24.7 Disorders of movement 5937 24.7.1 Subcortical

24.7 Disorders of movement 5937 24.7.1 Subcortical structures: The cerebellum, basal ganglia, and thalamus 5937 Mark J. Edwards and Penelope Talelli

24.6.3 Hearing loss 5931 FURTHER READING Brandt T, Dieterich M, Strupp M (2013). Vertigo and dizziness— common complaints. 2nd edition. Springer, London. Brandt T, Dieterich M (2017). The dizzy patient: don't forget disorders of the central vestibular system. Nat Rev Neurol, 13, 352–62. Brandt T, Steddin S, Daroff RB (1994). Therapy for benign parox- ysmal positioning vertigo, revisited. Neurology, 44, 796–800. Brandt T, Strupp M, Dieterich M (2015). Five keys for diagnosing most vertigo, dizziness, and imbalance syndromes: an expert opinion.
J Neurol, 261, 229–31. Herdman, SJ, Clendaniel R (2014). Vestibular rehabilitation, 4th edi- tion. FA Davies, Philadelphia, PA. Leigh RJ, Zee DS (2015). Neurology of eye movements, 5th edition.
FA Davies, Philadelphia, PA. Lempert T, et al. (2012). Vestibular migraine: diagnostic criteria.
J Vestib Res, 22, 167–72. Lopez-Escamez JA, et al. (2015). Diagnostic criteria for Menière's dis- ease. J Vestib Res, 25, 1–7. Staab JP, Eckhardt-Henn A, Horii A et al. (2017). Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Barany Society. J Vestib Res, 27, 191–208. Strupp M, et al. (2014). Central ocular motor disorders, including gaze palsy and nystagmus. J Neurol, 261

Suppl 2, S542–58. Strupp M, et al. (2015). Pharmacotherapy of vestibular and cere- bellar disorders and downbeat nystagmus: translational and back- translational research. Ann N Y Acad Sci, 1343, 27–36. Strupp M, Kim JS, Murofushi T et al. (2017). Bilateral vestibulopathy: Diagnostic criteria Consensus document of the Classification Committee of the Barany Society. J Vestib Res, 27, 177–89. Strupp M, Lopez-Escamez JA, Kim JS et al. (2016). Vestibular paroxysmia: diagnostic criteria. J Vestib Res, 26, 409–15. von Brevern M, Bertholon P, Brandt T et al. (2015). Benign par- oxysmal positional vertigo: Diagnostic criteria. J Vestib Res, 25, 105–17. 24.6.3 Hearing loss Linda Luxon Our hearing is a choice and dainty sense, and hard to mend, yet soon it may be marred. Blows, falls and noise . . . all these . . . breed tingling in the ears and hurt our hearing. Physicians of the Medical School of Salerno ESSENTIALS The World Health Organization has estimated that 360 million people worldwide are affected by disabling hearing loss, making hearing impairment—the hidden handicap frequently overlooked by all clinicians—the most common sensory impairment. Most of those affected are in low- and middle-income countries, but 17% of the adult population in the United Kingdom are affected, with three- quarters being over 60 years of age. Causes may relate to cochlear, neurological, general medical, or iatrogenic pathology, with half of all cases being preventable by primary prevention. Clinical examination includes visual inspection of the anatomy of the external ear and tympanic membrane, and tuning-fork tests, which may distinguish conductive from sensorineural hearing loss. Audiological investigations will (1) identify impairment (i.e. quan- tify audiometric thresholds at each frequency) and (2) determine the site of pathology (i.e. differentiate conductive from sensorineural de- fects); differentiate cochlear from retrocochlear abnormality; define central auditory dysfunction in the brainstem, midbrain, or auditory cortex and identify nonorganic loss. Epidemiology and causes—(1) Prevalence in adults—factors include age, gender, genetic susceptibility, occupational group, ototoxicity, smoking, drinking, obesity, head injury, and hazardous noise ex- posure. (2) Congenital hearing impairment in children—over one- half of cases are explained by factors associated with admission to a neonatal intensive-care unit, genetic factors, and craniofacial ab- normalities. (3) Acquired hearing impairment in children—the com- monest cause is a conductive hearing loss due to chronic secretory otitis media; meningitis (particularly meningococcal) is the com- monest cause of acquired sensorineural hearing loss in the United Kingdom. (4) Many of the preventable causes of hearing impairment remain common in the developing world: consanguineous mar- riages, birth trauma, childhood infections, noise exposure, and the unlicensed sale of ototoxic drugs. Treatment—this may involve (1) protection from noise hazards and ototoxic drugs and management of chronic secretory otitis media; (2) auditory rehabilitation—including environmental aids, Box 24.6.2.5 Vestibular migraine Clinical features • At least five attacks of vertigo/dizziness, duration 5 min to 72 hours • Migraine or history of migraine • More than 50% of the attacks associated with migraineous symptoms Examination finding During the attack • Pathological spontaneous or positional nystagmus (about 70%) • Postural imbalance (about 90%) During the attack-free interval • Central ocular motor signs (>60%) less severe than in the attack • Peripheral vestibular deficit (10–20%) Incidence/age/sex • The most frequent cause of spontaneous recurrent attacks of vertigo • In children the most frequent cause of any vertigo and dizziness • Females are more often affected than males (about 2:1) Management of vestibular migraine • Treatment of attacks with aspirin (not in children) or other nonsteroidal anti-inflammatory drug (NSAID) and dimenhydrinate • Prophylactic treatment with β-blocker, topiramate, or valproic acid, if patient has more than two attacks per month

section 24 Neurological disorders 5932 instruction in communication skills, and (if accepted by the patient) hearing aids; (sometimes) (3) surgery—restorative in some cases of conductive hearing loss; implantable devices for totally deafened adults and children; and (4) psychological/social support to ad- dress the increased prevalence of mental health disorders, isola- tion, and limited occupational choices associated with significant hearing loss. Tinnitus Defined as a noise in the head or ears lasting for more than five minutes and unrelated to an external stimulus. Tinnitus increases in frequency with age, affecting about 20% of people over 60 years,
although only 4% complain of the symptoms. However, 1–2% report severe impairment of quality of life. It can be associated with many conditions, frequently in association with hearing impairment. Management—this is primarily medical, including the following interventions: (1) psychological—explanation of tinnitus mechan- isms, cognitive behavioural therapy, or tinnitus retraining therapy and, if necessary, treatment of anxiety/depression; (2) prosthetic— provision of hearing aids, noise generators to 'mask' tinnitus with desirable environmental noise; and (rarely) (3) pharmacological— intravenous lidocaine (lignocaine) can result in the disappearance or amelioration of tinnitus, but the short duration of the effect
and the adverse reactions prevent its use. There is no evidence to support pharmacotherapy in reducing the severity and intrusiveness of tinnitus. Hearing loss Pathophysiology For clinical purposes the ear is separated into three parts: the ex- ternal, middle, and internal ear (Fig. 24.6.3.1). The external ear is important in funnelling sound to the tympanic membrane and in the localization of sound. The middle-ear ossicles connect the tym- panic membrane to the oval window of the cochlea, such that sound waves cause displacement within the fluid-filled compartment of the membranous labyrinth. Within the internal ear, the mechanical ac- tivity at the oval window is transduced into neural responses by the hair cells of the organ of Corti (Fig. 24.6.3.2). Disorders of the external and middle ear result in abnormalities of the mechanical transmission of sound from the environment to the internal ear, and give rise to a conductive hearing loss (i.e. bone-conducted sounds are louder than air-conducted sounds). Common examples include impacted wax, serous otitis media (glue ear), chronic otitis media, and disorders of the ossicular chain (e.g. otosclerosis, and traumatic discontinuity). Disorders of the internal ear and cranial nerve VIII characteristic- ally give rise to a sensorineural hearing loss, in which the perception of both bone- and air-conducted sounds is reduced and the appreci- ation of the intensity of sound and the frequency resolution of com- plex sounds are impaired. Many conditions may affect the cochlea, ranging from inherited, congenital, or iatrogenic nonsyndromal or syndromal malformations to ototoxic damage (aminoglycoside, antimalarial, loop diuretics, chemotherapeutic drugs), ischaemia including in the posterior circulation, vasculitides, infections (mumps, rubella, syphilis, cytomegalovirus), autoimmune dis- orders, degenerative disorders, trauma, and idiopathic conditions such as Menière's disease. Much doubt has been cast on so-called 'presbyacusis', which may merely reflect an accumulation of toxic/ traumatic insults to the ear over many years, and recent advances in molecular biology and genetics have shown the role of genetic mutations/deletions in late-onset/progressive hearing impairments. Sudden sensorineural hearing loss, usually of cochlear origin, most commonly results from viral, vascular, or autoimmune disease. Importantly, recent studies have emphasized auditory plasticity with tonotopic reorganization in the auditory cortex, following audi- tory stimulation both with hearing aids and cochlear implantation. Pathology of cranial nerve VIII leading to auditory neuropathy and hearing impairment may present as an isolated phenomenon, but has also been defined in genetic disorders, including spinocerebellar degenerations, trauma, cerebellopontine angle tumours, bony dis- orders such as Paget's disease, infective disorders (meningitis) and inflammatory conditions

