lateral ventricles and thinning of the cortex; 24hr ICP monitoring shows abnormal pulsatility. Treatment Abnormal pulsatility on 24hr CSF pressure monitoring, short duration of symptoms, improvement of symptoms after therapeutic re moval of 40–50mL of CSF, and NPH secondary to an identified cause are predictors of good response to ventriculo-peritoneal shunt.

Reversible causes of cognitive impairment Chronic subdural haematoma An insidious and fluctuating syndrome of cognitive and motor impairment may result from an undetected chronic SDH. An SDH results from rupture of the bridging veins between the dura and arachnoid mater and tends to occur over the frontal and/or parietal cortices. In 30% of cases, there is bi lateral SDH. SDH should be suspected where there is a fluctuating pattern in cognitive function, especially if risk factors for SDH exist: elderly after a fall, infancy, cerebral atrophy (e.g. chronic alcoholism), clotting disorders, or anticoagulant treatment. Clinical features An SDH may only manifest with symptoms months after it develops; therefore, there may be no history of recent trauma. Headache, altered level of consciousness, and amnesia may all occur, often with fluc tuations in severity. Typically, the mental state may be variable on different occasions, and there may be periods of unusual drowsiness, as well as both cognitive and physical slowness and sluggishness. Minor focal signs are sometimes detected. The general picture is of a subcortical dementia of relatively rapid onset. Investigations CT scan during the first 3wks may not show the SDH, as it is isodense during the early phase. Therefore, contrast should be used. Later on, as the SDH liquefies, a low-density convexity may be detected over the fronto-parietal cortex. Treatment Surgical drainage of SDH via burr holes. Steroids may be helpful for conservative treatment.

156 Chapter 4 Neuropsychiatry Alzheimer's disease 1 Also termed 'dementia of the Alzheimer type' (DAT), this is the most common cause (70%) of dementia in older people. It is a degenerative dis ease of the brain, with prominent cognitive and behavioural impairment that is sufficiently severe to interfere significantly with social and occupational func tion. It affects 7850,000 people in the UK and >46 million worldwide. As the percentage of the total population aged over 65 in the developed world con tinues to increase, the burden of DAT-related healthcare is also increasing. Epidemiology Risk of DAT increases with age: 1% at age 60yrs; doubles every 5yrs; 40% of those aged 85yrs. Age-specific incidence is the same for men and women— 750% excess prevalence in women is explained by their longer lifespan. Mean survival from time of diagnosis is 4–8 years; most will be fully de pendent within 4yrs. • Risk factors—increasing age, Down's syndrome, apolipoprotein E ε4 allele, diabetes, smoking, hypertension in middle age. • Protective factors—apolipoprotein E ε2 allele, higher level of premorbid education, higher level of physical activity in middle age, non-steroidal anti-inflammatory drugs (NSAIDs). • Genetics—first-degree relatives are at a slightly i risk. Carriers of the apolipoprotein E ε4 allele on chromosome 19 (15% of Europeans) are at further i risk; apolipoprotein E ε2 is protective. Single-gene autosomal dominant inherited DAT is rare, affecting <1% of those with DAT and associated with early onset; identified mutations include amyloid precursor protein (APP) on chromosome 21 and the genes for presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Pathophysiology • Amyloid plaques—insoluble β-amyloid peptide deposits as senile plaques or β-pleated sheets in the hippocampus, amygdala, and cerebral cortex. i density with advanced disease. • Neurofibrillary tangles (NFTs)—consist of phosphorylated tau protein and are found in the cortex, hippocampus, and substantia nigra. Also found in normal ageing, Down's syndrome, and PSNP. • The co-occurrence of amyloid plaques and NFTs was described by Alois Alzheimer in his 1906 description of the disorder and is still accepted universally as a hallmark of the disease. • Up to 50% loss of neurons and synapses in the cortex and hippocampus. • Cholinergic hypothesis—the pathological changes lead to degeneration of cholinergic nuclei in the basal forebrain (nucleus basalis of Meynert). This results in dcortical ACh. Assessment • Detailed history—including an informant history is essential. Informant rating scales, such as IQCODE, are helpful. Physical examination, including full neurological examination (E Neurological examination in psychiatry, p. 128), and blood tests (E Neurological investigations in

psychiatry, p. 130) should be performed to rule out reversible causes (E Reversible causes of cognitive impairment, p. 154).

Alzheimer's disease 1 • Cognitive testing—may begin with MMSE, MOCA, or ACE-III. • Imaging—CT: cortical atrophy, especially over parietal and temporal lobes, and ventricular enlargement. MRI: atrophy of grey matter (hippocampus, amygdala, and medial temporal lobe). Where diagnosis remains uncertain: SPECT shows temporal and posterior parietal hypoperfusion and fludeoxyglucose-PET (FDG-PET) shows reduced metabolism in temporal and posterior parietal lobes. Clinical features • Early—failing memory, disorientation in time, muddled efficiency with activities of daily living (ADLs), spatial dysfunction, and changes in behaviour (e.g. wandering and irritability). By the time the patient presents, cognitive deficits are usually apparent. • Middle—global intellectual deterioration—aphasia, apraxia, agnosia, impaired visuospatial skills, and executive dysfunction. • Late—fully dependent. Physical deterioration, incontinence, gait abnormalities, spasticity, seizures (3%), tremor, weight loss, primitive reflexes, extra-pyramidal signs. • Behavioural and psychological symptoms in dementia (BPSD)—delusions (15%) usually of a paranoid nature. Auditory and/or visual hallucinations (10–15%). Depression in up to 20% of patients. Behavioural disturbances include aggression, wandering, explosive temper, sexual disinhibition, inappropriate toileting, excessive eating, and searching behaviour. Clinical subtypes and overlapping syndromes • Posterior cortical atrophy—an atypical variant of DAT in which the parietal, occipital, and occipito-temporal cortices are first affected; memory and language are relatively preserved in early stages, but impairments of visuospatial function are prominent. Gerstmann's syndrome (acalculia, agraphia, finger agnosia, left–right disorientation) and/or Balint's syndrome (simultanagnosia, oculomotor apraxia, optic ataxia, environmental agnosia) may be present. Progresses to global impairment. • Logopenic aphasia—a subtype of semantic dementia, with dverbal output, phonological errors with preserved grammar, and impaired sentence repetition. Most have DAT pathology. Pray, do not mock me: I am a very foolish fond old man, Fourscore and upward, not an hour more or less; And, to deal plainly, I fear I am not in my perfect mind. Methinks I should know you and know this man; Yet I am doubtful: for I am mainly ignorant what place this is, and all the skill I have remembers not these garments; nor I know not where I did lodge last night. Do not laugh at me; For as I am a man, I think this lady to be my child Cordelia. Shakespeare: King Lear, Act II Scene 7

