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CONTENTS 24.4.1 Disturbances of higher cerebral function 5821 Peter J. Nestor 24.4.2 Alzheimer’s disease and other dementias 5830 Jonathan M. Schott 24.4.1 Disturbances of higher cerebral function Peter J. Nestor ESSENTIALS Clinicopathological and imaging studies indicate strong associ- ations between particular disorders of cognition and focal disease in the brain, but not all focal lesions induce specific loss of higher functions. Neuropsychological research has deepened our under- standing by suggesting organizational frameworks for human cog- nitive faculties. Neurological basis for cognition The neocortex around the primary sensory and motor cortices is made up of unimodal association areas, which link to heteromodal association areas, with the linkage of topographical region to spe- cific functional attribute becoming progressively less tightly de- fined. Other areas of the brain that interact with these association areas in a critical way for cognition include (1) limbic system— particularly in the domains of memory and emotion; (2) basal fore- brain nuclei—important to the successful encoding of memory; (3) basal ganglia—relating to attention and speed of cognitive
processing; (4) brainstem reticular formation—determining the level of arousal. Clinical testing of

cognition Regardless of the suspected disorder, the clinician should always proceed in the following way: (1) ensure adequate attention to undergo further testing—if the patient has a profound attention deficit, then their cognition cannot be properly assessed; (2) assess language comprehension—almost all tests are going to be presented with verbal instruction; (3) leave tests of executive function and praxis to the end of the examination—they often require adequate levels of function in all other cognitive domains; and (4) always ask, 'can this apparent disorder be explained in terms of a more elem- ental deficit?' Particular tests of cognitive function can aid clinical diagnosis of cerebral disease and monitor treatment. It may also be possible to define the specific needs and deficiencies for which supportive aids may assist the patient. Specific cognitive domains Disorders of the higher functions of the brain can be described in terms of the following specific domains: Attention—the ability to attend to a specific sensory stimulus and to maintain attention is an obligatory first step to any further cogni- tive processing. Breakdown in attentional processing is the central deficit in delirium or acute confusional states. Language and related disorders—numerous terms are used to describe aphasic syndromes, but the best approach is to consider language fluency and paraphasias in spontaneous conversation, comprehension, naming, and repetition. Particular types of language and related disorders may be associated with particular anatomical lesions. Visuospatial and perceptual disorders—a dorsal occipitoparietal pathway is concerned with spatial information and preparation for reaching ('where?' and 'how?'); a ventral occipitotemporal pathway is concerned with identifying visual stimuli ('what?'). Striking neuro- psychological syndromes are seen following selective damage to one pathway. Memory—(1) Implicit memory—unconscious memory sys- tems, such as that responsible for conditioning as well as memory for motor tasks. (2) Explicit memory—the consciously appreciated memory, which is the category most relevant to clinical disease; div- ided into (a) episodic memory, referring to autobiographical recol- lection of personal events; typically impaired in Alzheimer's disease and lesions of the limbic system; and (b) semantic memory, referring to factual knowledge and the store of objects and meanings; lesions of the temporal lobes cause loss of this memory, with a severe incap- acity to name objects and recall the meaning of words. Apraxia—a loss of ability to carry out skilled motor tasks that cannot be explained in terms of an elementary disorder of motor control (weakness or ataxia), primary sensory disturbance, or a global impairment of cognition. Usually the result of damage to the left 24.4 Higher cerebral function

 (dominant) hemisphere, particularly the superior parietal lobule and the premotor area of the frontal lobe. Personality and behavioural change—alterations in complex be- haviour, personality, and social comportment cannot be simply defined, but are broadly associated with frontal or anterior temporal lobe pathology. Introduction Modern scientific study of higher cerebral function began in the late 19th century with the case studies of Broca and Wernicke. Their observations of language disorders associated with damage to the left hemisphere gave rise to the notion that specific mental faculties could be dissociated from each other and localized to specific regions within the cerebral hemisphere. Since that time clinicopathological and, more recently, imaging studies have estab- lished associations between specific cognitive disorders and focal brain lesions; these studies also show that some lesions do not give rise to highly specific deficits. The field of neuropsychology has offered complementary insights into this area by providing con- cepts of how cognitive faculties are organized. The border between psychiatry and neurology is a medical con- struct rather than a real boundary; many patients with structural brain diseases have psychiatric symptoms, cognitive complaints are prominent in depression and schizophrenia, and in the dementias it is typical to find a combination of both