(sarcoidosis). Central auditory disorders may be developmental or acquired in origin and present with difficulties hearing in background noise and discriminating degraded speech (e.g. over a loudspeaker), and with sound localization, often with a normal or near-normal audiogram. Unilateral neurological pathology rarely gives rise to an audiometric hearing impairment as a consequence of bilateral representation of each cochlea at every level of the central auditory pathway above the cochlear nuclei. Rarely, bilateral brainstem pathology may present as a symmetrical sensorineural hearing loss, whereas bitemporal cor- tical pathology may give rise to cortical deafness or auditory agnosia. Clinical examination Clinical examination requires examination of the anatomy of the ex- ternal ear to define visible signs of congenital ear disease (pits, tags, nodules, or malformations) and evidence of other craniofacial fea- tures suggestive of syndromal hearing impairment. In addition, a detailed examination of the tympanic membrane is required to de- fine the presence of pathology within the middle ear. Wax or debris obstructing the external auditory meatus should be removed by or under the supervision of an experienced clinician. Syringing is External auditory meatus Pinna Tympanic membrane Eustachian tube Semicircular canals Ossicles Oval window Cochlea Vestible External ear ear Internal ear Eighth nerve Middle Fig. 24.6.3.1 Diagram to illustrate the anatomy of the peripheral auditory system.

24.6.3 Hearing loss 5933 contraindicated in the presence of an infection or possible tympanic membrane perforation. Tuning-fork tests (Fig. 24.6.3.3) remain the most valuable clinical test of auditory function and frequently enable a clinician to distinguish a conductive from a sensorineural hearing loss. The tests are based on two physiological facts: first, the inner ear is normally more sensitive to sound conducted by air than to that conducted by bone; second, in the presence of a purely con- ductive hearing loss, the affected ear is subject to less air-conducted environmental noise, making it more sensitive to bone-conducted sound. A general medical and neurological examination is manda- tory to define syndromes and the plethora of general medical con- ditions associated with hearing impairment. A detailed vestibular assessment is also of value. Investigations A battery of audiological tests is required to: • quantify audiometric thresholds at each frequency • differentiate a conductive from a sensorineural hearing loss • differentiate a cochlear from a retrocochlear abnormality • identify central auditory dysfunction in the brainstem, midbrain, or auditory cortex • identify a nonorganic component Tests can be defined as subjective or objective (i.e. dependent or in- dependent of patient cooperation) in terms of providing auditory data. Two pathophysiological phenomena are of importance in the dif- ferentiation of a cochlear, sensorineural hearing loss from a neural VIII nerve or cochlear nuclei dysfunction: • Loudness recruitment is defined as an abnormally rapid increase in loudness, with an increase in intensity of the stimulus, and is characteristic of disorders affecting the hair cells of the organ of Corti, but is absent in the pathology of nerve VIII. • Abnormal auditory adaptation is a decline in discharge frequency with time, observed after an initial burst of neural activity in re- sponse to an adequate continuing stimulus applied to the organ of Corti. This phenomenon is characteristic of nerve VIII and brain- stem auditory dysfunction. Pure-tone audiometry is the most widely available, subjective, quan- titative test of auditory thresholds. Electronically generated pure tones are delivered by earphones and the individual is required to respond to the quietest tone, at given frequencies between 125 and 8000 Hz in each ear. The sound may be delivered by air con- duction or, if the tones are delivered by a bone vibrator on the mastoid process, by bone conduction. In the latter test condition, as the intra-aural attenuation for a bone-conducted sound is neg- ligible, masking of the ear not under test with narrow-band noise is mandatory. Bone-conduction thresholds significantly better than air-conduction thresholds (Fig. 24.6.3.4a) indicate a conductive

hearing loss, whereas similar bone-conduction and air-conduction thresholds (Fig. 24.6.3.4b) are characteristic of sensorineural (i.e. cochlear or neural hearing loss). Impedance studies. The middle ear stapedius muscle contracts bi- laterally in response to loud sound, directed into either ear. Using an impedance bridge, the minimum intensity of sound at a given fre- quency required to this response and thus a movement of the tym- panic membrane, can be measured (the acoustic reflex threshold). This objective measure enables recruitment and abnormal auditory adaptation to be measured, and allows assessment of middle ear, cochlear, nerve VIII, and brainstem auditory function. Scala vestibuli Reissner's membrane Spiral limbus Inner sulcus Cochlear nerve fibres Osseous spiral lamina Habenula perforata Inner rod Tunnel of Corti Scala tympani Basilar membrane Spiral ligament Outer sulcus Stria vascularis Claudius' cells Hensen's cells Deiter's cells Outer hair cells Reticular lamina Scala media Tectorial membrane Outer rod Inner hair cell
Fig. 24.6.3.2 Diagram of the organ of Corti. (c) (b) (a) S S S Fig. 24.6.3.3 Diagram to illustrate the Weber tuning-fork test in (a) a normal individual, (b) a case of unilateral sensorineural hearing loss, and (c) a case of unilateral conductive hearing loss, in which the sound is heard more effectively in the affected ear because of the lack of masking by environmental sounds. S, direction sound heard; o, tuning-fork placement.

section 24 Neurological disorders 5934 Otoacoustic emissions are weak signals that can be recorded in the ear canal and are the result of contractile properties of the outer hair cells of the cochlea. Measurement of otoacoustic emissions, thus provides objective information about cochlear function and has become the mainstay of universal neonatal hearing screening. Suppression of the otoacoustic emissions by delivery of sound to the contralateral ear allows a measure of efferent auditory function and is of particular diagnostic value in neurological diseases affecting auditory function. Speech audiometry is a subjective test requiring the individual to repeat standardized lists of words delivered at varying intensities through headphones. The responses are scored and provide an as- sessment of auditory discrimination. They are of particular value in assessing the efficacy of hearing-aid provision. Electrophysiological tests provide the major objective means of assessing auditory function and siting pathology in the auditory system. Electrocochleography enables the measurement of the elec- trical output of the cochlea and cranial nerve VIII in response to an auditory stimulus, whereas brainstem auditory-evoked responses are of particular value in discriminating between cochlear and nerve VIII cochlear nuclei dysfunction (Fig. 24.6.3.5). Recordings are obtained by averaging a series of time-locked responses gen- erated by the major processing centres of the auditory system in response to a repetitive sound stimulus. Analysis of the waveform must be undertaken in conjunction with knowledge of the pure- tone thresholds to interpret the responses appropriately. Modifications of the test technique (e.g. use of 1000 Hz tone burst and binaural rapid rate stimulation) may facilitate clinical iden- tification or monitoring of intracranial lesions. Middle latency responses are generated in the thalamocortical pathway in the audi- tory cortex and, despite some practical difficulties, are deemed to be a valid objective test in the assessment of central auditory dys- function, although sleep and/or sedation may affect the response. Cortical- or late-evoked auditory responses are the most effective method of defining auditory threshold at each frequency in a pa- tient, who is unable or unwilling to cooperate and are essential in legal cases, in which a nonorganic loss should always be excluded. Behavioural tests of central auditory function, include subjective tests of monaural low-redundancy speech; pattern recognition, such as the frequency pattern test and duration pattern test, which rely primarily on right hemisphere function; auditory temporal reso- lution, such as the Gaps-in-Noise and dichotic speech, which relies on an intact corpus callosum to transfer information from

the right to left hemisphere. Vestibular investigations and imaging are frequently required to confirm a diagnosis (e.g. congenital inner-ear anomaly, Menière's disease, and acoustic schwannoma), whereas cardiac, renal, gastro- intestinal, endocrine, and metabolic investigations may be highly relevant in specific cases (e.g. Jervell–Lange–Neilsen syndrome, aminglycoside ototoxicity, collagen vascular disease, ulcerative col- itis, Pendred syndrome, and autoimmune disorders). Right –20 –10 0 10 20 30 40 50 60 70 80 90 100 110 120 Hearing level (dBISO) 125 250 500 1000 2000 4000 6000 Frequency (Hz) Right Bone condition Left Masked Frequency (Hz) –20 –10 0 10 20 30 40 50 60 70 80 90 100 110 120 Hearing level (dBISO) 125 250 500 1000 2000 4000 6000 Left (a) (b) Fig. 24.6.3.4 Pure-tone audiograms showing both air- and bone-conduction thresholds and illustrating a right conductive hearing loss (a) and a left sensorineural hearing loss (b). 0 2 LL 0.3 V V III I V III II I RR 10 8 6 4 Fig. 24.6.3.5 Illustration of auditory-evoked brainstem responses showing normal waves I, II, III, and V from the right ear (RR) and delayed waves III and V from the left ear (LL), in a case of a left acoustic neurinoma.