158 Chapter 4 Neuropsychiatry Alzheimer's disease 2: pharmacological treatments There are as yet no truly disease-modifying drugs available for DAT; available drugs provide mild symptomatic benefits in some patients. Acetylcholinesterase inhibitors (AChEIs) were the first drugs to be licensed for the treatment of DAT. They act by enhancing ACh at cholinergic syn apses in the CNS and, in this way, may cause mild clinical improvements in cognitive, functional, and behavioural symptoms, reducing time spent in full nursing care. They are recommended as first-line agents in the treatment of mild to moderate DAT (see Box 4.4). Acetylcholinesterase inhibitors Similar efficacy over 6mths; long-term efficacy unknown. Switching between agents is acceptable. • Donepezil—piperidine derivative, developed in 1996; gastrointestinal tract (GIT) absorbed, with liver metabolism; long half-life (70hrs); highly selective (acts centrally only); linear kinetics. Problems: GIT side effects at high dose; bradycardia; GIT bleed (rare); contraindicated in asthma. Benefits: selective, therefore dside effects; no liver toxicity; predictable kinetics; narrow dose range; 1× daily dosage. Dose: 5–10mg/day. • Rivastigmine—developed in 1998; short half-life (12hrs); inhibits acetylcholinesterase and butyrylcholinesterase in CNS. Problems: GIT Box 4.4 NICE

guidance on donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease (TA217) AChEIs—donepezil, rivastigmine, or galantamine—are recommended: • For managing mild to moderate Alzheimer's disease. Memantine is recommended: • For moderate Alzheimer's disease in patients who are intolerant to, or have a contraindication to, AChEIs. • In severe Alzheimer's disease. For all of the above medications: • Treatment should be started on the advice of either a secondary care medical specialist (psychiatrist, geriatrician, and neurologist) or by another healthcare professional (e.g. GP, nurse specialist) with specialist expertise in diagnosing and treating Alzheimer's disease. • Treatment should be continued only while it has a worthwhile effect on cognitive, global, functional, or behavioural symptoms. Non-Alzheimer dementias and mild cognitive impairment (MCI): • AChEIs and memantine should not be prescribed for VaD or MCI, except as part of properly constructed clinical research studies. • People with DLB who have non-cognitive symptoms causing significant distress to the individual, or leading to behaviour that challenges, should be offered an AChEI. Source: Data from M https://www.nice.org.uk/guidance/ta217 [accessed 30 May 2018].

Alzheimer's disease 2: pharmacological treatments side effects; twice daily dosage. Benefits: not metabolized by the liver and least likely to cause drug–drug interactions. Dose: start with 1.5mg twice daily (bd); increase to 3–6mg bd—now available in a modified- release once-daily (od) form or 24hr patch [thought to be helpful in reducing gastrointestinal (GI) side effects]. • Galantamine—selectively inhibits acetylcholinesterase and acts as an allosteric ligand at nicotinic ACh receptors; metabolized in the liver; short half-life (5hrs); selective. Problems: twice daily dosage. Dose: 4–12mg bd. Other drugs • Memantine—a partial NMDA receptor antagonist that may protect neurons from glutamate-mediated excitotoxicity. Trials show benefits of memantine augmentation of donepezil. A Cochrane review indicates mild benefit in moderate to severe DAT.29 Future treatment strategies? Although only at experimental stages, there is some evidence for other approaches to DAT. These include: monoclonal antibodies to amyloid-B (crenezumab; solanezumab); anti-inflammatories; secretase inhibitors; drugs targeting insulin resistance; and vaccination against abnormal forms of tau protein. Mild cognitive impairment (See Box 4.5.) 29 McShane R, Sastre AA, Minakaran N (2006) Memantine for dementia. Cochrane Database Syst Rev M http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003154.pub5/full [accessed 30 May 2018]. Box 4.5 Mild cognitive impairment The term mild cognitive impairment (MCI) is widely used in the dementia research community but does not translate well to clinical practice. MCI refers to patients with mild cognitive symptoms not severe enough to meet diagnostic criteria for dementia. Recent research suggests that the pathological changes of Alzheimer's disease begin to appear many years before clinical symptoms develop. Researchers are keen to identify those with the earliest clinical manifestations, as 'conversion' to Alzheimer's dis ease is therefore a key target for study and treatment. MCI (particularly amnestic MCI) is therefore currently used as a proxy measure to iden tify this 'at-risk' group. However, in clinical practice, MCI is an imperfect construct, a description of symptoms, rather than a diagnosis, with the potential to cause great anxiety in patients and families. Although around 10% of elderly individuals with MCI will progress to dementia each year, others will never develop dementia and some return to normal levels of cognition.

