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Cognitive function, neuropsychological evaluation, and syndromes of cognitive impairment

1.1 Domains of cognitive function

Without necessarily subscribing to an explicitly modular concept of cerebral function, it is nonetheless convenient from the clinical standpoint to think in terms of cognitive domains or functional systems ("a congeries of mental faculties") in the brain, specifically attention, memory, language, perception, praxis, and executive function. These subdivisions, all working in concert not in isolation to produce in sum what we understand by consciousness, may direct a structured approach to the clinical assessment of cognitive function. Nowadays, a model of distributed neural networks with nodal points more specialized for certain functions has supplanted the idea of particular brain centers [1].

The neurocognitive domains may be described as either *localized*, implying lateralization to one hemisphere or part thereof, focal damage to which may impair that specific function; or *distributed*, implying a nonlocalized function often involving both hemispheres and/or subhemispheric structures (basal ganglia, brainstem), widespread damage being required to impair these functions [2]. Furthermore, particular domains may be subdivided, or fractionated, into subsystems or specific functions that may be selectively impaired,

suggesting the existence of functionally distinct neuropsychological substrates.

1.1.1 Attention

It is surely redundant to point out that before any meaningful assessment of "higher cognitive function" can be made, it should be ascertained that "lower cognitive function" is intact, assuming that the workings of the nervous system are hierarchical (in the Jacksonian sense) in their operation. To indulge in *reductio ad absurdum*, it would not be reasonable to expect a comatose patient, or a sleeping subject, to perform well on tests of memory, although memory function may be intact or impaired on recovery from coma or awakening from sleep.

The nature of consciousness is an area of great interest to both neuroscientists and philosophers [3–7], but other than to assume that it is an emergent property of brain function, nothing further about its possible neuroanatomical and neurophysiological bases will be considered here, other than to note that dissociation between apparent preservation of consciousness and absence of cognitive function may occur, as in vegetative states [8], although this has been questioned on the basis of neuroimaging [9] and electroencephalography (EEG) studies [10].

Disturbance of consciousness may encompass both a quantitative and a qualitative dimension. Hence, one may speak of a "level" of consciousness, perhaps in terms of arousal, alertness, or vigilance, forming a continuum from coma to the awake state; and an "intensity" or quality of consciousness, in terms of clarity of awareness of the environment, and ability to focus, sustain, or shift attention. There are various clinical descriptors of states of impaired consciousness including coma [11], vegetative state [8], and minimally conscious state [12]. Coma implies a state of unresponsiveness from which a patient cannot be roused by verbal or mechanical stimuli. Lesser degrees of impaired consciousness, sometimes labeled clinically as stupor, torpor, or obtundation (although these terms lack precision, their meaning often varying between different observers), may also interfere with cognitive assessment. These states may be obvious clinically, such as drowsiness, or difficulty rousing the patient, but may also be occult, perhaps manifesting as increased distractibility. Impairments in level of consciousness are a *sine qua non* for the diagnosis of delirium, as enshrined in the diagnostic criteria of the *Diagnostic and Statistical Manual* (DSM-IV) and the *International Classification of Diseases* (ICD10), although these deficits may be subtle and not immediately obvious at the bedside but yet sufficient to impair attentional mechanisms. These attentional deficits may be responsible for the impaired cognitive function that is also a diagnostic feature of delirium (Section 12.1) [13,14].

Attention, or concentration, is a nonuniform, distributed cognitive function. It may be defined as that component of consciousness which distributes awareness to particular sensory stimuli. The nervous system is bombarded with stimuli in multiple sensory domains, only some of which reach awareness or salience while many percepts are not consciously noticed. Attentional resources, which are finite, are devoted to some channels but not to others. Attention is thus effortful, selective, and closely linked to intention. Distinction may be made between different types of attentional mechanism: sustained attention implies devotion of most attentional resources to one particular stimulus, whereas selective attention is the directing of attentional resources to one stimulus among many (the "cocktail party phenomenon"); divided attention implies a division of attentional resources between competing stimuli. Various neuroanatomical structures are thought to be important in mediating attention, including the ascending reticular activating system in the brainstem, the thalamus, and prefrontal cerebral cortex of multimodal association type, particularly in the right hemisphere, as damage to any of these areas may result in impairments of attention [15]. Dopaminergic and cholinergic tracts are thought to be the important

neurotransmitter pathways mediating attention [16].