24.6.3 Hearing loss 5935 Management Appropriate management of both acute and chronic hearing loss re- quires a detailed history and examination to ensure both appropriate management of related general medical, neurological, and oto- logical conditions and protection from leisure (discothèques) and occupational noise hazards, and ototoxic drugs. Conductive hearing loss due to trauma, chronic middle-ear disease, or otosclerosis may be surgically remediable, whereas recent animal studies have highlighted the possible future role of antioxidants in the ameli- oration of sensorineural hearing loss caused by chemotherapeutic agents, aminoglycoside antibiotics, and noise. Sudden sensorineural hearing loss is deemed to be a medical emergency, but there are no randomized controlled trials confirming the efficacy of the various therapeutic interventions advocated: steroids, antiviral agents, and haemodilution techniques. Auditory rehabilitation is a problem-solving exercise centred on each individual patient, and depends on assessing both the audi- tory disability of the individual and the relevance of this to other important people in the patient's life. Not only auditory impairment, but also communication skills, including lip-reading ability, the use of visual cues, and the level of speech and language, together with psychological and sociological factors, must be considered. The remedial process may be straightforward in a highly motiv- ated patient in whom there is an uncomplicated hearing loss, al- though over-the-counter aids, without expert consultation, are in general less satisfactory than those prescribed following assessment. However, in the presence of a complicating factor, such as a hearing loss which is difficult to improve with a hearing aid (e.g. an audi- tory neuropathy or a patient with physical handicap (e.g. arthritis making hearing aid manipulation difficult), the particular problem must be addressed to ensure optimal support). In patients who have a negative view of hearing aids, environmental aids, and instruction in communication skills before the introduction of a hearing aid may facilitate long-term rehabilitation. In general, the provision of a hearing aid is effective only when the patient themselves, rather than well-meaning family members, wishes to get help. Although hearing aids play a pivotal role in audiological rehabili- tation, a detailed description of their provision and selection is out- side the scope of this chapter. For many patients, wearable hearing aids, which bring sound more effectively to the ear, are invaluable, but environmental aids (assisted-listening devices such as amplification systems, alerting warning devices, e.g. flashing lights connected to a doorbell or an alarm clock) may be adequate. In addition, sensory substitution systems, for example, where visual signals are generated in response to auditory cues such as a telephone or doorbell ringing, or a baby crying, may be helpful to a hearing-impaired person. The general principles of hearing-aid provision include the fitting of a

comfortable ear mould, which provides a secure mounting for the aid and a good acoustic connection between the aid and the ear canal. Hearing-aid selection involves matching the amplification output of the aid at specific frequencies with that required by the user. A particular disability experienced in most hearing-impaired people is that of hearing speech in a noisy environment and, although pro- grammable digital processing hearing aids are of some help in this situation, conventional aids provide selective amplification of the frequencies relevant to speech, with minimal amplification at the peak frequency of background noise. For patients with a markedly asymmetric sensorineural loss, the better hearing ear is usually amp- lified, while for patients with bilateral symmetrical loss, bilateral amplification generally results in better outcomes. Conventional aids may be divided into body-worn and head-worn aids, which can be in spectacles, behind the ear, in the ear, or in the canal in design. The major advantage of body-worn aids is the very high gain and max- imum output that can be achieved, whereas the disadvantage is the unsightly nature of the device and the poor microphone placement. Cochlear implantation is one of the most significant advances in modern medicine, which transforms the life of patients with pro- found hearing loss. It carries a low major complication rate of ap- proximately 4%, although, usually transient, vestibular symptoms are common. Electronic devices convert sound into electrical cur- rent for the purpose of directly stimulating residual auditory nerve fibres to produce hearing sensations. The devices are implanted in the cochlea, usually with an electrode array, with an externally worn microphone and processor. Bilateral cochlear implants have been used, more effectively than unilateral implantation, in totally deafened adults and children with good results, and should be con- sidered in all cases of profound acquired hearing loss and in chil- dren in whom there is good evidence of auditory nerve preservation in both congenital and acquired hearing impairment. Recent ad- vances have demonstrated the benefit of cochlear implantation in single sided sensorineural hearing loss case, hearing preservation after cochlear implantation and the use of ‘short’ electrodes in iso- lated high frequency loss. Current work aims to develop a totally implantable device avoiding the use of an external microphone, pro- cessor, and transmitting coil. In the bilateral absence of a functional cranial nerve VIII (e.g. neurofibromatosis) brainstem implants have been shown to be of value. The value of counselling for the hearing-impaired person by a skilled hearing therapist must be emphasized. Such simple hearing tactics as encouraging the individual to ensure that the light is al- ways on the speaker’s face, that he or she places himself so that the better ear is towards the speaker, and sitting close to the sound source thereby minimizing background noise, can greatly improve communication ability. For profoundly hearing-impaired individ- uals, psychological problems associated with isolation and occu- pational handicaps are significant and it is therefore essential that psychological, medical, and social support are readily available. Tinnitus Tinnitus may be defined as a perception of sound that originates from within the head rather than from within the external world. Rarely, the sound may have an externally detectable component and is then termed ‘objective tinnitus’ as opposed to the more common ‘subjective tinnitus’. Less than 10% of tinnitus sufferers will report pulsatile tinnitus. The experience of tinnitus is universal, but the complaint of tinnitus is rare. Many conditions are associated with tinnitus, but it is frequently, although not always, associated with hearing impairment. The pro- posed pathophysiological mechanisms include: • decoupling of the stereocilia of the hair cells • misinterpretation of auditory neural activity by higher auditory centres

 • self-sustaining oscillation of the basilar membrane • spontaneous optoacoustic emissions • an abnormality of the spontaneous resting activity of primary audi- tory nerve fibres, either secondary to the hypo or hyperexcitability of damaged hair

cells or as a direct consequence of the derange- ment of primary neurons themselves • damage to the myelin sheath between auditory nerve fibres, allowing ephaptic transmission (cross-talk) between adjacent nerve fibres • derangement of efferent fibres of the vestibulocochlear nerve, pro- ducing aberrant auditory behaviour Several studies have demonstrated that tinnitus complaint does not correlate with psychoacoustic features of the tinnitus, but there is a significant correlation between tinnitus complaint and psycho- logical symptoms. Importantly, the onset of tinnitus complaint may be associated with negative life events such as retirement, redun- dancy, bereavement, and divorce. The assessment of tinnitus includes a detailed history, clinical examination, and audiometric investigation as outlined for hearing impairment. The most common causes of objective tinnitus include palatal myoclonus, temporomandibular joint abnormalities, vascular abnormalities such as an arteriovenous fistula, and vascular bruits. Rarely, a patulous auditory tube may give rise to tinnitus, in which the patient complains of a blowing sound associated with respiration. Bilateral subjective tinnitus with evidence of a cochlear hearing loss is associated most commonly with presbyacusis, endolymphatic hydrops, vascular labyrinthine lesions, and noise-induced hearing loss. However, it is also common with head injury, whiplash injury, ototoxicity, barotrauma, surgical intervention, and after such simple clinical practices as syringing. Unilateral subjective tinnitus, with or without an associated sensorineural hearing loss, must be fully in- vestigated to exclude an underlying cerebellopontine angle lesion, in particular an acoustic neurinoma. Pulsatile tinnitus may be related to changes in blood flow with turbulence, or normal flow sounds, which are perceived more intensely, secondary to increased bone conduction or loss of the masking effect of environmental sounds. Despite detailed investigation, including imaging, up to 30% of cases remain undiagnosed. Management The primary management of tinnitus is medical, although surgical intervention is required for the correction of arterial stenosis, giving rise to bruits, for glomus jugulare tumour and arteriovenous mal- formations. Destructive surgery (e.g. labyrinthectomy or auditory nerve section), has no place in the management of tinnitus as there is no evidence that destruction of the peripheral cochlear elements brings about improvements in tinnitus complaint. The medical management of tinnitus can be divided into psy- chological, pharmacological, and prosthetic intervention. The psychological management includes an explanation of tinnitus, reassurance that the symptom will not progressively deteriorate or indeed remain unchanged, the exclusion of sinister pathology to allay fear, and, if necessary, the appropriate formal psychiatric management of depression/anxiety. Cognitive behavioural therapy and mindfulness have both been demonstrated to be effective management strategies. In the presence of a hearing impairment, the provision of hearing aids to ‘mask’ tinnitus with desirable en- vironmental noise may be of value. In the absence of such a loss, tinnitus maskers and noise generators have been advocated to pro- mote ‘adaptation’, but there is no evidence that tinnitus maskers are superior to placebo devices. Pharmacologically, intravenous lidocaine has been shown to result in the disappearance or ameli- oration of tinnitus, but there is no evidence to support pharma- cotherapy in reducing the severity and intrusiveness of tinnitus. Psychiatric drugs may be required for psychological management, although no single drug has been shown to be uniformly effective. Tinnitus retraining therapy is a management strategy based on a neurophysiological model of tinnitus. The retraining is a com- bination of prosthetic and psychological intervention, which in essence provides a structured framework for the various well- established mechanisms of tinnitus management outlined earlier in this chapter. In conclusion, positive reassurance, appropriate psychiatric management, and prosthetic support remain the main- stays of the medical management of tinnitus. FURTHER READING Davies R, et al. (2016) Neuro-otology: problems of dizziness, balance and hearing. In: Clarke C, et al. (eds) Neurology: a queen square textbook, 2nd