neuropsychological (cog- nitive) deficits with a range of neuropsychiatric (behavioural and personality) alterations. Another critical area has been the study of anatomy: the finding that neocortical histology varies by region led to the development of cytoarchitectonic maps such as that of Brodmann. Brodmann's map has become a shorthand way of discussing regional special- ization across the cortex. Meanwhile, anatomical studies of neural tracts have provided insights into how topographically distinct re- gions may interact. Handedness and hemispheric dominance The finding of asymmetrical functions in the human cerebral cortex led to the introduction of the term 'hemispheric dominance'. Neuroscientists often refer to cognitive processes being a function of the 'dominant' or 'nondominant' hemisphere; when such termin- ology is used, the 'dominant' hemisphere is synonymous with that which underpins language function. In right-handed individuals, over 95% have left hemisphere dominance; only rarely does aphasia arise from right hemisphere damage, in which circumstance it is re- ferred to as 'crossed aphasia'. In left-handed individuals, dominance is more complex and language skills are more often shared between the hemispheres, although the left hemisphere is relatively dom- inant in about 70% of individuals. While the left hemisphere usually specializes in language, the nondominant hemisphere plays an im- portant role in spatial cognition (with damage to the frontoparietal regions resulting in spatial neglect) and particularly in face pro- cessing (with damage to the right occipitotemporal junction produ- cing prosopagnosia). Primary sensory input and motor output Motor The primary motor area lies in the precentral gyrus, immediately ros- tral to the central sulcus. The body is represented 'somatotopically' along the precentral gyrus: the lower limb at the superomedial and the face at the inferolateral extremity, with the upper limb in be- tween. This is of clinical importance because the vascular supply of the superomedial region is from the anterior cerebral artery whereas the rest of the motor cortex is from the middle cerebral artery. Thus, middle cerebral artery territory infarction will affect face and upper limb with relative sparing of the lower limb, and the converse will be the case with anterior cerebral territory occlusions. Vision After passing from the retina, via optic nerves and tracts to the lateral geniculate body of the thalamus, visual information passes to the striate cortex of the occipital lobes (primary visual cortex) through the optic radiations (see Chapter 24.6.1). As images pre- sented to the right visual field are represented on the left retina and conveyed to the left occipital lobe, a lesion of the latter will cause a right homonymous hemianopia (and vice versa for right occipital lesions). Fibres in each optic radiation separate such that input from the superior half of the retina (inferior visual field) runs from lateral geniculate to the striate cortex via parietal white matter whereas that from the inferior retina (superior visual field) loops down into the temporal lobe. Consequently, a lesion of the parietal lobe can cause a contralesional inferior quadrantanopic field defect whereas a tem- poral lobe lesion can cause a contralesional superior quadrantanopia. Large temporoparietal lesions (e.g. due to middle cerebral artery oc- clusion) may also cause homonymous hemianopia, which can be distinguished from that resulting from an occipital lesion by pres- ervation of opticokinetic nystagmus in the latter but not the former. Bilateral lesions to the primary visual cortex lead to 'cortical blind- ness' in which vision is lost, but, unlike blindness secondary to ret- inal or optic nerve diseases, pupillary reflexes are preserved. Some cortically blind individuals deny that they have any visual disorder at all (namely visual anosagnosia)—a condition known as Anton's syndrome. These cases tend to have more extensive lesions involving both striate and adjacent visual association cortices. Somatosensory The primary somatosensory cortex occupies the postcentral gyrus of the parietal lobe with a somatotopic representation of the body analogous to that of the primary motor area. Sensory deficits due to lesions of the thalamus, or lower components of the sensory system, cause gross abnormalities in the appreciation of touch, pinprick, temperature, and other sensations, and must

be excluded before comment can be made on higher sensory function. Parietal lesions cause specific impairment of ‘discriminative’ sensation, including joint position sense and two-point discrimination. Parietal drift (the patient is asked, with eyes closed, to maintain the upper limbs outstretched in front of the trunk at 90°) is a sign of impairment of the former ability. It is considered specific for a contralateral par- ietal lesion when the drift is upward, because a downward drift may also be a consequence of subtle motor weakness. The normal sep- aration distance at which one can discriminate one point from two

24.4.1 Disturbances of higher cerebral function 5823 varies according to body region: fingertips 3 mm, palm 1 cm, and body surface 4–7 cm. Other signs of parietal sensory impairment are an inability to name numbers traced on the palm of the hand (agraphaesthesia), and an inability to name small objects (such as keys and coins) placed in the patient’s hand (astereognosis). Obviously there is potential to confuse true astereognosis with a more general deficit of object naming such as that caused by loss of semantic know- ledge or aphasia (see next). However, ambiguous results on par- ietal sensory testing can largely be avoided if the examiner adopts a methodical approach of: (1) excluding a lesion below the parietal lobe by establishing that the patient can appreciate, for instance, a pinprick or light touch; and (2) examining from the suspected normal to abnormal side to exclude a more general impairment of cognitive faculties. Auditory Auditory information coming from the cochlear nuclei via the inferior colliculus and the medial geniculate nucleus of the thal- amus travels to the primary auditory cortex (Heschl’s gyrus) in the posterosuperior temporal lobe. Clinically apparent cortical hearing impairment is uncommon due to the bilateral representation of audi- tory material from each ear by the cerebral cortex. Bilateral lesions of this area (as a result of strokes, prolonged hypotension, or carbon monoxide poisoning) will cause ‘cortical deafness’, a rare disorder manifest by inability to understand spoken language or recognize sounds although presence or absence of noise can be determined. Unlike Wernicke’s aphasia (see next), individuals can understand written text and their language output is normal. Cognitive domains Beyond the primary sensory and motor cortices, the neocortex is made up of unimodal and heteromodal association areas. Unimodal association cortices lie adjacent to their respective primary modality whereas heteromodal association cortex is found in the prefrontal and temporoparietal regions. Moving from primary through uni- modal to heteromodal association cortex, the linkage of topograph- ical region to a specific functional attribute becomes progressively less tightly defined. Heteromodal association cortices, as the name implies, receive inputs from multiple unimodal areas, but also from nonneocortical areas. Anatomically, as the neocortex approaches the diencephalon, upon which the cerebral hemispheres sit, it trans- forms into a histologically distinct area: the limbic system. These areas also have critical roles in cognition, particularly in the do- mains of memory and emotion, and have reciprocal projections with heteromodal association cortices. Other brain regions that have important modulatory roles on cognition include: (1) the basal forebrain nuclei, which contain cho- linergic neurons that project extensively to limbic and neocortical regions and are known to be important to the successful encoding of memory; (2) the basal ganglia, which have reciprocal links to frontal association cortices and have important modulatory roles relating particularly to attention and speed of cognitive processing; and (3) brainstem reticular formation nuclei which project into the hemispheres via the thalami, the most clearly defined role for these projections being at the level of arousal. Although the remainder of this chapter discusses various dis- orders of higher mental function individually, one should not view these specific deficits as a random and independent collection of phenomena. It cannot be overemphasized that one should always follow a logical