The term "working memory" is used by neuropsychologists to describe a limited capacity store for retaining and manipulating information over a short term, one to two minutes, and for "online" manipulation of that information. This system has a limited capacity wherein information rapidly degrades unless continuously rehearsed (hence "unstable," compared to longer-term memory). Working memory may be fractionated into a number of subsystems: verbal (phonological or articulatory loop) and visual (visuospatial sketch pad) components, governed by a supervisory central executive, as well as a postulated episodic buffer that acts as a multimodal temporary store to interface with perception and long-term memory [17]. Working memory function is dissociable from "long-term memory" function (Section 1.1.3); for example, in patients with amnesia as a consequence of Wernicke–Korsakoff syndrome, working memory is preserved (Section 8.3.1.1). Working memory is perhaps better envisaged as a component of the selective attention system (the "specious present" of William James), and is certainly not congruent with the usage of the term "short-term memory" by patients, which generally refers to recent long-term memory. Grammatical complexity, for example in sentence construction, is associated with working memory capacity, which mediates the need to keep many elements in play and not lose the train of thought before completing the sentence.

Another clinical phenomenon related to attentional processes is neglect. Sometimes also known as inattention, neglect is a failure to orient to, respond to, or report novel or meaningful stimuli in the absence of sensory or motor deficits (such as hemiparesis or hemianopia), which could explain such behavior. Extinction, the failure to respond to a novel or meaningful sensory stimulus on one side when a homologous stimulus is given simultaneously to the contralateral side (i.e., double simultaneous stimulation), sometimes called "suppression," may be a lesser degree of neglect. In the visual domain, neglect may be categorized as a disorder of spatial attention, which is more common after right-sided rather than left-sided brain damage, usually of vascular origin. This observation may be accounted for by the ability of the right hemisphere to attend to both sides of space whereas the left hemisphere attends to the right side of space only (i.e., there is some lateralization of function). The angular gyrus and parahippocampal gyrus may be the critical neuroanatomical substrates underpinning the development of visual neglect [18,19].

In terms of clinical assessment, the Glasgow Coma Scale (GCS) is the instrument most commonly used for monitoring the level of consciousness [20]. Introduced originally to assess the severity of traumatic head injuries, it has subsequently been applied in other clinical situations (e.g., delirium, stroke), although its validity in some of these circumstances remains to be confirmed. In the individual patient, use of the individual components of the GCS (best eye, verbal, and motor response or EVM) is more useful than the summed score (out of 15), although for the purposes of demographic research use of the summed score is preferable. It should be noted that a GCS score of 15/15 does not guarantee intact attention, as deficits may be subtle, and therefore it may be necessary to undertake other tests of attentional function before other neuropsychological instruments are administered.

Many tests of attention are available. Examples included the Trail Making Test, the Continuous Performance Test, the Paced Auditory Serial Addition Test (PASAT) and its visual equivalent (PVSAT), and the Symbol Digit Modalities Test. Simple bedside tests that tap attentional mechanisms include orientation in time and place, digit span forward and/or backward (also WAIS-R Digit Span subtest), reciting the months of the year or the days of the week backward, or counting back from 30 down to 1. Distractibility may be evident if the patient loses his or her way, or starts the more automatic forward recital. In the Mini-Mental State Examination (MMSE), the most commonly administered "bedside" or office test of cognitive function [21], subtracting 7 from 100 repeatedly (serial sevens:

93,86,79,72,65, etc.) or spelling the word "world" backward are labeled as tests of attention or concentration, but it should be realized that failure in these tests may be for reasons other than impaired attention (e.g., poor mental arithmetic abilities in serial sevens).