edition. John Wiley and Sons Inc, New York, NY. Moller A (2012). Hearing: anatomy, physiology, and disorders of the auditory system. Plural Publishing. San Diego, CA.

24.7 Disorders of movement CONTENTS 24.7.1 Subcortical structures: The cerebellum, basal ganglia,
and thalamus 5937 Mark J. Edwards and Penelope Talelli 24.7.2 Parkinsonism and other extrapyramidal diseases 5946 Elisaveta Sokolov, Vinod K. Metta, and K. Ray Chaudhuri 24.7.3 Movement disorders other than Parkinson's disease 5956 Bettina Balint and Kailash Bhatia 24.7.4 Ataxic disorders 5976 Nicholas Wood 24.7.1 Subcortical structures:
The cerebellum, basal ganglia,
and thalamus Mark J. Edwards and Penelope Talelli ESSENTIALS Less is known of the function of the cerebellum, thalamus, and basal ganglia than of other structures in the brain, but there is an increasing appreciation of their complex role in motor and nonmotor functions of the entire nervous system. These structures exercise functions that far exceed their previously assumed supporting parts as simple 'relay stations' between cortex and spinal cord. The subcortical structures receive massive different inputs from the cerebral cortex and peripheral sense organs and stretch receptors. Through recurrent feedback loops this information is integrated and shaped to provide output which contributes to scaling, sequencing, and timing of movement, as well as learning and automatization of motor and nonmotor behaviours. Cerebellum Functional neuroanatomy—the cerebellum can roughly be divided into (1) vestibulocerebellum—integration of vestibular information; (2) spinocerebellum—integration of sensory information from the body; (3) pontocerebellum—integration of information from the cortex regarding planned or ongoing movement. Function—these are proposed to be as follows: (1) a timing device for movement; (2) facilitation of motor learning; and (3) facilitation and correct scaling and harmonization of muscle activity. Clinical features of cerebellar lesions—these include impairment of movement with dysmetria ('past-pointing'), dysdiadochokinesia, truncal and gait ataxia (in midline vermal lesions), dysarthria, and ab- normal eye movements (commonly nystagmus). Basal ganglia Functional neuroanatomy—the basal ganglia participate in multiple parallel loops which take information from different (mainly cortical) areas and then feedback (mainly) to those same areas. Input is mainly from the striatum; output comes almost exclusively from either the globus pallidus interna or the substantia nigra pars reticulate, which send inhibitory projections to the thalamus; dopamine is the main neurotransmitter that regulates activity. Function—four main roles are hypothesized: (1) release of desired movement from inhibitory control; (2) inhibition of undesired move- ment; (3) facilitation of sequential automatic movements; (4) in- tegration of attentional, reward, and emotional information into movement and learning. Clinical features of basal ganglia lesions—these include rigidity, akinesia, and dystonia. Thalamus Functional neuroanatomy—the thalamus receives afferent input from the special senses, basal ganglia, cerebellum, cortex, and brainstem reticular formation; efferent output is mainly directed to cortical areas and striatum. Function—the main thalamic functions are thought to include (1) modulation of sensory information by integration of brain- stem (in particular reticular activating complex) and relevant cortical information; and (2) modulation of cortical activity via cortico-thalamocortical loops. Clinical features of thalamic lesions—these include (1) sensory abnormalities—ranging from loss to deep-seated, severe pain; (2) motor disorders (e.g. hemiplegia); and (3) movement abnormal- ities (e.g. myoclonus, dystonia) usually in the context of lesions also involving the basal ganglia.

section 24 Neurological disorders 5938 Cerebellum Gross anatomy The cerebellum is located in the posterior fossa, bordered above by the tentorium cerebri and below by the foramen magnum. Anteriorly it borders the lower pons and medulla, separated from them by the fourth ventricle. The cerebellum is connected to the pons and medulla by the superior, middle, and inferior cerebellar peduncles. Afferents to the cerebellum enter largely through the in- ferior and middle peduncles, whereas most of the cerebellar effer- ents exit through the superior cerebellar peduncle. The cerebellum receives its blood supply from the posterior circulation via (rostrally to caudally) the superior, anteroinferior, and posteroinferior cere- bellar arteries. The anatomical divisions of the cerebellum (as is the case for the other subcortical structures discussed here, particularly the thal- amus) are complicated by several overlapping classifications. The simplest anatomical division of the cerebellum is into the two cere- bellar hemispheres and the midline structure called the vermis. A further division is into the flocculonodular lobe, comprising a nodular structure at the base of the cerebellum and an adjacent area of the hemisphere, the anterior lobe—the part of the cerebellum rostral to the primary fissure—and the posterior lobe—the part of the cerebellum caudal to the primary fissure. This division is in line with the proposed evolutionary development of the cerebellum, something that underlies an alternative classification scheme dividing the cerebellum into archicerebellum (flocculonodular lobe, receiving mainly vestibular input), paleocerebellum (anterior lobe, receiving mainly spinal cord input), and neocerebellum (pos- terior lobe, receiving mainly cerebral cortical input via the pons). Deep within the cerebellum are the cerebellar nuclei, which both re- ceive input and produce output from the cerebellum. These nuclei, medially to laterally, are called the fastigial, globose, emboliform, and dentate nuclei. Cytoarchitecture The cellular architecture of the cerebellum is complex but remark- ably uniform (Fig. 24.7.1.1). It comprises five cellular types: Purkinje cells, granule cells, basket cells, Golgi cells, and stellate cells. These are arranged in three distinct cortical layers. These are, from the out- side in, the molecular layer (layer 1), the Purkinje cell layer (layer 2), and the granule cell layer (layer 3). Afferent input arrives at the cerebellum in the form of mossy fibres and climbing fibres. These are excitatory neurons arising from the input structures to the cere- bellum. Only the inferior olivary complex sends mossy fibres to the cerebellum, with the rest of the input structures sending climbing fibres. These fibres may synapse on cerebellar nuclei or ascend into the cerebellar cortex directly. The only efferents from the cerebellum are the axons of Purkinje cells. Mossy fibres synapse with granule cells in layer 3, the axons which then ascend to layer 1, there forming parallel fibres that synapse with the dendrites of Purkinje cells directly, or synapse with basket cells and stellate cells in layer 1; these, in turn, form synaptic connections with dendrites of Purkinje cells. Climbing fibres ascend directly to layer 1 where they synapse with the dendrites of Purkinje cells. Axons of Purkinje cells give off collaterals as they descend both to adjacent Purkinje cells and to Golgi cells that lie in the outer part of layer 3. Functional anatomy The aforementioned brief description of cerebellar gross and cellular architecture goes some way to showing how the cerebellum is well placed to integrate a large amount of afferent information and to provide output of this integrated information to many cerebral and spinal targets. A first step to understanding the functional anatomy of the cere- bellum is to consider the main input and output pathways. The cere- bellum can roughly be divided into three functional areas, which receive particular inputs and produce output to particular areas either directly via the axons of Purkinje cells or via synapses of Purkinje cell axons on to cerebellar nuclei, which then connect to other structures. Vestibulocerebellum The main input is afferent fibres from the ipsilateral vestibular ganglion and vestibular nucleus, and the contralateral inferior oli vary complex. This input either goes directly to the flocculonodu lar lobe or reaches there via the fastigial nucleus of the cerebellum. Output is to

the vestibular nuclei either directly or via the fastigial nucleus. Spinocerebellum The main inputs are ipsilateral cutaneous and proprioceptive affer- ents from the body and face via dorsal and ventral spinocerebellar, cuneocerebellar, trigeminocerebellar, and spinoreticular tracts. Further input comes from motor and sensory areas of the cerebral cortex and vestibular nuclei via pontine reticulospinal nuclei and the contralateral red nucleus, and from the contralateral inferior olivary complex. All these inputs either go directly to the anterior lobe of the cerebellum, or reach there via synapses in the globose and emboliform nuclei. Output, either direct or via these same cere- bellar nuclei, goes to the pontine reticular nuclei, the contralateral red nucleus, and a major projection to the contralateral posterior division of the ventrolateral nucleus of the thalamus. Output Cerebellar Hemispheres Flocculonodular lobe Mossy fibres Climbing fibres Intrinsic nuclei Vestibular nuclei Precerebellar nuclei Cerebral cortex Olive Pontine nuclei Spinal cord Fig. 24.7.1.1 A simplified diagram showing the principal afferents to cerebellar cortex and to intrinsic cerebellar nuclei. Both mossy (left) and climbing (right) fibre inputs project to both cortex and intrinsic nuclei.