sequence in assessing cognitive function so as to avoid false-positive diagnoses due to sequential effects. For example, tests of executive function that utilize analysis of complex verbal material would be beyond the grasp of a patient with Wernicke's aphasia due to the fundamental disorder of language comprehen- sion without needing to implicate frontal lobe damage. Likewise, a patient with an acute delirium may be unable to perform even the most basic memory tasks as a consequence of the attention deficit and, therefore, ought not to be labelled amnesic. Therefore, regard- less of the suspected disorder, one should always bear the following sequence in mind: (1) ensure adequate attention to undergo further testing; (2) as almost all tests are going to be presented with verbal instruction, assess language comprehension; and (3) as tests of ex- ecutive function and praxis often require adequate levels of function in all other cognitive domains, these should be left to last. In sum- mary, always ask: 'Can this apparent disorder be explained in terms of a more elemental deficit?' Attention The ability to attend to a specific sensory stimulus, such as a human voice or passage of text, and to maintain attention is an obligatory first step to any further cognitive processing. Humans are continu- ously bombarded with sensory stimuli from both within and be- tween individual sensory input modalities; loss of ability to focus and sustain attention (or, alternatively, block out irrelevant 'noise') renders the individual incapable of following a specific sensory stimulus (such as a conversation) and at the same time vulnerable to random irrelevant environmental stimuli. Although disorders of the frontal lobes, basal ganglia, and ascending reticular for- mation are associated with poor attention, it is overly simplistic to consider attention as a localizable brain function. The most common causes of acute attention failure are diffuse brain insults such as a metabolic encephalopathy or closed head injury; break- down in attentional processing is the central deficit in delirium or acute confusional states, the main features of which are summar- ized in Table 24.4.1.1. Digit span is one of the most simple methods of assessing atten- tion, especially in the backward condition; normal individuals have a forward span of at least six digits and a reverse span one or two digits less. The digits must be presented as individual items (read the string to be repeated at a rate of one digit per second). A common pit- fall is to cluster digits as one does when reciting telephone numbers. This inflates span as each cluster becomes an individual item: com- pare repeating '6953–8127' with '6 . . . 9 . . . 5 . . . 3 . . . 8 . . . 1 . . . 2 . . . 7'. Ability to persevere at a given task is another way of considering at- tention, and can be tested by asking the patient to recite the months of the year in reverse order. Orientation is heavily dependent on attention and is assessed by questions of time and place. Testing personal orientation adds little, because only profoundly aphasic or hysterical patients are unable to relate their own name. A recent onset of profound disorienta- tion and attention deficit is typical of a delirium. It should be noted that many patients with episodic memory problems (such as early Alzheimer's disease) remain well oriented.

SECTION 24 Neurological disorders 5824 Language and related disorders Numerous terms are in use to describe aphasic syndromes, although some serve more to confuse than enlighten. The terms 'expres- sive' and 'receptive' particularly seem to mislead: on the one hand, all patients with aphasia have some form of difficulty 'expressing' themselves and, on the other, 'receptive' aphasia is often, errone- ously, taken to mean that patients have difficulty only with incoming language, but can produce their own language perfectly well. Less ambiguous terms for the two principal divisions of aphasia are 'nonfluent' and 'fluent', which correspond in classic aphasia nomen- clature to Broca's and Wernicke's aphasias. The classic aphasia syn- dromes are, however, rarely seen in the acute stages after stroke and do not characterize the language deficits found in the dementias. A better approach is therefore to consider language fluency and paraphasias in spontaneous