Neglect may be clinically obvious, for example if a patient fails to dress one side of the body, but it is sometimes more subtle, in which case its presence may be sought using cancelation tests (e.g., stars in an unstructured array, or letters in a structured array), figure copying (e.g., the Rey–Osterrieth complex figure), line bisection tasks, numbering a clock face, or drawing from memory.

1.1.2 General intelligence (IQ)

Formal neuropsychological assessment often involves testing of general intelligence (IQ) before any specific assessment of the individual domains of cognitive function. This is legitimate as a general intelligence factor "g" seems to account for a significant proportion of the individual differences among test scores for groups of people [22]. General intellectual function is most often measured by administration of one of the Wechsler Intelligence Scales, most often the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [23] or the Wechsler Adult Intelligence Scale-III (WAIS-III) [24]. Updating of these tests is required periodically because of changes in the abilities of the normative group from which standardized scores are derived [22]. Studies over time and from around the world suggest that IQ is rising at the rate of three points every decade, the "Flynn effect" [25].

Administration of these tests may take up to two hours or more, sometimes necessitating more than one testing session to avoid patient fatigue. Subtests in these batteries fall into two categories, verbal and performance, the former including tests of general knowledge, vocabulary, comprehension, and verbal abstract thinking (e.g., digit span, arithmetic, similarities), and the latter including tests of perceptual organization, complex visuospatial function, and psychomotor speed (e.g., digit symbol, picture completion and arrangement, block design, object assembly). These subtests yield an index of verbal intelligence, verbal IQ (VIQ), and of performance intelligence, performance IQ (PIQ), as well as an overall full scale IQ (FSIQ). Based on extensive normative data from healthy North Americans and Europeans, these measures have a mean score of 100 with a standard deviation of 15 such that 95% of the population will fall within the range 70–130. Generally VIQ and PIQ are correlated, but occasional discrepancies may be seen in normal individuals. The belief that the VIQ–PIQ split can be reliably used to infer the lateralization of brain pathology (VIQ more impaired in left-sided lesions, PIQ with right-sided lesions) should be viewed with some caution [26].

When assessing individuals complaining of cognitive disorders, especially memory disorders, an IQ score per se may not be particularly helpful. However, change in IQ, possibly reflecting cognitive decline, is more useful, but it is seldom the case that an individual patient will have undergone previous testing with which a comparison may be made. Previous educational and occupational history may give clues to premorbid intelligence, as may performance on verbal subtests of the WAIS batteries. This difficulty may also be partially circumvented by administering a test specifically designed to estimate premorbid intellectual abilities, such as the National Adult Reading Test (NART) [27], because the overlearned ability to read a series of words with irregular spelling-to-sound correspondences is relatively preserved in a number of neurodegenerative disorders (there are exceptions such as frontotemporal lobar degenerations causing linguistic syndromes; Sections 2.2.2 and 2.2.3). The NART IQ may then be compared with the Wechsler FSIQ to give some indication of whether general intellectual function is stable or has declined. A difference of 20 points is probably significant, 40 points certainly so.

Nonverbal tests of general intelligence are also available, such as the Progressive Matrices described by Raven [28,29]. Other tests examining

general cognitive functioning by means of neuropsychological batteries and assessment of premorbid intelligence are available.

1.1.3 Memory

Memory is a nonuniform, distributed cognitive function or "subassembly" [30]. In other words, subdivisions in memory function may be differentiated, which involve various neuroanatomical substrates.

Current taxonomies of memory propose a distinction between declarative (also known as explicit or conscious memory) and nondeclarative memory (implicit, procedural, unconscious memory). Declarative or explicit memories are intentional or conscious recollections of previous experience. Declarative memory may be subdivided further into episodic memory and semantic memory. Episodic memories are specific personal events, sometimes known as autobiographical memories, which are time and place (context) specific, whereas semantic memories are facts, a database of culturally approved knowledge independent of any specific context. A distinction may also be drawn between anterograde memory, the laying down of new memories, and retrograde memory, the store of previously encoded material. An autobiographical–semantic dissociation of retrograde memory loss may be noted. In contrast with explicit memory, implicit memories refer to a heterogeneous collection of faculties, such as skill learning, priming, and conditioning, which are not available to conscious thought or report [31–33].