160 Chapter 4 Neuropsychiatry Fronto-temporal dementia The FTDs are a set of overlapping clinical syndromes caused by disease primarily affecting the frontal and temporal lobes.30,31,32 FTDs account for 720% of cases of early-onset dementia. Personality change and social dis

inhibition or language impairment often precede memory impairment (E Box 4.9, p. 171). Early disease is commonly mistaken for primary psychiatric disorder. Pathology Fronto-temporal lobar degeneration (FTLD) refers to a range of underlying pathologies: neuronal loss, gliosis, and protein inclusions consisting of either tau (Pick bodies) in 40% (FTLD-tau), TDP-43 in 50% (FTLD-TDP), and FUS in some cases (FTLD-FUS). Genetics Forty per cent have a positive family history, 10% due to autosomal dom inant mutations—the most common are MAPT, GRN, and C9ORF. Clinical subtypes • Behavioural variant FTD (bvFTD) (Pick's Disease)33—most common subtype. Onset usually 45–65yrs. Mean survival from diagnosis: 8yrs (range 2–20). • Clinical features: disinhibition, loss of social empathy with tactlessness and breaches of etiquette, apathy, stereotypic behaviours (without anxiety, unlike OCD), changes in food preference (overeating and preference for sweet foods). Early cognitive symptoms of poor attention and executive dysfunction progress to include all cognitive domains. • Neurological: a minority have signs of MND (up to 15% with MND develop a bvFTD syndrome). • Investigations: imaging may be normal; or CT/MRI: bilateral (asymmetrical) abnormalities of frontal/temporal lobes; and SPECT: frontal and/or temporal lobe abnormalities. EEG is normal. • Diagnosis: based on clinical criteria (see Box 4.6). • Primary progressive aphasia (PPA)—initial symptoms are due to impaired language function, caused by temporal lobe disease, but symptoms of bvFTD may also be present or may develop as disease progresses. • Progressive non-fluent aphasia (PNFA)—non-fluent, effortful speech with agrammatism. Pathology: atrophy in Broca's area. 30 Rascovsky K, Hodges JR, Knopman D, et al. (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134:2456–77. 31 Neary D, Snowden J, Mann D (2005) Frontotemporal dementia. Lancet Neurol 4:771–80. 32 Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC (2011) Clinical, genetic and patho logical heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry 82:476–86. 33 Lanata SC, Miller BL (2016) The behavioural variant fronto-temporal dementia (bvFTD) syn drome in psychiatry. J Neurol Neurosurg Psychiatry 87:501–11.

Fronto-temporal dementia • Semantic dementia (SD)—fluent speech with loss of concepts/meaning. Pathology: left > right temporal lobe atrophy (sometimes called temporal variant or tvFTD). • Logopenic progressive aphasia (LPA)—impaired sentence repetition. A variant of Alzheimer's type dementia. Management: currently, no specific treatments; SSRIs of limited benefit for behavioural symptoms (disinhibition, overeating, and compulsions). Box 4.6 International consensus criteria for bvFTD There must be a progressive deterioration of behaviour and/or cogni tion, and symptoms must not be better accounted for by a psychiatric, non-degenerative neurological or medical disorder. Possible bvFTD Three of the following behavioural/cognitive symptoms are persistent or recurrent: • Early behavioural disinhibition (one of: socially inappropriate behaviour; loss of manners or decorum; impulsive, rash or careless actions). • Early apathy or inertia. • Early loss of sympathy or empathy (one of: diminished response to other people's needs and feelings; diminished social interest, interrelatedness, or personal warmth). • Early perseverative, stereotyped, or compulsive/ritualistic behaviour (one of: simple repetitive movements; complex, compulsive, or ritualistic behaviours; stereotypy of speech). • Hyperorality and dietary changes (one of: altered food preferences; binge eating, i consumption of alcohol or cigarettes; oral exploration or consumption of inedible objects). • Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of: deficits in executive tasks; relative sparing of episodic memory; relative sparing of visuospatial skills). Probable bvFTD • Meets criteria for possible bvFTD. • Exhibits significant functional decline (by caregiver report or rating scale). • Imaging consistent with bvFTD

(one of: frontal and/or temporal atrophy on MRI or CT; frontal and/or temporal hypoperfusion or hypometabolism on PET or SPECT). Definite bvFTD • Meets criteria for possible or probable bvFTD. • Histopathological evidence of FTLD on biopsy or at post-mortem OR presence of a known pathogenic mutation. Source: data from Lanata, S.C. and Miller, B.L. (2016) The behavioural variant fronto-temporal dementia (bvFTD) syndrome in psychiatry. Journal of Neurology, Neurosurgery & Psychiatry, 87:501–11.

162 Chapter 4 Neuropsychiatry Dementia with Lewy bodies34 Common form of dementia in the elderly (720% of new diagnoses of de mentia in hospital35 and 4% of new community cases) that lies on a clinical and pathological continuum with Parkinson's disease. Epidemiology Age of onset: 50–83yrs. Age at death: 68–92yrs. ♂ > ♀. Clinical features Dementia with fluctuating cognitive performance and consciousness and early sparing of memory; Parkinsonism (70%: bradykinesia, rigidity, gait dis order, tremor); complex hallucinations—visual (760%: often people and ani mals) and auditory (720%)—with associated emotional responses varying from fear to amusement); significant depressive symptoms (740%); recur rent falls/syncope (730%: due to autonomic dysfunction), transient dis turbances of consciousness (mute and unresponsive for several minutes); antipsychotic sensitivity (760%). The mean survival time/rate of cognitive decline is similar to Alzheimer's disease (but rapid deterioration over 1–2yrs does occur). See Box 4.7 for a summary of diagnostic criteria. Pathological features Eosinophilic A–synuclein neuronal inclusions (Lewy bodies), with neuronal loss in brainstem nuclei (especially basal ganglia) and paralimbic and neo cortical structures. Associated neuronal loss. Lewy neurites—distinctive pat tern of ubiquitin and A-synuclein immunoreactive neuritic degeneration—in the substantia nigra, hippocampal region (CA2/3), dorsal vagal nucleus, basal nucleus basilis of Meynert, and transtentorial cortex. Alzheimer-type changes—senile plaques present in a similar density and distribution, fewer NFTs, less tau pathology. Vascular disease—in 730%. Differential diagnosis Other dementia syndromes (especially DAT), delirium, Parkinson's disease (in which motor symptoms appear ≥1yr prior to cognitive symptoms; 80% ultimately develop dementia which is pathologically equivalent to DLB), PSNP, MSA, CJD, psychiatric disorders (e.g. late-onset delusional disorder, depressive psychosis, mania). Investigations • CT/MRI—relative sparing of medial temporal lobes in most cases. Moderate increases in deep white matter lesions, frequent periventricular lucencies on MRI. • HMPAO SPECT scan—(blood flow) Global (especially occipital), medial, temporal lobes relatively preserved. • FP-CIT SPECT—(presynaptic dopamine transporter) Reduced in the putamen, as in Parkinson's disease. 34 Walker Z, Possin KL, Boeve BF, Aarsland D (2015) Lewy body dementias. Lancet 386:1683–97. 35 Jones SV, O'Brien JT (2014) The prevalence and incidence of dementia with Lewy bodies: a sys tematic review of population and clinical studies. Psychol Med 44:673–83.