conversation, comprehension, naming, and repetition. Examining patients with aphasia Fluency and paraphasic errors Speech can be described as fluent if the patient is able to produce some well-formed sentences or phrases even if empty or anomic (such as ‘Oh, you know, the thing you put the stuff in when you’re going somewhere and . . . ’). Nonfluent language, in contrast, is a consequence of breakdown of the language production and syn- tactic (grammatical) aspects of language, and is the hallmark of damage to Broca’s area and the left insula. Output is laboured or ‘telegraphic’, with often as few as two or three words per mi- nute; despite this, patients can convey meaning fairly successfully (e.g. ‘I . . . go . . . hospital’). Paraphasic errors are substitutions of a correct word for one re- lated in sound or meaning. The former, known as phonological or phonemic paraphasias, involve the substitution of related sound fragments (‘phonemes’) such as ‘dobble’ for ‘bottle’. Semantic para- phasic errors involve substitution of words of related meaning; the substituted word is typically a higher-frequency example of the same semantic category (such as ‘dog’ for ‘fox’) or else of a superordinate category (such as ‘animal’ for ‘fox’). In more extreme circumstances, paraphasic substitutions may not be words at all (‘neologisms’); fluent output with virtually continuous neologisms is an utterly incomprehensible state sometimes referred to as ‘jargon aphasia’. Patients with lesions to Wernicke’s area invariably make a mixture of phonemic and semantic errors. Semantic errors are also very common in Alzheimer’s disease and semantic dementia. In Broca’s aphasia, phonological errors predominate. Comprehension Some degree of impairment of language comprehension can be de- tected in both fluent and nonfluent aphasia. Patients with fluent aphasia have more overtly impaired comprehension of word meaning (e.g. ordinary nouns). In mild cases this can be demonstrated with semantically complex language tasks (e.g. ‘Can you point to a source of artificial illumination?’) or by defining uncommon words (e.g. ‘What is an aubergine, accordion’, and so on). Comprehension of single nouns is preserved in patients with nonfluent aphasia, but comprehension—in addition to production—of complex grammar is impaired. This can be tested with reversible passive sentences (e.g. ‘The lion was eaten by the tiger; who survived?’) or by asking the patient to obey syntactically complex commands (e.g. ‘Touch the keys after touching the book’). Anomia Naming is a complex task that requires the integrity of three basic processes: visual analysis, semantic knowledge (see ‘Memory’ section, later on), and word production (phonology). Virtually all patients with aphasia are anomic when tested using items of low fa- miliarity and late age of acquisition. The type of naming error and the ability to circumvent the deficit varies, however, according to the locus of damage. Patients with visuoperceptive deficits that produce visual errors (a ‘head’ for a ‘mushroom’, and so on) have retained tactile naming and can give correct responses when asked to put a name to a description (‘What do we call the large grey African animal with a trunk?’). A breakdown in the central semantic process causes impairment in naming from all modalities, whereas phonological deficits pro- duce phonological errors regardless of the mode of input. Repetition Lesions involving any of the perisylvian language structures are al- most always associated with impaired repetition, although this may not be apparent unless multisyllabic words (‘caterpillar’, ‘funda- mental’, and so on) and phrases (‘no ifs, ands, or buts’) are tested. Certain aphasic syndromes (see next) show either disproportionate impairment or preservation of repetition. Aphasic syndromes Broca’s aphasia This classic form of nonfluent aphasia is characterized by grossly distorted speech output with impaired production and comprehen- sion of syntax. Speech is typically halting and distorted by sound- based errors and simplification of grammar. There is great difficulty repeating words and phrases. It is associated with lesions to the left ventrolateral frontal lobe (Broca’s area); owing to its close proximity Table 24.4.1.1 The features of delirium Onset Usually acute/subacute Course Fluctuating, nocturnal exacerbations Conscious state May be impaired, derangement of normal

sleep–wake cycle Cognitive profile Disoriented in time and place Severe impairment of attention (with knock-on effects to other cognitive domains, i.e. due to poor registration) Psychiatric features Incoherent and perseverative Mood disorders: agitation, apathy Visual illusions and hallucinations Paranoid ideas common Physical signs Asterixis May be evidence of general medical illness (pyrexia, signs of hepatic failure, and so on) Reproduced from Hodges JR (ed.) (2001). Early onset dementia: a multidisciplinary approach. Oxford University Press with permission from Oxford University Press.

24.4.1 Disturbances of higher cerebral function 5825 to the motor cortex, when focal lesions (such as stroke or tu- mour) cause Broca's aphasia, it is typically associated with a right hemiparesis. The distortion of language output, often described as speech apraxia, is thought to relate to concurrent damage to structures within the insula, which is almost always affected. Wernicke's aphasia In Wernicke's aphasia there is fluent, although vacuous, output with a mixture of semantic and phonological paraphasic errors and often neologisms. There is also impaired comprehension of word meanings and impaired repetition. In contrast to the fun- damental loss of word meaning seen in patients with semantic dementia and destruction of the left inferior temporal lobe after herpes simplex encephalitis, patients with Wernicke's aphasia have breakdown in the mapping between speech and meaning systems. Lesions localize to the posterior portion of the left superior tem- poral gyrus—known as Wernicke's area. As this area overlies the optic radiation, the most common neighbourhood sign is a right homonymous hemianopia. Conduction aphasia This form of aphasia, as the name implies, is due to a disconnec- tion of the two principal language areas. Comprehension is relatively preserved and output is fluent, although phonological paraphasias occur. The striking abnormality is an impairment of repetition even for single syllable words such that attempts at repeating are laboured and contain phonological errors. Likewise, naming produces phono- logical errors even for high-frequency items (such as for 'cup': 'cah . . . cab . . . cub', and so on). Lesions producing conduction aphasia occur in the region of the supramarginal gyrus and, particularly, the underlying arcuate fasciculus, the tract linking the anterior and pos- terior language areas. Global aphasia In this devastating form of aphasia there is derangement of all aspects of language; patients with global aphasia are nonfluent and have impaired word comprehension, repetition, and naming. Language output is restricted to infrequent unintelligible noises or, at best, a single word or clichéd phrase. As the blood supply to both language areas is from the middle cerebral artery, global aphasia is not uncommon secondary to proximal occlusion of this vessel. Consequently, these patients are usually also hemiplegic and hemianopic. Aphasia in degenerative dementias Although the early hallmark of Alzheimer's disease is typically memory impairment, aphasia becomes a universal feature as the disease progresses. It manifests predominantly with word-wording difficulties in conversation. Underlying semantic knowledge also be- comes impaired, though the key early deficit is lexical retrieval (i.e. retrieving the word that corresponds to the semantic concept). This manifests as anomia in confrontation naming tasks but with rela- tively preserved performance when the patient is given a word and must define, or point to, it. A minority of patients with Alzheimer's disease can actually present with this kind of aphasia, instead of the usual memory impairment. In other words, Alzheimer's can occa- sionally present as a form of primary progressive aphasia in which case it is often given the syndromic label 'logopenic' primary pro- gressive aphasia. The other forms of progressive aphasia include semantic dementia (also called the semantic variant of progressive aphasia) and non- fluent progressive aphasia. The core deficit of semantic dementia is a loss of semantic knowledge (see 'Semantic memory' section) that, in turn, has a knock-on effect on language in that one cannot name items if