In clinical practice, lay observers and primary care physicians frequently distinguish between problems with "short-term memory" and "long-term memory," most usually referring to material learned recently or in the more distant past, respectively. Such a division persists in professional terminology, although the meanings are different. Professional "short-term memory" is analogous to "working memory," best conceptualized as an attentional function (Section 1.1.1). Patient "short-term memory" is in fact one component of professional "long-term memory" (which encompasses all the subdivisions previously mentioned), specifically that for the learning of new information. Amnesia is the syndrome of impaired memory and new learning, which may be variously characterized as anterograde or retrograde and acute/transient or chronic/persistent. Anterograde amnesia may be clinically manifested as repeated questioning about day-to-day matters, inability to carry out simple chores, or repeating the same information. A better distinction may be between "recent" and "remote" memory.

The neuroanatomical substrates of explicit memory are partially understood, based on studies of experimental animals and of patients developing memory problems as a consequence of focal brain lesions that may be examined by means of neuropsychological testing and, more recently, neuroimaging. The literature makes reference to hippocampal, diencephalic, and frontal and basal forebrain amnesia, largely based on lesion and neuropathological studies. Structures in the medial temporal lobe, centered on the hippocampus, and in the diencephalon surrounding the third ventricle are thought to be crucial to episodic memory. Lesions anywhere along the circuit originally described by Papez (entorhinal area of the parahippocampal gyrus, perforant and alvear pathways, hippocampus, fimbria and fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nuclei, internal capsule, cingulate gyrus, and cingulum) may lead to anterograde and retrograde amnesia. Furthermore, memory functions are lateralized in a material-specific manner, with verbal memory functions being associated with the dominant (usually left-sided) structures, and visual memory with the nondominant (usually right) side [34,35].

The experience of the patient known as HM was a key indicator of the importance of these structures for memory function (Section 4.1). Because of his medically refractory epilepsy, HM underwent bilateral medial temporal lobectomy, encompassing the amygdala, entorhinal cortex, anterior dentate gyrus, hippocampus, and subiculum. Surgery

was followed by a dense anterograde amnesia, and retrograde amnesia covering about a decade prior to the surgery [36]. Similar outcomes have been reported, following unilateral surgery, presumably because of subclinical contralateral pathology [37]. Evocative terms used to describe the predicament of HM and other similarly affected patients include "marooned in the moment," "fossilized in the past," and living in a "world of isolated impressions." HM was followed up for many years with essentially no improvement in his neuropsychological deficits. His importance in the field of memory research continues to be emphasized [38].

There are many causes of memory disorder [32,39,40]. Impairment of episodic memory is the most common presenting feature of Alzheimer's disease (AD; Section 2.1), sometimes occurring in isolation although other cognitive deficits may be apparent on clinical or neuropsychological assessment. For this reason, and because AD is the most common cause of dementia, neuropsychological test batteries, particularly "bedside" tests, are often weighted toward memory testing, to the relative exclusion of other cognitive domains such as executive function, which has consequences when using such tests to try to identify other neurocognitive disorders in which memory is not the principal domain affected. Anterograde amnesia may also occur as a consequence of open or closed head injury (post-traumatic amnesia), Wernicke–Korsakoff syndrome (Section 8.3.1.1), herpes simplex encephalitis (Section 9.1.1), limbic encephalitis of paraneoplastic or nonparaneoplastic origin (Sections 6.12.1 and 6.12.2, respectively), strategic brain infarcts (Section 3.2), and surgery to remove temporal lobe or third ventricle lesions (Section 7.2.3). Transient amnesias may be of epileptic origin (transient epileptic amnesia; Section 4.3.1) or, in transient global amnesia, of probable vascular etiology (Section 3.6.2). Psychogenic amnesia may also enter the differential diagnosis of transient amnesia (Section 12.5.1). In addition, a temporal gradient of retrograde amnesia may be present in some of these conditions, but rare cases of focal retrograde amnesia with relative sparing of anterograde memory have been described, sometimes following head injury or an encephalitic illness [41].