163 DEMENTIA WITH LEWY BODIES Management • Antipsychotics—avoid/use with great caution: severe sensitivity reactions (40–50%), e.g. irreversible Parkinsonism, impairment of consciousness, neuroleptic malignant syndrome (NMS)-like autonomic disturbances— 2- to 3-fold increase in mortality. • AChEIs—recommended by national guidelines for treatment of non-cognitive symptoms (e.g. apathy/psychosis/agitation). • Other—no clear evidence for antidepressants, anticonvulsants, or BDZs. Clonazepam may be useful for sleep disturbance (vivid dreams, muscle atonia, excessive jerking, and other complex movements). Anti- Parkinsonian medication—use cautiously for clinically significant motor symptoms, but note the risk of exacerbating psychotic symptoms. Box 4.7 Consensus criteria for the diagnosis of dementia with Lewy bodies • Central feature required for a diagnosis of DLB: • Progressive dementia severe

enough to interfere with normal social or occupational function. • Deficits on tests of attention, executive function, and visuospatial ability might be especially prominent. • Two of the following core features are essential for a probable diagnosis of DLB; one is essential for a possible diagnosis of DLB. • Fluctuating cognition. • Recurrent visual hallucinations. • Spontaneous motor features of Parkinsonism. • Features supportive of the diagnosis are: • Repeated falls, syncope, transient unexplained LOC, severe autonomic dysfunction, non-visual hallucinations, systematized delusions, depression, relative preservation of medial temporal lobe structures, generalized low uptake on SPECT or PET with reduced occipital activity, abnormal myocardial scintigraphy, prominent slow wave activity on EEG with temporal lobe transient sharp waves. • A diagnosis of DLB is less likely if: • Cerebrovascular disease accounts for part or all of the clinical signs and symptoms. • Parkinsonism does not appear until severe dementia. Source: data from McKeith, I. G., et al. (2005). Diagnosis and management of dementia with Lewy bodies third report of the DLB consortium. Neurology 65: 1863–1872.

164 Chapter 4 Neuropsychiatry Vascular dementia (vascular neurocognitive disorder) Vascular dementia (VaD) is the second most common cause of dementia after DAT,36 accounting for 20% of cases. It often coexists with DAT and results from thromboembolic or hypertensive infarction of small and medium-sized vessels. Features that suggest a vascular cause of cognitive impairment include: sudden onset, stepwise deterioration, and risk factors for cardiovascular disease. Its presentation is variable, and three syndromes of vascular cognitive impairment are commonly recognized:37

1. Cognitive deficits following a single stroke Not all strokes result in cognitive impairment, but when they do, the deficits depend upon the site of the infarct. Difficulties with language, praxis, or executive function are most common; isolated memory symptoms are unusual. Cognitive deficits may remain fixed or recover, either partially or completely.
2. Cognitive deficits as a result of multiple strokes (multi-infarct dementia) Multiple strokes lead to stepwise deterioration in cognitive function. Between strokes, there are periods of relative stability. There are often risk factors for cardiovascular disease.
3. Progressive small-vessel disease (Binswanger disease) Multiple microvascular infarcts of perforating vessels lead to progressive lacunar formation and white matter hyperintensities on MRI. This is a subcortical dementia with a clinical course characterized by gradual intellectual decline, generalized slowing, and motor problems (e.g. gait disturbance and dysarthria). Depression and pseudobulbar palsy are not uncommon. Epidemiology Most common onset: age 60–70yrs; ♂ > ♀. Other risk factors include: family or personal history of cardiovascular disease, smoking, diabetes mellitus, hypertension, hyperlipidaemia, polycythaemia, coagulopathies, sickle-cell anaemia, valvular disease, atrial myxoma, and carotid artery disease. There are rare familial cases with onset in the 40s—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Clinical features Onset may follow a stroke, with associated motor symptoms, and is more acute than DAT. Emotional, personality, language, and executive impair ments are common and often early; memory impairments occur later. Symptoms may fluctuate in severity. Depression and emotional lability are common, and catastrophic emotional reactions are sometimes reported. 36 Calabrese V, Giordano J, Signorile A, et al. (2016) Major pathogenic mechanisms in vascular dementia: Roles of cellular stress response and hormesis in neuroprotection. J Neurosci Res

94:1588–603. 37 Rossor M, Brown J (1998) Vascular and other dementias. In: Butler R, Pitt B (eds). Seminars in Old Age Psychiatry, pp. 73–86. London: Gaskell.

Vascular dementia (vascular neurocognitive disorder) Physical signs include features of generalized vascular disease, together with neurological impairments (e.g. rigidity, akinesia, brisk reflexes, pseudobulbar palsy). Ten per cent have seizures at some point. Prognosis is poorer than in DAT, with an average lifespan of 5yrs from onset. Cause of death is usually ischaemic heart disease (50%), stroke, or renal failure. Investigations • Routine 'dementia screen' (E Standard blood tests in psychiatric practice, p. 130). • Serum cholesterol, clotting screen, vasculitis screen [ESR, CRP, complement, anti-nuclear factor (ANF), rheumatoid factor, anti-DNA antibodies, antiphospholipid antibodies, etc.), and syphilis serology are additional tests in unusual cases (e.g. 'young strokes'). • ECG, CXR, CT, and MRI are essential. • Other investigations may include: echocardiography (for cardiac/ valvular defects or ventricular failure) and carotid artery Doppler ultrasound. Management • Establish causative factors. Contributory medical or surgical conditions should be treated early. • There is no evidence that daily aspirin is effective in delaying the course of VaD, and it is associated with a risk of haemorrhage. • General health interventions include changing diet, stopping smoking, managing hypertension, optimizing diabetic control, and increasing exercise.