they do not recognize them in the first place (in contrast to word-finding difficulties seen in early Alzheimer's disease where the patient recognizes an item but just cannot produce its precise name). Conversation in semantic dementia may contain substitutions of higher-frequency words (e.g. 'at Christmas I cooked the big chicken' instead of turkey), but often conversation can sound remarkably normal. This is, presumably, because they do not search for the names of items or concepts when they no longer have knowledge of such items. As such, there can be a striking discrepancy between fairly normal sounding patient-initiated conversation and their be- wilderment when asked to define specific words. Nonfluent progressive aphasia, as the name suggests, causes slow, effortful speech that is typically easy to recognize in conversation. A difference to the classic Broca's aphasia resulting from stroke is that the language is typically not telegraphic. Grammatical dysfunc- tion typically manifests with simplification of grammatical structure rather than overt grammatical errors. Dyslexia Patients with aphasia show dyslexic difficulties in keeping with their type of aphasia, so those with fluent aphasia will struggle to under- stand the meaning of words in printed form, whereas those with nonfluent aphasia have trouble with grammatical aspects of reading (particularly word endings: -ed, -ing, and so on). Within acquired dyslexia, however, dissociations have been defined for reading single words; these syndromes are known as deep and surface dyslexia. Deep dyslexia and surface dyslexia There may be a dissociation between ability to read orthograph- ically regular (pronounced as they are spelt) words such as 'mint', 'flint', and 'hat', and irregular words such as 'pint', 'cellist', and 'island'. Difficulty reading the latter type is known as surface dyslexia and is one of the hallmarks of semantic dementia; for an irregular word such as 'pint' or 'yacht' to be read correctly, the reader must access knowledge of the word meaning because the graphical representa- tion of the word alone (i.e. its 'surface' structure) will not lead to cor- rect pronunciation. If the semantic knowledge base (located in the dominant temporal lobe) breaks down, the word can be pronounced only according to the rules of graphical-to-phonological translation and thus 'pint' will be pronounced like 'mint' (known as a 'regular-ization' error)—in other words, analogous to how a normal person would pronounce a nonword, such as 'rint'. A complementary syndrome is that of deep dyslexia in which pa- tients produce semantic paralexias when reading (reading 'prison' for 'gaol' or 'beer' for 'pint'), are unable to read nonwords, and have greater difficulty with abstract than with concrete words. This, sim- plistically, is thought to represent a loss of the grapheme-to-phoneme route with intact semantic knowledge (i.e. its 'deep' meaning). Deep

 dyslexia is typically seen in patients with extensive left hemisphere lesions and global aphasia. Alexia without agraphia This syndrome represents a classic disconnection syndrome of visual input from language areas due to a lesion in the left occipital lobe and adjacent splenium (disrupting input from the right occipital lobe); as such, although the right occipital cortex is capable of registering text, the information cannot be decoded by the language hemisphere. Patients are not aphasic and can write normally; they cannot read but can say words spelt out loud to them. Visual field testing shows a right homonymous hemianopia. Patients rapidly relearn how to read by identifying individual letters and reconstructing words by a laborious and slow letter-by-letter reading strategy. Agraphia Various acquired disorders of writing occur as homologues of other cognitive deficits, for example patients with aphasia make writing errors consistent with their aphasic syndrome (e.g. patients with Broca's aphasia will make errors in writing syntax), deep and surface dysgraphias give rise to similar errors as deep and surface dyslexia, and ideomotor apraxia (see next) will cause a disorder in motor exe- cution such that writing will be of poor quality. Visuospatial and perceptual disorders The regions of the brain

concerned with the higher-order analysis of visual information can be divided into a dorsal (occipitoparietal) pathway concerned with spatial information and preparation for reaching, and a ventral (occipitotemporal) pathway concerned with identifying visual stimuli. In other words, the dorsal stream is involved in ‘where?’ and ‘how?’ and the ventral with ‘what?’ information for a given visual stimulus. Some of the most striking neuropsychological syndromes are seen following selective damage to one stream. The dorsal stream and Balint’s syndrome Constructional apraxia, an inability to draw or copy line drawings such as wire cubes and clock faces, is a common finding in par- ietal pathology, particularly with right-sided lesions. More severe breakdown in spatial cognition, causing individuals to misreach for visually guided targets, trip on steps, or collide with furniture when walking, is seen with bilateral parietal diseases (such as watershed infarction, the ‘posterior cortical atrophy’ variant of Alzheimer’s dis- ease, and venous sinus thrombosis) and results clinically in Balint’s syndrome, the features of which are simultanagnosia, optic ataxia, and ocular apraxia. Simultanagnosia is the inability to integrate and make sense of an overall visual scene in spite of preservation in the ability to identify individual elements. Such patients are relatively better at identifying small objects; this can also be demonstrated by an inability to read vertically printed words although they can be read when printed normally. Ocular apraxia describes the inability to direct gaze to a novel visual stimulus, whereas optic ataxia is the inability to reach accurately for a visually guided target. Spatial neglect Although considered under the visuospatial heading, spatial neglect is really a cross-modality disorder that typically involves the neglect of all sensory information (visual, tactile, auditory) from the side contralateral to the lesion. Chronic neglect virtually only occurs in the context of right parietal lobe damage. Right hemispatial neglect after an acute left parietal lesion can occur, but is usually less se- vere and tends to resolve within days. In addition to being a cross- modality disorder, it is not correct to define a ‘hemispatial field’ in purely retinotopic terms, for example, if a patient who exhibits neg- lect on visual field testing has the body turned to face the neglected extrapersonal hemispace (with head and eyes fixed in the original position), the neglected space is reduced. Visual neglect is best tested by cancellation (crossing off ‘A’s on a sheet of paper containing randomly arranged letters), drawing (clock, house, flower), or line bisection tasks. Patients with severe visual neglect may even appear to be hemianopic. A milder form of neglect can be elicited by ‘sensory extinction’ of the neglected side during bilateral sensory stimulation (visual and somatosensory at the bedside, although auditory neglect can be demonstrated experi- mentally). Patients often have associated hemiparesis, although as part of their neglect syndrome they may deny this impairment— a phenomenon known as anosagnosia. When presented with the hemiparetic limb they may even deny that it is their own. The ventral stream Lesions to the occipitotemporal pathway give rise to difficulty recognizing visual stimuli which is not a consequence of being unable to appreciate where an object is in space, as is the case in simultanagnosia. This deficit is known as visual object agnosia and has been divided further into aperceptual and associative var- ieties. In aperceptual agnosia, basic aspects of vision (acuity, fields, and contrast sensitivity) are intact, but patients cannot identify, or match, identical objects and have grave difficulty copying line drawings, although knowledge of these objects is intact if tested using other inputs such as describing from name. In contrast, as- sociative agnosia describes a state where loss of object knowledge occurs such that, although patients can copy line drawings well and match perceptually identical pictures, they cannot match nonperceptually identical images such as different angles of the same face or, for example, tell that two different types of clock are both clocks. Associative agnosia is a cross-modality disorder such that knowledge of objects is impaired in nonvisual modalities— in other words one component of generalized failure of semantic knowledge (see next). Differentiation of