24.7.1 Subcortical structures 5939 Pontocerebellum This receives input from the contralateral pontine nuclei, which in turn receive massive input from widespread areas of cerebral cortex, particularly the frontal and parietal lobes. Input is also received from the contralateral inferior olivary complex. Input either proceeds dir- ectly to the posterior lobes of the cerebellum or reaches there via synapses in the dentate nucleus. Output (either direct or via synapses in the dentate nucleus) goes to the contralateral red nucleus and to the cortex via the contralateral posterior division of the ventrolateral nucleus of the thalamus. Thus, in simple terms, the cerebellum has three main func- tional divisions: the vestibulocerebellum, concerned mainly with integrating vestibular information; the spinocerebellum, concerned mainly with integrating sensory information from the body; and the pontocerebellum, concerned mainly with integrating information from the cortex regarding planned or ongoing movement. All areas of the cerebellum also receive input from the contralateral inferior olivary complex. The inputs to the cerebellum are largely excitatory, using glutamate as a neurotransmitter. In contrast, Purkinje cells, the output cells of the cerebellum, are inhibitory, using γ-aminobutyric acid (GABA) as a neurotransmitter. Recent advances in understanding of cerebellar functional archi- tecture have revealed that the cerebellum appears to be divided into multiple ‘modules’ with similar cell structure, but receiving and giving out highly topographically organized information (Fig. 24.7.1.2). These modules are longitudinally arranged strips of the cerebellar cortex about 1–2 mm across, each 5–6 mm in length. This modular organization has been studied in most detail in relation to receptive fields from the forelimb of the cat. This work has demonstrated that particular sensory receptive fields in the forelimb map to particular areas of the inferior olivary complex, which in turn given off projec- tions to particular areas within cerebellar modules, called cerebellar microzones. Each area of the inferior olive may project to a variety of microzones which may be distributed widely in the cerebellar hemispheres. Crucially, however, these distributed microzones all send output to a specific area of the cerebellar output nuclei. This or- ganizational structure (called multizonal microcomplexes) permits topographically organized input to be fed into a variety of discrete areas in the cerebellum. These discrete microzones might respond to and process a particular aspect of movement control, such as timing, direction, or scaling of movement. These various aspects of movement control could then be integrated by the common output of these areas to a particular part of the cerebellar output nuclei. Parallel fibres may in addition allow integration of information be- tween microzones responsible for movements at several different muscles, but which are commonly recruited as a group or ‘synergy’. This would allow for the coordination of complex multijoint move- ments such

as reaching and grasping. Function and dysfunction The main functions of the cerebellum (which are still the subject of much debate) are proposed as (1) a timing device for movement, (2) a structure that facilitates (motor) learning, and (3) a structure that allows integration of information (including information about SENSORY INPUT NUCLEUS RECEIVES CONVERGENT OUTPUT FROM ASSOCIATED CEREBELLAR MICROZONES TOPOGRAPHICALLY ORGANIZED OUTPUT FROM INFERIOR OLIVARY COMPLEX IS FED TO DIFFERENT CEREBELLAR MICROZONES CEREBELLAR OUTPUT CEREBELLAR MICROZONES CONTRALATERAL INFERIOR OLIVARY COMPLEX IPSILATERAL GLOBOSE NUCLEUS Fig. 24.7.1.2 This figure gives an example of the organization and connections of cerebellar microzones. In this example, sensory information from the limbs (which is topographically organized) is mapped onto specific topographically arranged areas of the inferior olivary complex. Output from one of these areas is shown, which is fed to several different cerebellar microzones. Output from these microzones converges onto a specific area of one of the cerebellar nuclei.

section 24 Neurological disorders 5940 planning of a movement and sensory feedback information on the progress of a movement) in order to facilitate correct scaling and harmonization of muscle activity. In patients with cerebellar lesions several abnormalities can be seen in simple reaching tasks. Normal movements are usually ac- companied by precisely timed agonist–antagonist–agonist bursts that allow the limb to arrive exactly at the desired target. In patients with cerebellar lesions, there is first a delay in movement initiation, followed by a delay in the antagonist burst so that the patient fre- quently overshoots the target. This is the basis for dysmetria or ‘past- pointing’, examined at the bedside during finger–nose or heel–shin testing. This overshoot may be a partial cause of intention tremor (worsening tremor towards the end of movement) as well as an add- itional effect of cerebellar lesions on the timing of activity in muscle-stretch reflex loops (via cerebellar projections to γ-motoneurons). Clinically, the timing and scaling role of the cerebellum can be as- sessed by looking for dysdiadochokinesia: a breakdown in force, rate, and rhythm of movement. This is often tested by asking pa- tients to tap gently, regularly, and rapidly on a table or the examiner’s hand with their fingers. This breakdown of smooth repetitive move- ments can even be detected by feel or by sound (‘listening to the cerebellum’). Midline vermal lesions usually cause truncal and gait ataxia, often in the absence of limb ataxia. The gait is wide based and particularly precarious on turning or on heel–toe walking. Unilateral cerebellar hemispherical lesions cause deviation or falling to the ipsilateral side. Unlike a sensory ataxia, cerebellar ataxia is not made worse by shutting the eyes. Cerebellar dysarthria may often simply manifest as slurred speech, as if intoxicated. However, in addition some patients may have either scanning or explosive speech, due to an inability to modulate its rate, rhythm, and force appropriately. Dysarthria is usually present with lesions of the vermis, whole cerebellum, or its connections, but may be absent if one lateral hemisphere alone is involved. Eye movements are frequently abnormal in disease of the cerebellum or its connec- tions. This may relate in part to the extensive connections from vestibular areas to the cerebellum. The following eye-movement abnormalities may be seen: gaze-evoked, rebound, downbeat, or positional nystagmus, dysmetric voluntary saccades, and jerky pursuit, square-wave jerks (macrosaccadic oscillations), impaired vestibulo-ocular reflex suppression, and skew deviation. Basal ganglia Gross anatomy There is no complete consensus on what structures make up the basal ganglia, but most would include the caudate nucleus, pu- tamen, globus pallidus, subthalamic nucleus, and substantia nigra (Fig. 24.7.1.3). The globus pallidus is subdivided into the globus pallidus externa and interna (GPe/GPi), and the substantia nigra is subdivided into the pars reticulata and pars compacta (SNr/SNc). As

with the cerebellum and thalamus, the basal ganglia have additional nomenclature systems that are still in use. The most important term is the word ‘striatum’ (or sometimes neostriatum) which is used to describe the caudate nucleus and the putamen together. The globus pallidus may be called the pallidum or paleostriatum, and the globus pallidus and putamen together may be called the lentiform nucleus. The phrase ‘corpus striatum’ is used to refer to the caudate, putamen, and globus pallidus together. The basal ganglia occupy a position near the base of the cerebral hemispheres. The putamen lies lateral to the thalamus, separated from it (and from most of the caudate nucleus, except anteriorally) by the internal capsule. The caudate nucleus, with its head lying anterodorsomedial to the putamen, arcs back, following, and pro- gressively tapering with, the lateral ventricles, its tail swinging for- ward until its anteriorly pointing tip terminates in the amygdaloid nucleus. The pallidum lies medial to the putamen but still lateral to the internal capsule. The substantia nigra lies in the midbrain, transversely above the cerebral peduncles. Its pars reticulata, the termination of the striatonigral pathway, is below the internal seg- ment of the globus pallidus, and its pars compacta contains the dopaminergic neurons that form the nigrostriatal pathway. Below the thalamus, medial to the internal capsule and rostral to the mid- brain, is the subthalamic nucleus. Most of the caudate, putamen, and globus pallidus derive their arterial supply from the anterior Substantia Nigra (SN) Subthalamic Nigra (STN) Thalamus Globus Pallidus externa (GPe) Caudate nucleus Putamen Striatum Globus Pallidus interna (GPi)
Fig. 24.7.1.3 Components of the basal ganglia seen in a coronal section of the brain. Reproduced from Edwards et al. Oxford Specialist Handbook of Parkinson’s Disease and Other Movement Disorders, Oxford University Press, 2008 with permission from Oxford University Press.