166 Chapter 4 Neuropsychiatry Other specific neurodegenerative conditions Huntington's disease A genetic disease characterized by a combination of dementia and worsening chorea. There is autosomal dominant inheritance with 100% penetrance; thus, 50% of a patient's offspring will be affected. Genetic testing allows presymptomatic diagnosis, but as no treatment is available and a positive test has implications for other family members, there are ethical issues around presymptomatic testing. Pathology The genetic defect is a trinucleotide repeat of CAG—between 37 and 120 repeats on chromosome 4. ddGABA neurons in the basal gan glia; this leads to i stimulation of the thalamus and cortex by the globus pallidus. Also increase in DA transmission. Clinical features Chorea, dementia, and a family history of HD. Chorea is a movement disorder characterized by initial jerks, tics, gross involuntary movements of all parts of the body, grimacing, and dysarthria. There is i tone, with rigidity and stiffness, positive primitive reflexes, and abnormal eye movements. Clinical course Onset usually during 30s and 40s; a small number of juvenile-onset cases; deteriorating course to death within 10–12yrs. Psychiatric syndromes Occur in 60–75% of patients with HD. • Anxiety and depression are common. • Psychosis is common and often occurs early. • Executive dysfunction with impulsivity and aggression. • Subcortical dementia—slowing, apathy, and amnesia. Investigations EEG: slowing. CT/MRI: atrophy of the basal ganglia, with 'boxing' of the caudate and dilatation of the ventricles. PET: dmetabolism in the basal ganglia. Treatment No treatment arrests the course of the disease. Antipsychotic and antidepressant medications may provide symptomatic relief of psychi atric symptoms. Tetrabenazine, antipsychotics, and BDZs may help reduce abnormal movements. Wilson's disease A rare genetic disease caused by a mutation of the APT7B gene on chromo some 13, which prevents normal hepatic excretion of excess copper into bile. Inheritance is autosomal recessive. Copper deposits in the liver cause cirrhosis and in the basal ganglia result in degeneration of the lentiform nu cleus (hepato-lenticular degeneration). Clinical features Onset in childhood or early adulthood. Liver cirrhosis. Extra-pyramidal signs include: tremor, dystonia, i tone, flapping tremor of the wrists, wing-beating tremor of the shoulders, risus sardonicus of the face, bulbar signs (dysphagia, dysarthria), and Kayser–Fleischer rings (green- brown corneal deposits).

Other specific neurodegenerative conditions Psychiatric syndromes • Mood disturbances—common. • Subcortical dementia—25%. • Psychosis—rare. Investigations iserum/urine copper; dcaeruloplasmin. Treatment Copper-chelating agents: penicillamine or trientine. Pantothenate kinase-2-associated neurodegeneration (PKAN) One of a group of rare inherited conditions responsible for neurodegeneration with brain iron accumulation (NBIA),38 which are as sociated with abnormal accumulation of iron in the brain. PKAN (formerly Hallervorden–Spatz syndrome)39 is an autosomal recessive disorder with onset typically in childhood or early adulthood. Clinical features Symptoms include dystonia, Parkinsonism, spasticity, seiz ures, ID or dementia, optic atrophy, and pigmentary retinopathy. Psychiatric syndromes • OCD. • Schizophrenia-like psychosis. • Depression. Investigations Characteristic 'eye of the tiger' sign on T2-weighted MRI, caused by iron deposits in the basal ganglia. Genetic tests are available. Treatment There is no treatment available to reverse the condition. Iron- chelating agents (e.g. desferrioxamine) may slow progression. 38 Schipper HM (2012) Neurodegeneration with brain iron accumulation—clinical syndromes and neuroimaging. Biochim Biophys Acta 1822:350–60. 39 The term pantothenate kinase neurodegeneration is now used in preference to Hallervorden– Spatz syndrome, because it is now known that Hugo Spatz and Julius Hallervorden (who described the syndrome in 1922) were members of the Nazi party who performed research using the brains of executed prisoners during World War II.

168 Chapter 4 Neuropsychiatry Prion diseases Prion diseases are rare, rapidly progressive dementing illnesses caused by the spread of deposits of abnormal prion protein (PRNP) throughout the brain as a result of either inherited genetic mutation, sporadic mutation, or infection. The typical pathological finding is spongy encephalopathy, and in terms of the nosology of the dementias, prion disease is considered a multifocal dementia. While prion diseases tend to respect the species bar rier (e.g. 'scrapie' is a prion disease limited to sheep), this is not always the case (e.g. vCJD). Creutzfeldt–Jakob disease A rare disease of 50–70yr olds, with equal sex distribution, resulting in around 100 UK deaths per year. Eighty-five per cent of cases result from spontaneous mutation of PNRP, 10% from inherited mutations, and 5% re sulting from vCJD or iatrogenic transmission during transplant surgery of dura, corneal grafts, and pituitary growth hormone. The clinical picture is one of rapidly progressive dementia, cerebellar and extra-pyramidal signs, myoclonus, and death within a year. EEG shows periodic complexes. CT atrophy of the cortex and cerebellum. Elevated levels of 14-3-3 protein are found in the CSF. New variant CJD—bovine spongiform encephalopathy The rise of vCJD followed an epidemic of bovine spongiform encephal opathy (BSE) in cattle. BSE is a prion disease of cows that is thought to have been spread by cattle feeds that contained CNS material from infected cows. The disease in humans affects mainly young people in their 20s and is characterized by early anxiety and depressive symptoms, followed by per sonality changes, and finally a progressive dementia. Ataxia and myoclonus are prominent, and the typical course is 1–2yrs until death. EEG changes are only seen late in disease. Rare inherited prion diseases • Fatal familial insomnia (FFI)—causes progressive and profound insomnia, anxiety, hallucinations, and ultimately rapidly progressive dementia. Inherited PRNP mutation. • Gerstmann–Sträussler–Scheinker syndrome (GSS)—causes dysarthria, ataxia, memory problems, and rapidly progressive dementia. Inherited PRNP mutation. Kuru This was a rare disease of Papua New Guinea cannibals who ate the brains of their deceased relatives. The incubation period was prolonged—up to 40yrs before disease onset, then progression was rapid and fatal (see Box 4.8).