these agnosias requires the use of test material found only in neuropsychology labora- tories. One component of object knowledge is colour, loss of which (achromatopsia) usually accompanies occipitotemporal lesions and is more accessible to bedside evaluation. A restricted form of impaired object recognition relates to faces. Known as prosopagnosia, the person can no longer recognize previ- ously familiar faces but can recognize their voices and have access to knowledge from their names. Usually bilateral lesions of the inferior occipitotemporal junction are responsible, although cases with le- sions restricted to just the right side have been described. Memory Memory is divided by researchers into implicit and explicit sub- types (also known as nondeclarative and declarative, respectively).

24.4.1 Disturbances of higher cerebral function 5827 Implicit memory refers to unconscious memory systems such as that responsible for conditioning as well as memory for motor tasks such as hitting a golf ball or playing a piece of music ‘by heart’. Explicit memory, in contrast, refers to consciously apprehended memory and is further divided into episodic and semantic memory. In clin- ical terms, when one refers to memory, it is only the explicit type of memory that is considered. When assessing memory complaints it is useful to apply a theoretically motivated approach to analysing symptoms according to the subcomponent of memory involved. In broad terms, memory subtypes can be considered under the fol- lowing headings. Working memory Working memory refers to the amount of information that can be held by the brain ‘online’ (such as reading a phone number then holding it as the object of one’s attention until the number can be dialled, or solving mathematical problems in the head); in the ab- sence of rehearsal, when the focus of one’s attention has moved to a novel topic for more than a few seconds, such items are lost. Working memory is also referred to as ‘short-term’ memory by psychologists, although this latter term is often used by patients and their doctors to describe recently acquired episodic memory (see next); it also in- volves aspects of attention (see earlier) so, to avoid confusion, the term ‘working memory’ is preferable. Slips of working memory are often erroneously seen by patients as the harbinger of dementia and thus these individuals are commonly referred to memory clinics: these lapses of attention (such as forgetting why you opened the refrigerator door or went into the study, or immediately forget- ting a new telephone number) are common everyday phenomena which are increased with anxiety and depression, and also occur more commonly with advancing age. Complaints of this type are also common after head injury and in basal ganglia disorders. Semantic memory Semantic memory refers to the brain’s knowledge store of, for ex- ample, objects and word meanings; it is also the term applied to knowledge of facts, such as that Paris is the capital of France, can- aries are small yellow birds kept as pets, or Ronald Reagan was a president of the United States of America. Evidence from the study of semantic dementia suggests that the ventral region of the tem- poral lobes (particularly the rostral fusiform gyrus) are particularly critical to supporting semantic knowledge. The extent to which hemispheric specialization for different types of semantic know- ledge (words, objects, people, and so on) exists remains a subject for debate; loss of word knowledge appears to relate preferentially to left temporal damage whereas some visual material including faces may be more dependent on the right temporal lobe. Loss of memory for words is the usual complaint in patients with a primary disorder of semantic memory such as semantic dementia and after herpes simplex virus encephalitis. However, it is important to distinguish between the occasional word-finding lapse, usually for proper nouns, which occurs normally (especially in later life), and the relentlessly progressive loss of vocabulary, which occurs in association with left temporal lobe pathology. Low-frequency words are the most vulnerable and patients with semantic dementia often have some