 circulation via the lateral lenticulostriate arteries and branches of the anterior choroidal and middle cerebral arteries. The thalamus, subthalamic region, and substantia nigra are supplied by the pos- terior circulation. Functional anatomy The basal ganglia receive a huge variety of input from the cerebral cortex, limbic system, and cerebellum. Although the role of the basal ganglia in motor control has been heavily emphasized, it is clear that the basal ganglia have a key role in many other aspects of behaviour, reflected in the diversity of input to and output from many ‘non- motor’ areas of the brain. A key concept of basal ganglia functional anatomy is their partici- pation in several parallel loops, which take information from dif- ferent (mainly cortical) areas, and then feed back, mainly to those same areas. Although the basal ganglia would seem well set up to integrate information from these various loops, in fact they seem not to do so, and information is kept remarkably separate. Five main loops are recognized: motor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate. The motor loop has received by far the most attention, given its presumed role in move- ment disorders such as Parkinson’s disease. The main interest has fo- cused on how activity in this loop is modulated by the basal ganglia, and in particular how dopamine plays a role in this. Basic basal ganglia pathways An important first step to aid understanding of the functional or- ganization of the basal ganglia is to consider that input to the basal ganglia, whatever its source, arrives almost exclusively at the pu- tamen or caudate (i.e. the striatum). Therefore, the striatum is the main input structure of the basal ganglia. Output from the basal ganglia comes almost exclusively from either the GPi or the SNr. Therefore, the GPi/SNr forms the main output from the basal ganglia. Crucially, these output structures send inhibitory projec- tions to the thalamus (Fig. 24.7.1.4). Ninety-eight per cent (98%) of the neurons in the striatum are medium spiny neurons, which mainly receive excitatory input from glutamatergic neurons of the cerebral cortex. The rest of the stri- atal neuronal population is made up of large nonspiny cholinergic interneurons and GABA-ergic interneurons. The medium

spiny neurons are inhibitory and use GABA as their neurotransmitter. They form two main groups (bundled together in structures called ‘Wilson’s pencils’) which have different routes to get to the output structures (GPi/SNr). One group projects directly to the GPi/SNr— the direct pathway—there colocalizing substance P and dynorphin as neurotransmitters. Activity in this pathway therefore inhibits basal ganglia output. The other group has an indirect route to the GPi/SNr, projecting first to the GPe, there colocalizing enkephalin and neurotensin as neurotransmitters. The pathway continues via an inhibitory projection from GPe to subthalamic nucleus (STN), and finally via an excitatory glutamatergic projection from STN to GPi/ SNr. The net effect of activation of this indirect pathway (combining two inhibitory and one excitatory synapse) is to excite GPi/SNr. Activity in the indirect pathway therefore facilitates basal ganglia output (see Fig. 24.7.1.4). Output from the basal ganglia is via GABA-ergic projections from GPi and SNr to the thalamus. The projections from GPi travel in two fibre bundles through the internal capsule; the one from the outer part of GPi is called the ansa lenticularis, and the other from the inner part of GPi is called the lenticular fasciculus. After traversing the internal capsule they meet with neurons from the SNr and join to form the thalamic fasciculus, which terminates in various nu- clei of the thalamus (for motor fibres this is mainly the ventrolat- eral medial nucleus). Additional output from GPi and SNr goes to the pedunculopontine nucleus and the superior colliculus. A crucial point is that the basal ganglia inhibits the structures to which it pro- jects; this is vital to understand the models of basal ganglia function described next. The most important neurotransmitter that regulates the activity of the basal ganglia is dopamine. Dopamine has different effects on the direct and indirect pathways. Dopaminergic neurons from the SNc ascend and synapse on striatal neurons (this is called the nigrostriatal pathway). Striatal neurons that will form the direct pathway express mainly dopamine D1-receptors at the nigrostriatal synapses: these are stimulated by dopamine. In contrast, striatal neurons that will form the first projection of the indirect pathway express mainly dopamine D2-receptors, which are inhibited by dopamine. Therefore, the net effect of dopamine on the striatum is to increase direct pathway activity, decrease indirect pathway activity, and therefore reduce the inhibitory output of GPi/SNr (Fig. 24.7.1.5). How is dopamine release controlled in the basal ganglia? The an- swer may lie in recent discoveries regarding the exact make-up of the striatum. It appears that, as well as the direct and indirect path- ways, the striatum also sends out projections direct to the SNc which stimulate activity in dopaminergic neurons projecting to the stri- atal neurons that form the direct and indirect pathways. So, the stri- atum is not formed by a homogeneous population of medium spiny neurons, but in fact is divided into two distinct subpopulations. One population forms ‘striosomes’, which are more densely packed groups of medium spiny neurons that have less cholinergic input and are rich in opiate receptors. These are the neurons that send projec- tions to the SNc (the striatonigral projection). The other population CORTEX THALAMUS SNc GPi/SNr STN GPe I D2 D1 D PUTAMEN Fig. 24.7.1.4 The direct and indirect pathways. Pink arrows indicate inhibitory connections, white arrows indicate excitatory connections. D1, dopamine receptor type 1; D2, dopamine receptor type 2; STN, subthalamic nucleus; GPi, globus pallidus interna; GPe, globus pallidus externa; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulate; I, indirect pathway; D, direct pathway. Reproduced from Edwards et al. Oxford Specialist Handbook of Parkinson’s Disease and Other Movement Disorders, Oxford University Press, 2008 with permission from Oxford University Press.

 forms the ‘matrix’, which is made up of less densely packed medium spiny neurons with no output to SNc. These are the neurons that form the direct and indirect pathways. The putamen is almost all matrix, whereas the caudate has many striosomes.

The striosomes receive input mainly from limbic structures, whereas the matrix re- ceives input from a variety of cortical areas, but not limbic struc- tures. The connections of these different striatal neurons has led to the idea of two striatal systems: the ventral striatum (striosome), which, via its connections with the limbic system, feeds emotional, reward and attentional information into the basal ganglia, and via its ability to modulate dopaminergic output from the SNr it can influ- ence activity in the dorsal striatum (matrix). Basic pathways and the rate model of basal ganglia function The earlier discussion about the connections of the various nuclei of the basal ganglia sets the scene for the most influential model of basal ganglia function proposed by DeLong and colleagues in 1990 (against the background of work by many others). The key to under- standing this model is to appreciate that: • output from the GPi and SNr is inhibitory to the thalamus (and therefore to the cortex), and therefore, from a motor circuit point of view, an increase in rate of GPI/SNr firing is hypothesized to inhibit movement; • as the direct and indirect pathways have opposite effects on basal ganglia output, the rate model hypothesizes that they will have op- posite effects on movement; • dopamine has opposing effects on the direct and indirect path- ways, tending to increase direct pathway activity via D1-receptors and decrease indirect pathway activity via D2-receptors. The net result of dopaminergic stimulation is, therefore, to decrease GPi/ SNr rate of firing, promoting movement. This model, sometimes described as the 'rate model', is successful in explaining several aspects of motor dysfunction related to the basal ganglia (e.g. the pathology of Parkinson's disease leads to a dopamine-depleted state which would be predicted to decrease direct pathway activity and increase indirect pathway activity). This would tend to cause an increase in GPi/SNr (inhibitory) output to the thalamus, therefore inhibiting movement (Fig. 24.7.1.6). In con- trast, hemiballism (flinging movements of the arm and leg) is known to occur frequently with damage to, or close to, the subthalamic nu- cleus. The rate model would predict the effect of a subthalamic nu- cleus lesion to be a drop in indirect pathway activity, leading to a reduction in GPi/SNr activity and a consequent increase in thalamic activity, promoting movement (Fig. 24.7.1.7). There is experimental support for this model (e.g. the finding from functional imaging studies that in Parkinson's disease there is hypermetabolism of the GPi, which reverses with the administration of levodopa). However, problems occur when considering other clinical aspects of movement disorders (e.g. a lesion of the GPi in experi- mental animals tends not to cause excessive movement, as the model would predict). In fact, a lesion of the GPi can be a very successful CORTEX THALAMUS GPi/SNr I D STN PUTAMEN D2 D1 GPe SNc Fig. 24.7.1.5 The effect of dopamine and the direct and indirect pathways. Dopamine released from the substantia nigra pars compacta stimulates the direct pathway via its action on DI receptors and inhibits the indirect pathway via its action on D2 receptors. Abbreviations are the same as for Fig. 24.7.1.4. Reproduced from Edwards et al. Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders, Oxford University Press, 2008 with permission from Oxford University Press. THALAMUS CORTEX STN D I GPi/SNr SNc PUTAMEN D1 D2 GPe Fig. 24.7.1.6 How a lesion in the substantia nigra pars compacta can cause parkinsonism. Abbreviations are as in Fig. 24.7.1.4. Reproduced from Edwards et al. Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders, Oxford University Press, 2008 with permission from Oxford University Press. CORTEX THALAMUS I D GPe SNc PUTAMEN D2 D1 GPi/SNr STN Fig. 24.7.1.7 How a lesion in the subthalamic nucleus can cause hemiballismus. Abbreviations are as in Fig. 24.7.1.4. Reproduced from Edwards et al. Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders, Oxford University Press, 2008.with permission from Oxford University Press.