Prion diseases Box 4.8 A ‘cannibalism genotype’ protects against CJD Researchers at University College London in 2003 suggested that canni balism was common and widespread in human ancestors. They analysed DNA from 30 elderly Fore women from Papua New Guinea who had participated in many cannibalistic feasts before they were banned by the Australian government in the 1950s. It was the practice of the Fore for women and children to consume the brains of dead kin in the belief that this act would ‘recycle’ the spirit of the dead within the living. At the peak of the epidemic (1920–1950), kuru—an acquired prion disease— killed up to 2% of the population annually. Most of the women survivors tested by researchers had a novel PrP variant G127V that was much less common in the younger population, indicating that it conferred substantial protection against the disease. At the time of publication in 2003, none of the patients who had, to date, contracted new vCJD in Britain carried the protective genotype. This suggests that this genotype is protective against prion diseases in humans. The researchers then examined DNA from various ethnic groups around the world and found that all, except the Japanese, carried the protective genotype to a similar degree. Genetic tests showed that this gene could not be there by chance but was a result of natural selection. This implies that ancestral human populations were exposed to some form of prion disease. Researchers concluded that fre quent epidemics of prion disease caused by cannibalism in human ances tors would explain the worldwide existence of the protective genotype in modern humans. Source: data from Mead S, Stumpf MP, Whitfield J, et al. (2003) Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. Science 300: 300, Issue 5619, pp. 640–643.

170 Chapter 4 Neuropsychiatry Amnestic disorders Amnestic disorders are syndromes characterized by memory impairment (anterograde and/or retrograde amnesia), which are caused by a gen eral medical condition or substance use and where delirium and dementia have been excluded as causative of the amnesia. Amnestic disorders may be transient or chronic (< or >1mth). Amnestic conditions usually involve some or all of the following neuroanatomical structures: frontal cortex, hippocampus and amygdala, dorsomedial thalamus, mamillary bodies, and periaqueductal grey matter (PAG). In terms of neurochemistry, glutamate transmission at the NMDA receptor is often implicated in amnesia, mainly due to its role in memory storage in the limbic system—long-term potenti ation (LTP). A number of amnestic disorders are recognized: Wernicke’s encephalopathy An acute syndrome, with a classic triad of symptoms (ataxia, ophthalmo plegia/nystagmus, and altered mental status), caused by thiamine depletion, usually related to alcohol abuse, and associated with pathological lesions in the mamillary bodies, PAG, thalamic nuclei, and the walls of the third ven tricle (E Wernicke–Korsakoff syndrome, p. 606). Korsakoff psychosis Amnesia and confabulation with atrophy of the mamillary bodies, associ ated with alcohol excess and Wernicke’s encephalopathy (E Wernicke– Korsakoff syndrome, p. 606). Vascular disease Aneurysm of the anterior communicating artery may result in amnestic dis order, but amnesia due to stroke is rare. Brain injury An open or closed brain injury involving acceleration or deceleration forces may result in injury to the anterior temporal poles (as this structure col lides with the temporal bone). Anterograde post-traumatic amnesia (PTA) is prominent, with retrograde amnesia relatively absent (E Traumatic brain injury, p. 172). Herpes simplex virus encephalitis Affects the medial temporal lobes and results in deficits in short-term memory (STM) storage. Treatment with IV aciclovir where the condition is suspected may prevent deficits from becoming permanent. Hypoxic brain damage Hypoxia following asphyxia from CO poisoning, near drowning, etc. may damage sensitive CA1 and CA3 neurons in the hippocampus. This results in problems with STM storage. Alcohol blackouts (‘palimpsest’) Significant alcohol intoxication may lead to amnesia

for the period of intoxi cation, usually in the context of chronic alcohol misuse.

Amnestic disorders Electroconvulsive therapy There may be a period of mild anterograde and/or retrograde amnesia for a few hours following administration of ECT. In exceptional cases, there may be reported ongoing patchy memory loss for up to 6–9mths (E Does ECT cause brain damage? p. 308). Transient global amnesia (TGA) This is a syndrome of amnesia and disorientation with repetitive questioning lasting 4–10hrs. Age 40–80. Aetiology remains unknown. Transient epileptic amnesia (TEA) Recurrent episodes of amnesia and disorientation lasting 30mins to 1hr, often occurring from sleep or on waking, due to medial temporal lobe seiz ures in epilepsy. Interictal EEG suggestive in 30%. Accelerated long-term forgetting leads to lacunes in remote autobiographical memory. Dissociative amnesia Sudden retrograde autobiographical memory loss, ranging from hours to years. May be associated with depersonalization or derealization (E Dissociative (conversion) disorders, p. 869). Other causes of amnesia Substances (BDZs, anticholinergics); SOLs (e.g. tumours); hypoglycaemia. NMDA receptor antibody encephalitis. (See Box 4.9.) Box 4.9 Patient HM On 23 August 1953, patient HM underwent a bilateral medial temporal lobotomy in an attempt to control his epileptic seizures. This resulted in severe anterograde memory impairment that made HM one of the most studied patients in the history of cognitive psychology, up until his death in 2008. HM’s syndrome was surprisingly isolated, with impairment mostly limited to his inability to register new facts into long-term memory, des pite immediate memory being preserved for both verbal and non-verbal tasks. Although his operation was performed when he was 27, his mem ories were intact until age 16, with an 11-year retrograde amnesia. His IQ was above average, with almost normal language production and comprehension—he could understand and produce complex verbal material (but was impaired on tests of semantic and symbolic verbal flu ency). His perceptual abilities were normal, except for his sense of smell (secondary to damage of the olfactory tracts). Despite the fact that some of his spatial abilities were compromised, he did not have any attentional deficit.