Many tests are available to neuropsychologists to probe the specific areas of episodic and semantic long-term memory. The Wechsler Memory Scale, now in its third edition (WMS-III), is a battery testing auditory and visual declarative (and working) memory. Other specific tests of episodic memory sometimes deployed include the Buschke Selective Reminding Test [42], the California Verbal Learning Test [43], the Hopkins Verbal Learning Test [44], the Camden Recognition Memory Test and the Topographical Recognition Memory Test [45,46], and the Rey Auditory Verbal Learning Test. Recall of the Rey–Osterrieth Complex Figure may be used as a test of visual memory. Retrograde memory may be investigated using the Autobiographical Memory Interview [47], which covers both personal semantic information and autobiographical incidents, although this may underestimate the true extent of retrograde amnesia, missing "islands" of memory loss unique to the individual. The Famous Faces Test may be used to study remote memory [48]. Integrity of the semantic network, including semantic memory, may be tested using category (or semantic) fluency tests (Section 1.1.7). Reading words with irregular sound-to-spelling correspondence may produce surface dyslexia (regularization errors) in patients with impaired access to or breakdown of semantic networks. Other tests accessing associative semantic networks include the Pyramids and Palm Trees Test [49].

Of the frequently used "bedside" neuropsychological test instruments, some are specific cognitive tests for memory, such as the Memory Impairment Screen (MIS) [50] and the Free and Cued Selective Reminding (or Five Words) Test [51]. General, multidomain, cognitive screening instruments (e.g., MMSE [21], Addenbrooke's Cognitive Examination [52,53], and Montreal Cognitive Assessment [54]) test memory to a greater or lesser extent; for example, the MMSE has only perfunctory examination of memory function (registration of the names of three objects, e.g., ball, flag, tree, and recall after distractor items). Longer (supraspan) word lists are used in the

DemTect [55] and the Hopkins Verbal Learning Test [44], and the latter includes both recall and recognition paradigms to try to ascertain whether failures result from encoding or retrieval defects. Generally, examination of implicit memory functions is not undertaken in clinical practice.

Rather less has been written about forgetting, as opposed to remembering, but this is presumably also a physiological memory function [56]. It was Nietzsche's belief that "For healthy and effective action, it is as important to forget as to remember, and forgetting, even more than memory, must be an effect of time rather than will" (*On the Uses and Disadvantages of History for Life*). The phenomenon of accelerated long-term forgetting has attracted increasing attention in recent times, whereby memory tests applied at extended intervals (usually greater than 24 hours) may disclose anterograde memory impairments not seen in standard test paradigms. This may be of particular relevance to some of the memory disorders seen in the context of epilepsy (Chapter 4).

1.1.4 Language

Language, "the wind-swift motion of the brain" (Sophocles *Antigone*, line 355), historically provided the first unequivocal evidence that loss of a higher brain function could be ascribed to damage to a specific brain region, based on the work of Paul Broca and, possibly, Marc Dax in the mid-nineteenth century [57]. The work of Carl Wernicke was also seminal in establishing the neural substrates of language function, indicating that language is a localized function. Every medical student now knows that most individuals, whether left- or right handed, have language in the dominant hemisphere, although around 30% of left handers and less than 1% of right handers have language in the nondominant hemisphere.

Aphasia, a primary disorder of language, is often mirrored by similar defects in reading (alexia) and writing (agraphia), all of which are amenable to clinical localization, within certain limitations [58], often on the basis of simple bedside examination. In addition to the Broca (nonfluent, anterior, motor, "expressive") and Wernicke (fluent, posterior, sensory, "receptive") types of aphasia, clinical distinctions may be drawn between conduction aphasia (impaired repetition) and transcortical aphasias (preserved repetition). A classification of aphasias as perisylvian (Broca, Wernicke, conduction), and extrasylvian has also been proposed [59].