24.7.1 Subcortical structures 5943 treatment for both levodopa-induced dyskinesia in Parkinson's dis- ease and primary dystonia. In addition, the movement disorders characterized by excessive movement (the hyperkinetic movement disorders—dystonia, tremor, tics, myoclonus, chorea) are variable in their clinical features, something that is difficult to explain via a model based solely on rate of GPi/SNr firing. Beyond basic basal ganglia connections:

The hyperdirect pathway and basal ganglia oscillations The connections between the basal ganglia are considerably more complex than the rate model permits (e.g. there is a 'hyperdirect' pathway—a glutamatergic pathway that directly links the supple- mentary motor area and the subthalamic nucleus). In addition, there are numerous basal ganglia–basal ganglia pathways (e.g. a direct excitatory connection from the subthalamic nucleus to GPe, and a direct inhibitory connection from GPe to GPi and SNr). These additional connections suggest the presence of two networks within the basal ganglia: an 'extrastriatal network' where the subthalamic nucleus is the main player, with links to GPe, GPi, and SNr, and a 'striatal network' that connects directly to GPi/SNr. The development of animal models of parkinsonism, and more recent developments in human deep brain stimulation surgery for Parkinson's disease and dystonia, have permitted direct recording from the basal ganglia. These recordings have demonstrated that alterations in pattern and synchrony of basal ganglia firing may be more important than changes in rate alone. So, for example, in patients with Parkinson's disease, direct recordings from the basal ganglia show an increase in bursting activity in the subthalamic nu- cleus that oscillates at a low frequency (in the β band: 10–20 Hz) and is synchronized across the basal ganglia and motor cortex. Successful treatment with levodopa is associated with a shift to higher-frequency oscillations (into the γ band >60 Hz). One way to try to unify these disparate aspects of basal ganglia physiology into a functional whole is to first consider the basal ganglia as having a strong inhibitory bias. Therefore, although STN neurons fire quite consistently in response to cortical activity, fed to them via the hyperdirect pathway, this is not translated on the whole into changes in firing from basal ganglia output nuclei (GPi/SNr), due to strong inhibitory control from the striatum, and therefore the tonic inhibitory discharge of the basal ganglia output continues. However, in the presence of dopamine, this situation is reversed, and the net effect of dopamine on the direct and indirect pathways causes a shift in basal ganglia output firing, allowing the information carried in the subthalamic nucleus firing patterns to be fed through to the thalamus. This occurs in a strictly segregated way, and the top- ography of input is preserved. In disease, there is a shift towards more synchronous firing within the basal ganglia with, in the case of Parkinson's disease, a shift to- wards low-frequency oscillations even when movement is attempted, reflecting a loss of the normal modulation of firing patterns during movement. In dystonia, a hyperkinetic disorder, the GPi shows lower firing rates compared with Parkinson's disease (as would be predicted by the rate model), but in addition there are more frequent and irregular bursts seen with long pauses of absent activity. This might link to the clinical picture of dystonia with excessive muscle activation that stops and starts with shifting coactivation of agonists and antagonists, leading to abnormal posture, writing movements, and often a jerky tremor. Synchronization of firing across the basal ganglia undermines its ability to focus and concentrate activation in a topographically discrete manner. Function and dysfunction The earlier discussion is complex, but reflects the evolving under- standing of the functional role of the basal ganglia. The basal ganglia are hypothesized to have four main roles, all of which have most often been related to the motor function of the basal ganglia: 1 To release a desired movement from inhibitory control (e.g. before a desired eye movement the tonic discharge of the basal ganglia output nuclei drops, and this allows the movement to occur). 2 To inhibit undesired movement: in the motor system this would be reflected

in the highly topographically organized nature of basal ganglia input and output. Therefore, as well as releasing the desired movement, the basal ganglia appear to play a key role in inhibiting other movements. This focusing role is also known as centre-surround inhibition, where the desired movement (centre) is surrounded by an area of undesired movement that is actively inhibited. 3 To facilitate sequential automatic movements: in motor learning experiments, basal ganglia activity tends to increase as learning occurs. This is thought to reflect a role for the basal ganglia in coding sequences of movements that become automated. This may explain the particular difficulty showed by patients with Parkinson's disease in performing multistage automatic move- ments, such as turning over in bed. 4 To integrate attentional, reward, and emotional information into movement and learning: via the connections of the limbic system with the ventral striatum, the basal ganglia form an important location for the integration of motivational and emotional in- formation with motor behaviour. This is particularly the case for reward-based learning. It has been suggested that the basal ganglia can be seen as integrating two aspects of reward-based learning: the 'critic', the ventral striatum system that holds infor- mation on how motivated the organism is towards a particular goal; and the 'actor', the dorsal striatum that holds information on the motor behaviour needed to achieve that goal. These various functions are certainly biased towards the motor system, but it is clear, from both the discussion of basal ganglia con- nections above, and the symptoms displayed by patients with dis- orders of the basal ganglia, that nonmotor aspects of behaviour are strongly linked to the function of the basal ganglia. It may be par- ticularly the case for motivation and reward-based learning, for ex- ample, lesions of the caudate nucleus have been associated with the psychiatric syndrome of abulia—a syndrome of apathy and lack of motivation that is thought to reflect failure of normal reward-based motivational mechanisms. The movement disorders are hypothesized to reflect dysfunc- tion within the basal ganglia, although, surprisingly, it is difficult to mimic some of these disorders simply by lesions to the basal ganglia alone. Thus, tics and myoclonus rarely occur in humans as a con- sequence solely of basal ganglia lesions. Likewise, chorea rarely occurs from lesions to the caudate nucleus alone, as one might ex- pect given the degeneration of this nucleus in Huntington's disease. Parkinsonism, combining akinesia (slowness—bradykinesia) and

 progressive fatiguing of repetitive movement), rigidity (stiffness of muscles in flexion and extension), rest tremor of 5–6 Hz, and pos- tural instability, can be seen in response to discrete lesions of the SNc. In terms of the various functions of the basal ganglia already out- lined here, both rigidity and akinesia could be seen as reflecting an inability to release the desired movement (akinesia) and a failure to inhibit undesired movement (rigidity). In Parkinson's disease, clear deficits in reward-related learning and performance of integrated automatic movements are seen, together with emotional and mo- tivational problems. Dystonia can also be produced by discrete basal ganglia lesions (usually to the putamen) and, in terms of the basal ganglia functions outlined here, dystonia could reflect an inability to inhibit unwanted movement, leading to the typical clinical picture of overflow of activity into adjacent muscles and cocontraction of agonists and antagonists. The huge variety of clinical presentation of movement disorders no doubt reflects the interaction of basal ganglia dysfunction with dysfunction caused by neurological dis- ease elsewhere in subcortical and cortical areas. Thalamus Gross anatomy The two thalami sit at the head of the brainstem, their medial borders largely separated by the third ventricle, but often partially fused as the massa intermedia. They constitute the largest nuclear mass in the diencephalon (the others being the hypothalamus and subthalamus). On the lateral surface of the thalamus is the external medullary lamina, containing thalamocortical and