172 Chapter 4 Neuropsychiatry Psychiatric aspects of brain injury Terminology Acquired brain injury (ABI) can occur as a result of trauma [traumatic brain injury (TBI)], hypoxia/ischaemia, stroke, toxic or metabolic insult, infec tion, or any pathological process causing sudden, irreversible, and non- progressive damage to the brain after the neonatal period. Management of brain injury • The acute psychiatric effects of brain injury can be challenging to manage. Those who require psychiatric input after the acute period have emotional and cognitive symptoms ranging from subtle to severe. • There is strong evidence for benefits of early intensive neurorehabilitation after moderate and severe brain injury; after mild brain injury, patients benefit from information, advice, and follow-up (E Mild traumatic brain injury, p. 174). Traumatic brain injury TBI is a common cause of death and lifelong disability (largely due to neuro psychiatric sequelae) in young adults. Common causes are road traffic ac cidents, falls, and assaults; ♂ > ♀; alcohol is often a contributory factor. Improved life expectancy has, however, led to an increase in TBI in the frail elderly in high-income countries, shifting the age of peak incidence from 20s to 40s. Acute effects of traumatic brain injury • PTA (post-traumatic delirium)—extends from the time of the injury until normal memory resumes. PTA may end abruptly or merge gradually into persisting deficits. • Retrograde amnesia (RA)—includes the period between the last clearly recalled memory prior to the injury and the injury itself. It is usually a dense amnesia, lasting seconds or minutes, but can be difficult to assess where there has been prolonged PTA. Factors associated with poorer long-term outcome after traumatic brain injury • Conscious level post-injury (mild: GCS score

13–15; moderate: GCS score 9–12; severe: GCS score <8). • Duration of loss of consciousness. • i duration of PTA (>24hrs, poorer outcome). • Age (older—poorer prognosis). • Pre-injury educational or occupational level. • Reduced pre-injury cognitive reserve, e.g. due to cerebrovascular disease or alcohol dependence. Long-term sequelae of moderate/severe acquired brain injury Memory Difficulties learning new information are common after brain injury, especially involving damage to frontal or temporal lobes. Bilateral hippocampal damage after hypoxic–ischaemic injury (HII) can cause an amnestic syndrome. Treatment: frequent orientation, cognitive rehabilitation.

Psychiatric aspects of brain injury Executive dysfunction Diffuse or prefrontal lesions can cause a dysexecutive syndrome: difficulties with planning, judgement, abstract thought, sustained attention, and social cognition, leading to impulsive, socially inappropriate behaviour, poor frustration tolerance with aggres sive outbursts, and disorganization. This can cause significant disability and family distress, even in the absence of significant memory impairment. Treatment: aggression and irritability may respond to propranolol where there are no contraindications (e.g. asthma). Perceptual problems Visuospatial neglect or agnosia, cortical blindness (especially after HII), or optic nerve damage may be missed as reasons for failure to progress with rehabilitation. Visual or auditory misinterpretations may be mistaken for psychosis. Treatment: occupational therapy (OT) input and adaptations. Speech and language disorders Dysphasia, dysarthria. Mood and anxiety disorders Depression occurs in 25% of individuals after TBI and should be considered where cognitive or behavioural symp toms worsen months or years after injury. Apathy or emotional lability due to damage to the prefrontal cortex or limbic lobe are less likely to re spond to treatment. Anxiety occurs commonly. Treatment: SSRIs; consider duloxetine if comorbid pain. Psychosis Psychotic symptoms may appear as part of a post-traumatic delirium following brain injury. A schizophrenia-like psychotic disorder after brain injury occurs relatively rarely 1–5yrs after injury and is associated with frontal and temporal damage. Premorbid psychosis is a risk factor for brain injury. Treatment: antipsychotics. Sequelae in children Less psychopathology after ABI due to i brain plasticity. Recovery may con tinue for up to 5yrs after injury (as opposed to 72yrs in adults). Problems may include aggression and ADHD-like syndromes. Complications associated with neuropsychiatric deterioration • Hydrocephalus—can occur days to months after injury and is associated with deteriorating cognitive function, gait, incontinence, and depressed conscious level. Treatment: neurosurgical. • Post-traumatic epilepsy—occurs in 5% of closed and 30% of open head injuries, usually during the first year, and worsens prognosis. Treatment: antiepileptic medication.

174 Chapter 4 Neuropsychiatry Mild traumatic brain injury (concussion) Epidemiology The majority of presentations to hospital after TBI are with mild TBI. Although in the majority, symptoms resolve within days to weeks; a mi nority are troubled by persistent symptoms and may seek psychiatric advice. Definition (WHO) • GCS score of 13–15 30mins post-injury. • Loss of consciousness (LOC) 30mins or less. • PTA <24hrs. • Not due to alcohol, medications, penetrating craniocerebral injury, or treatment of other medical conditions or injuries. Clinical course Early (first 24hrs) Headache, blurred vision, dizziness, confusion, memory problems, fatigue, sleep disturbance. Depersonalization/derealization may be described as dizziness or confusion. First month after injury In most, all symptoms will resolve in the first days after mild TBI. Headache, dizziness [persisting dizziness should raise suspi cion of benign paroxysmal positional vertigo (BPPV), common after mild TBI and easily treatable], mild cognitive symptoms, and fatigue may persist in a few. Symptoms persisting >3mths after injury Cognitive function usually returns to baseline within