insight into this problem in the early stages (e.g. a car- penter may complain that he can no longer remember the names of tools). People with Alzheimer's disease show a similar phenomenon, although it is usually a late feature compared to their profound early episodic memory deficit. Breakdown in semantic memory manifests as an inability to name objects or drawings with the production of broad superordinate re- sponses (such as 'animal' for 'elephant') and the inability to define the meaning of words. Category fluency (the ability to generate ex- emplars from a given semantic category such as types of animals, kitchen utensils, or birds) is another sensitive measure of semantic memory. Knowledge of famous people can be tested by identifying photographs and names, or asking the patient to list prime ministers in chronological order. Episodic memory Episodic memory refers to the event-based memories unique to each individual, in other words our recollection of personally experi- enced episodes (indeed, it is sometimes termed 'autobiographical' memory). Difficulty with the acquisition of new event-based mem- ories (such as inability to recall details of a television programme or conversation with a friend despite good attention at the time) is the hallmark of early Alzheimer's disease and other causes of the am- nesic syndrome (Table 24.4.1.2). Lesions that give rise to amnesia involve the limbic system of the brain (especially the hippocampi and their connections—Fig. 24.4.1.1). Although bilateral involve- ment is usually required to cause a full-blown amnesic syndrome, neuropsychological testing can often reveal a selective deficit in verbal or nonverbal memory in cases of left- or right-sided damage, respectively. Retrograde memory (established before the amnesic insult) is typically better than anterograde memory (established any time after) in amnesic syndromes and, within retrograde memory, very remote memory is classically (although not universally) better preserved than recent memory. On examination, patients with amnesia have a striking inability to relate anecdotes from their recent life, although in cases of basal forebrain amnesia they may offer confabulations. Amnesia can be assessed in the clinic by asking the patient to learn some information such as a new name and address; patients with amnesic syndromes (including early Alzheimer's disease) typically repeat a name and address perfectly after two to three trials, but show very rapid for- getting and recall little or nothing after a delay of a few minutes of a distracting task. Amnesia may occur as a temporary state as is seen with tran- sient global amnesia (TGA), in which there is a sudden onset of se- vere amnesia that lasts several hours before resolution; afterwards the patient, characteristically elderly, is left with an islet of amnesia for the hours of the episode. TGA typically occurs as a solitary epi- sode; recurrent attacks of self-limiting amnesia occasionally occur as a consequence of epileptic activity, hence the term 'transient epi- leptic amnesia' (TEA). Attacks of TEA are typically briefer than TGA (<1 h for TEA versus several hours for TGA) and frequently occur on waking. Apraxia Apraxia is defined as a loss of ability to carry out skilled motor tasks that cannot be explained in terms of an elementary disorder of motor control (weakness or ataxia), primary sensory disturbance, or a global impairment of cognition. In the early 20th century Liepmann

SECTION 24 Neurological disorders 5828 distinguished three types of apraxia—limb–kinetic, ideomotor, and ideational—and, although these terms have suffered from a lack of universally accepted definition, they are still widely used today. In an attempt to clear up ambiguity, the terms 'production' and 'concep- tual' apraxia are also now used to indicate ideomotor and ideational apraxia according to the definitions listed next. Limb–kinetic apraxia refers to the loss of fine motor dexterity that can be seen, for instance, with mild pyramidal lesions (such as after recovery from stroke). In spite of apparently good strength and co- ordination, the person cannot manage tasks requiring fine motor control such as tying a shoelace or buttoning a shirt. As such, ac- cording to

the aforementioned definition, this is not a ‘true’ apraxia but rather an artefact of the insensitivity of bedside tests of the motor system: in other words a primary motor deficit is unmasked only by tasks more demanding than routine tests of power and coordination. Ideomotor (production) apraxia refers to the inability to execute the motor programme for a given task (the temporal and spatial organization of movement) in spite of adequate comprehension, as demonstrated, for instance, by the ability to describe the cor- rect execution of the task (such as sharpening a pencil: ‘You put the pointed end of the pencil into the hole then turn it’) or to iden- tify correctly a task when done by someone else. Patients with ideomotor apraxia also have problems performing meaningless (nonsymbolic) gestures. Ideational (conceptual) apraxia, in contrast, is a loss of know- ledge of actions: there is an inability to either perform or recognize a given motor task. There is also an inability to match tools correctly to their actions, so a person may select a screwdriver to hammer a nail. Unlike patients with ideomotor apraxia, they do not show disorders of the spatial and temporal aspects of action and thus their tool use, although incorrect, is fluent. To screen for apraxia, patients should be asked to perform skilled motor tasks to verbal instruction or to imitation including both meaningful and meaningless gestures. If deficits are un- covered, tests such as correctly identifying mimes performed by the examiner and matching tools to functions should be given. Subtle disorders of praxis may be evident only with low-frequency tasks (such as using a vegetable peeler or a pencil sharpener as op- posed to a knife or a hairbrush). When asked to mime an action (such as hair combing or brushing teeth), ‘body part as tool’ errors are often cited as evidence for apraxia: the patient uses his or her hand as the tool (e.g. rubbing an extended index finger over the teeth as a toothbrush). It is, however, not uncommon for normal individuals to make these ‘body part as tool’ errors when asked to perform such tasks, hence it is essential when this type of error is committed to draw it to the person’s attention and reinstruct
Table 24.4.1.2 Causes of the amnesic syndrome Type Common aetiologies Transient Transient global amnesia Transient epileptic amnesia Closed head injury (may be permanent) After electroconvulsive therapy Drugs (especially ethanol) Anatomically defined Hippocampus (and adjacent mesial temporal structures) Alzheimer’ s disease Herpes simplex encephalitis Limbic encephalitis (paraneoplastic; autoimmune with voltage-gated potassium antibodies) Watershed infarction: cardiac arrest, CO poisoning, and so on Complicating epilepsy surgery Diencephalon (dorsomedial and anterior thalamus;
mamillary bodies) Korsakoff’s psychosis Infarction (watershed, deep perforator occlusion, ‘top of the basilar’ syndrome) Basal forebrain Ruptured anterior communicating artery Aneurysm Fornix Complicating colloid cyst removal from third ventricle Retrosplenial/posterior cingulate
Various: tumour, haemorrhage, and so on Alzheimer’s disease? Psychogenic (nonorganic)
Thalamus Posterior cingulate Fornix Mammillary body Basal forebrain Hippocampus Fig. 24.4.1.1 Principal connections of structures critical to sustaining human memory.