corticothalamic fibres ei- ther entering or exiting the internal capsule. The external medullary lamina and the internal capsule are separated by a thalamic nucleus called the reticular nucleus. The internal structure of the thalamus, already complex, is further confused by the existence of different nomenclatures (the one used here being that of Wessler). Inside the thalamus the internal medullary lamina (consisting of fibres leaving or entering the various thalamic nuclei) roughly divides the thalamus into three groups of nuclei—lateral, medial, and anterior—with each subdivided into ventral and dorsal areas. There are further nuclei that are not defined by this ventral/dorsal system such as those that lie within the internal medullary lamina (the intralaminar nuclei), and others such as the lateral and medial geniculate and the pulvinar. The blood supply to the thalamus derives from the posterior circulation via the posterior cerebral arteries and perforators from the terminal part of the basilar artery. Cytoarchitecture Before discussing the functional anatomy of the thalamus, we briefly summarize its cellular structure. The main output cells of the thalamus are called relay cells. These form excitatory glutamatergic projections to the cortex. These cells receive multiple inputs including GABA- ergic inputs from interneurons within the thalamus, cholinergic input from the brainstem reticular formation, as well as glutamatergic input from particular cortical areas (usually those areas to which the relay cells then project back, forming corticothalamocortical loops). Relay cells have two modes of firing—a burst mode and a tonic mode— which may have different functions (see next). Relay cells are mainly contained in the dorsal thalamic nuclei (the relay nuclei), whereas nuclei in the ventral thalamus (particularly the intralaminar nuclei) project mainly to the basal ganglia via glutamatergic projections. Functional anatomy The thalamus is in an ideal position to modulate information flow to and from the cortex. Although previously this role had been thought of as a mainly passive relay station, it is clear that the thalamus has a much greater role in moulding the information that passes through it than previously realized. Thalamic afferents arrive from five main sources. 1 Afferents from special senses (except olfaction): touch (from the body—ventral posterolateral nucleus; face—ventral posteromedial nucleus), taste (ventral posteromedial nucleus), vision (lateral geniculate nucleus), and hearing (medial geniculate nucleus) 2 Afferents from the output nuclei of the basal ganglia: GPi (centromedian nucleus, ventral anterior nucleus, ventral lateral nucleus oralis and medialis) and SNr (mediodorsal nucleus and ventral anterior nucleus magnocellularis) 3 Afferents from the cerebellum: ventral lateral nucleus caudalis, to the ventral posterolateral nucleus oralis 4 Cortical afferents from many cortical areas: mainly synapse on dorsal thalamic nuclei 5 Afferents from the brainstem reticular formation Efferents from the thalamus from three main groups: 1 Efferents from thalamic nuclei to representative areas of the cortex determined by the input to the nucleus (e.g. afferents from the retina project to the lateral geniculate nucleus, which then projects to the visual cortex) 2 Efferents to cortical areas that project directly to the thalamus (corticothalamocortical loops) 3 Efferents to the striatum (mainly from the intralaminar nuclei) The functional anatomy of thalamic circuits has been most closely studied for the visual system, and this can serve as a model for other thalamic circuits (Fig. 24.7.1.8). In the visual system, the “FIRST ORDER RELAY” “SECOND ORDER RELAY” Areas 4 and 6 VISUAL CORTEX THALAMIC INTERNEURONS RELAY CELLS OF LATERAL GENICULATE NUCLEUS BRAINSTEM RETICULAR FORMATION THALAMIC RETICULAR NUCLEUS SENSORY INPUT FROM RETINA Fig. 24.7.1.8 Main connections of the lateral geniculate nucleus as an example of primary and secondary relays in the thalamus. Black arrows indicate inhibitory connections, white arrows indicate excitatory connections.

 main input to be relayed to the appropriate area of cortex comes from the retina, but, interestingly, this forms only about 5% of the input to the relevant thalamic nucleus: the lateral geniculate body. The rest of the input comes from a variety of sources

including inhibitory input from thalamic interneurons and the thalamic reticular nucleus, excitatory input from the brainstem reticular formation, and layer 6 of the visual cortex. Output from the lateral geniculate is then primarily to layers 4 and 6 of the visual cortex. This system therefore has a primary function: transfer of visual information from the retina to the visual cortex (sometimes called the driver function or first-order relay), but this is subject to a huge amount of modulation from other areas, both cortical and brainstem. A secondary system, often called the higher-order relay, is dis- tinguished from this first-order system. This system takes cortical information down to the thalamus (typically the dorsal nuclei), and then back again to the same area (corticothalamocortical loops). As for the first-order system, this circuit is subject to mul- tiple modulatory inputs at the thalamic level. Of course, the cor- tical areas projecting as higher-order relays may have themselves been influenced by first-order relays, leading to a complex series of loops integrating and modulating information flow to and from the cortex. One of the most important modulating forces at work in the thal- amus arises from the brainstem reticular activating complex. This is demonstrated by the massive decease in thalamic activity seen during sleep, and the potential of certain thalamic lesions to cause coma. The influence of the reticular activating complex may occur via its ability to cause the ‘burst’ pattern of firing in thalamic relay cells. It is hypothesized that this is a ‘wake-up’ signal to the cortex, causing diversion of attention to the particular input in question, following which relay cells switch to their normal regular tonic discharge. Function and dysfunction The previous discussion clearly demonstrates the role of the thal- amus as more than a neuronal rest stop on the way to and from the cortex. The main functions of the thalamus are thought to include: • modulation of sensory information by integration of brainstem (in particular, the reticular activating complex) and relevant cortical information • modulation of cortical activity via corticothalamocortical loops A diverse range of clinical consequences of thalamic lesions has been described, as one would expect from a region where so many different information flows coalesce (e.g. sensory abnormalities are reported with thalamic lesions), from pure hemisensory loss to deep-seated, severe pain. Mild hemiplegia may be seen with thalamic lesions, sometimes in combination with hemisensory loss, dysaesthesia, hemiataxia, astereognosis, and hemichorea as in the thalamic syndrome of Déjèrine and Roussy. Other lesions, often spreading outside the thalamus to involve the basal ganglia, have been associated with myoclonus, dystonia, or a slow 3–4 Hz tremor of the limbs on one side of the body. Lesions of the ventral lateral nucleus caudalis (also known as the ventral intermediate nucleus) have been used as a treatment for parkinsonian and es- sential tremor. Conclusions These three subcortical structures, the cerebellum, basal ganglia, and thalamus, provide the bridge over which information passes to and from the periphery and the cerebral cortex. Through their intri- cate structure and interconnections, they play a major role in modu- lating and integrating this information. The recent discovery of a hitherto unknown direct connection between the cerebellum and the basal ganglia again underlines the importance of considering these structures as part of a coordinated system rather than in iso- lation. The question ‘What does the cerebellum/basal ganglia/thal- amus do?’ therefore becomes slightly nonsensical, because in fact they do nothing in isolation, and function only as part of a system. This system can certainly be affected in particular ways by dysfunc- tion of one of its parts, but the results of discrete lesions are often hard to predict and may have wide-ranging consequences for motor and nonmotor behaviour. FURTHER READING Apps R, Garwicz M (2005). Anatomical and physiological founda- tions of cerebellar information processing. Nat Rev Neurosci, 6, 297–311. Brown P (2003). Oscillatory nature of human basal ganglia activity: re- lationship to the pathophysiology of Parkinson’s disease. Mov Disorders, 18, 357–63. Hammond C, Bergman H, Brown P (2007). Pathological synchroniza- tion in Parkinson’s disease: networks, models and treatments. Trends Neurosci, 30, 357–64. Hoshi E, et al. (2005). The

cerebellum communicates with the basal ganglia. Nature Neurosci, 8, 1491–3. Lehericy S, et al. (2001). Clinical characteristics and topography of
lesions in movement disorders due to thalamic lesions. Neurology, 57, 1055–66. Lera G, et al. (2000). A combined pattern of movement disorders re- sulting from posterolateral thalamic lesions of a vascular nature: a syndrome with clinico-radiologic correlation. Mov Disorders, 15, 120–6. Middleton FA, Strick PL (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science, 266, 458–61. Middleton FA, Strick PL (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev, 31, 236–50. Nambu A (2004). A new dynamic model of the cortico-basal ganglia loop. Prog Brain Res, 143, 461–6.] Obeso JA, Rodriguez MC, DeLong MR (1997). Basal ganglia patho- physiology: a critical review. Adv Neurol, 74, 3–18. Obeso JA, et al. (2000). Pathophysiologic basis of surgery for Parkinson’s disease. Neurology, 55, (12 Suppl 6), S7–12. Rothwell JC (1994). Control of human voluntary movement, 2nd edi- tion. Croom Helm, London.

Revision #1
Created 2026-01-22 16:43:40 UTC by Omar Ayman
Updated 2026-01-22 16:43:40 UTC by Omar Ayman