3mths. A minority of patients develop persistent symp toms such as memory and concentration difficulties, fatigue, headaches, dizziness, and sleep disturbance. Psychological factors related to injury are likely to be important—similar symptoms occur in non-brain-injured trauma patients. In many, the ‘post-concussional syndrome’ (a term best discarded) can be considered a secondary functional neurological disorder. Risk factors for persistent (‘post-concussional’) symptoms • Alcohol excess—alcohol excess is a risk factor for mild TBI; post-injury memory and concentration problems, fatigue, headache, irritability, and sleep difficulties may reflect ongoing alcohol use, and alcohol is likely to underpin the apparent i risk of epilepsy after mild TBI. • Age—older age is associated with persistent symptoms. • Social stressors—may be premorbid or relate to circumstances of the injury (commonly assault) or to lost income due work absence. • Depression and anxiety—psychological distress around the injury can give rise to specific or generalized anxiety, PTSD, or depression, all of which perpetuate fatigue and cognitive symptoms. • Unhelpful illness beliefs—beliefs that the brain has been irreversibly damaged or that there is a high risk of dementia seem more common in those with persisting symptoms. • Litigation/compensation issues—ongoing litigation is strongly associated with persisting symptoms.

Mild traumatic brain injury (concussion) Management Clear, reassuring explanation and advice soon after mild TBI may help to prevent persistent symptoms. Advice (See also M http://www.headinjurysymptoms.org) • Mild TBI has a good prognosis and rarely causes lasting problems. • Common symptoms occurring in the first few days—headache, poor concentration, tiredness, or dizziness—do not indicate ‘brain damage’. • The risk of developing serious complications is low. If ‘red flag’ symptoms (LOC, drowsiness, seizure, CSF leak, severe headache, or focal neurological symptoms) occur, return to the Emergency Department as soon as possible. Serious problems are rare beyond the first week. • Prolonged rest is likely to be unhelpful, and return as soon as is comfortable to normal activities should be recommended. • Severe disabling symptoms may benefit from CBT or graded exercise therapy (GET) where fatigue is prominent. Chronic traumatic encephalopathy (See Box 4.10.) Box 4.10 Chronic traumatic encephalopathy ‘Punch drunk’ syndrome, or encephalitis pugilistica, was a condition of cognitive and neurological deterioration first noted in retired professional boxers in the early 1900s. Chronic traumatic encephalopathy (CTE) is a more recently described syndrome, in which neuropsychiatric symptoms (e.g. cognitive impairment, personality change, fatigue, depression, and suicidality) occur many years after mild TBI, particularly in retired profes sional sports people who have sustained multiple concussions. Although CTE has been the subject of extensive media attention, its definition and existence are not strongly supported by scientific evidence. There have been no prospective longitudinal studies. Retrospective studies, vul nerable to inclusion and recall bias, revealed multiple confounding risk factors, including strikingly high levels of drug and alcohol use in retired professional sports people. In fact, review of all pathologically described cases has cast doubt on the existence of CTE as a widespread problem in American footballers;* neuropathological findings overlap with many common neurodegenerative disorders, and there appears to be no i risk of dementia after mild TBI.** So while concussion is best avoided, patients can be assured that current evidence suggests that mild TBI does not in crease the risk of later-life dementia.

- Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, Miele V (2015) Chronic traumatic encephalopathy in contact sports: a systematic review of all reported pathological cases. PLoS One 10:e0117338. ** Godbolt AK, Cancelliere C, Hincapié CA, et al. (2014) Systematic review of the risk of dementia and chronic cognitive im-pairment after mild

traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95:S245–56.

176 Chapter 4 Neuropsychiatry Psychiatric sequelae of stroke A range of psychiatric problems may occur following stroke. These include the following. Cognitive disorders • Vascular neurocognitive disorder (E Vascular dementia (vascular neurocognitive disorder), p. 164). • Non-progressive, e.g. after a single stroke. • Progressive—also called VaD. • Amnestic disorder—e.g. after ruptured anterior communicating artery (ACOM) aneurysm (E Amnestic disorders, p. 170). Post-stroke depression Depressive illness is common, occurring in around a third of patients after stroke.40 Depression may occur early or late during stroke recovery and may be missed in the presence of cognitive or communication impairment, and it is associated with poor functional outcome and excess morbidity and mortality.41 Risk factors for post-stroke depression Physical disability, stroke severity, and cognitive impairment are the most consistent predictors of depression after stroke. Women are affected slightly more often than men.42 Lesion location does not influence depres sion risk.43 Treatment: antidepressants are effective, especially for severe depression, although after stroke, they may bring a higher risk of adverse effects. SSRIs are most widely used and usually well tolerated.44 Personality changes and executive dysfunction Damage to frontal lobes can cause a constriction in the range of interests, loss of intellectual flexibility, apathy and loss of volition, irritability, and loss of social sensitivity. Pseudobulbar affect Also called pathological emotionalism, emotional incontinence, or patho logical laughter/crying. Present in up to 50% after stroke and in many other neurological disorders. Presentation involves emotional lability with unpro voked and uncontrollable crying or laughter, inconsistent with the patient’s subjective emotional state. May respond to treatment with an SSRI or amitriptyline. 40 Hackett ML, Yapa C, Parag V, Anderson CS (2005) Frequency of depression after stroke: a sys tematic review of observational studies. Stroke 36:1330–40. 41 Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB (2011) Depression and risk of stroke: morbidity and mortality. JAMA 306:1241. 42 Hackett ML, Anderson CS (2005) Predictors of depression after stroke: a systematic review of observational studies. Stroke 36:2296–301. 43 Carson AJ, MacHale S, Allen K, et al. (2000) Depression after stroke and lesion location: a sys tematic review. Lancet 356:122–6. 44 Hackett ML, Anderson CS, House A, Xia J (2008) Interventions for treating depression after stroke. Cochrane Database Syst Rev 4:CD003437.

Psychiatric sequelae of stroke Psychosis Circumscribed delusions may arise in individuals with profound anosognosia or somatoparaphrenia (denial of ownership of a limb or half of one’s body), almost always due to right-sided lesions. Schizophrenia-like psychotic dis orders occur rarely and have also been associated with right-sided lesions. Peduncular hallucinosis is a rare syndrome of complex visual hallucinations associated with infarcts involving the pons and the midbrain.