 accordingly. Normal individuals are able to correct these errors, whereas those with apraxia cannot. In terms of the neural substrate for production (ideomotor) apraxia, the overwhelming majority of cases follow damage to the left (dominant) hemisphere. More specifically, there is evidence that a motor system incorporating the superior parietal lobule (Brodmann’s areas 5 and 7) and the premotor area of the left frontal lobe are particularly critical to the temporal and spatial organiza- tion of motor programmes. Conceptual apraxia is also indicative of left hemisphere dysfunction in most cases, although whether a more specific site can be identified is contentious. It is also important where a conceptual apraxia is suspected to ensure that it is not just one manifestation of a more generalized breakdown of semantic knowledge (see ‘Memory’, earlier). Buccofacial apraxia represents a specific form of

apraxia in which patients are unable to perform tasks such as licking the lips or blowing out matches to command. It is particularly associated with nonfluent aphasia, presumably as the motor programming of articulation and nonlinguistic buccofacial movements share a common pathway. Personality and behavioural change So far, disorders of higher mental function have been considered in quite discrete terms, in the sense of both the cognitive deficit and the cerebral location. Alterations in complex behaviour, personality, and social comportment cannot, however, be so simply defined, but are broadly associated with frontal or anterior temporal lobe pathology. The key to identifying such disorders is the presence of a sustained change from a previous state (thus differing from a lifelong eccentric personality), which cannot be explained by a primary psychiatric diagnosis. The only reliable way to confirm such changes is by taking a separate history from a partner or other close personal acquaint- ance with knowledge of the patient's premorbid personality. Prefrontal syndromes The prefrontal cortex comprises that part of the frontal lobe rostral to the premotor area; it is classified as heteromodal association cortex and receives extensive inputs from unimodal association areas pos- terior to the central sulcus. The frontal lobes also have loop projec- tions running to the basal ganglia, then the thalamus, and back to the frontal lobes. Thus, lesions along this loop (as seen in conditions such as Huntington's disease or progressive supranuclear palsy) may also share deficits in common with primary frontal lobe disorders. Anatomically, the prefrontal cortex can be divided into dorsolateral, orbital, and medial surfaces; although in many cases damage will not be restricted to just one of these regions, they provide a useful framework for considering prefrontal functions. Broadly, lesions to the dorsolateral surface are responsible for the frontal 'dysexecutive' syndrome, to the orbital surface for the classic frontal behavioural syndrome, and to the medial surface (anterior cingulate) for a pro- found amotivational state. The dysexecutive syndrome The term 'executive' refers to aspects of higher-order brain func- tion, such as problem-solving, reasoning, and mental abstraction, which rely on the dorsolateral prefrontal lobes. It is also associated with impulsivity, susceptibility to distraction, and failure to perse- vere with the task at hand. Various methods are available to measure these phenomena although no single test offers foolproof sensitivity in this domain, so one should apply as many as possible if the index of suspicion is high. The combination of letter- and category-based verbal fluency pro- vides much useful information. In letter fluency, the patient is asked to generate as many words as they can think of beginning with a given letter in 1 min. They are instructed not to use proper nouns and not to just change the endings to create new exemplars ('go, goes, going', and so on). Neuropsychologists typically use the letters F, A, and S for this test, so it is best to choose another letter if it is likely that patients are also going to have a formal neuropsychological as- sessment. In category fluency, patients are asked to produce as many exemplars as possible from a given category in 1 min. Normal in- dividuals usually generate 15 or more words on letter fluency and do slightly better on the 'animal' category. Patients with executive deficits secondary to frontal (or the subcortical loop) pathology show an exaggeration of this relationship, doing poorly on category fluency but even worse on letter fluency (patients with semantic impairments related to temporal lobe diseases such as semantic de- mentia and Alzheimer's disease typically show the reverse pattern of relatively worse performance on category fluency). The 'go–no go' test offers a way of assessing impulsivity: the pa- tient is asked to tap the desk once if the examiner does so, but, if the examiner taps twice, he should not tap at all. Patients with frontal pathology are often unable to stop themselves from tapping in both conditions. Failure to abstract meaning from proverbs ('What does 'too many cooks spoil the broth' mean?') is a common test but is influenced by background intellectual ability and is culture bound. The so-called 'cognitive estimates' test can be useful ('What is the dis- tance from London to Paris?' or 'How fast does a racehorse gallop?'), as are 'differences and similarities' ('What's the difference between a

child and a dwarf?’ or ‘In what way are a sculpture and a piece of music similar?’). Finally, the susceptibility to irrelevant stimuli mean that the tests of attention discussed here may also be impaired. It is important to note, however, that unlike cognitive neuro- psychological tests of, for instance, memory or language, executive function—indeed cognitive functions ascribed to the frontal lobes in general—is much more inconsistently related to pathology at an individual patient level. Abilities such as problem-solving, mental flexibility, and abstraction overlap considerably with general intelli- gence, for example, a patient who responds that a racehorse gallops at 100 miles/h, or, that London is 1000 miles from Paris, may simply have a poor knowledge of velocity and geography rather than being ‘dysexecutive’. On the other hand, patients with unequivocal frontal lobe pathology may sometimes be hard to fault on tests of executive function, in spite of problems in day-to-day life. This stands in con- trast to patients with, for example, Korsakoff’s psychosis who will display evidence of amnesia regardless of how one chooses to test memory. Orbitofrontal syndrome The striking changes in behaviour seen in patients with prefrontal lesions relate particularly to orbital (or ventral) surface damage. An important caveat to this locationist account is that most studies derive observations from either static lesions or frontotemporal dementia, in which damage usually extends beyond the orbital

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