It may be necessary to test auditory comprehension before undertaking any other neuropsychological testing of language; for example, using the Token Test [60] in which commands of increasing length and complexity are given for manipulating a deck of colored tokens of differing size and shape (some have objected to the word "token," preferring "item" [61]). Sentence comprehension skills may be ascertained by performance of the Test for the Reception of Grammar [62]. Wernicke-type aphasia typically has marked comprehension impairments, with fluent speech output but often with poverty of content, sometimes reduced to a meaningless jumble of words (jargon aphasia). Although Broca-type aphasia is often characterized as having preserved comprehension, this in fact may be impaired for more complex syntax.

There are many tests of language available to neuropsychologists. Comprehensive batteries include the Boston Diagnostic Aphasia Examination (BDAE) [63], the Western Aphasia Battery (WAB) [64], the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) [65], and the Comprehensive Aphasia Test [66]. Specific tests of naming often deployed include the Graded Naming Test [67] and the Boston Naming Test [68].

At the bedside, listening to speech output will generally permit a simple classification of aphasia as fluent or nonfluent, and also detect paraphasias (phonemic or semantic) and neologisms. From questioning or instructing the patient during history taking and clinical examination, comprehension difficulties may be evident. Testing of repetition may differentiate aphasias in which this ability is relatively preserved (transcortical aphasias) or impaired (conduction aphasia). Naming skills have less localizing value, although marked anomia

should raise the suspicion of semantic problems, either degradation of or access to semantic stores. Reading and writing function should also be examined, even if spoken language function seems intact, as various syndromes of alexia and agraphia are described. Idea density in written material reflects language processing ability.

Of the frequently used "bedside" neuropsychological test instruments, most are heavily weighted for language function, such that patients with primarily linguistic disorders (e.g., semantic dementia, aphasic presentations of AD) may find it difficult or impossible to complete them.

1.1.5 Perception

That perceptions are not a faithful brain response to external stimuli but are to some extent constructed by the brain, based on the expectations of time and culture, has been known by philosophers since Kant, and perception as illusion has been implicitly understood by artists such as Magritte ("the treachery of images") and manifested by artists such as Escher in certain of his graphical works (e.g., *Ascending and Descending, Belvedere*).

Higher-order deficits of sensory processing, not explicable in terms of failure of primary sensory function, or a disorder of attention, intellectual decline, or a failure to name the stimulus (anomia), are known as agnosias, a term coined by Sigmund Freud in 1891 and literally meaning "not knowing" or "without knowledge" [69]. Before this, Lissauer in 1890 [70] (abridged translation by Shallice and Jackson [71]), speaking of *Seelenblindheit*, literally "soul-blindness" or technically "psychic blindness," drew a distinction between apperceptive deficits and associative deficits. In the former, a defect of higher-order complex perceptual processing was deemed to be present, whereas in the latter, perception was held to be intact but a defect in giving meaning to the percept was present. The debate continues as to whether all agnosias, although clinically distinguishable as apperceptive or associative, are in fact attributable to faulty perception [72].

Although auditory and tactile agnosias are described, they seem to be relatively rare in comparison with visual agnosia, which has certainly been more extensively studied. The visual agnosias may be relatively selective; for example, an inability to recognize previously known human faces or equivalent stimuli, known as prosopagnosia. This may be developmental or acquired in origin, the latter usually a consequence of cerebrovascular disease causing bilateral occipitotemporal lesions, but occasionally it occurs as a feature of neurodegenerative disease, sometimes in relative isolation, associated with focal right temporal lobe atrophy (progressive prosopagnosia [73]). Pure alexia or pure word blindness is an agnosia for words that results in a laborious letter-by-letter reading strategy to arrive at a word's identity. Pure alexia may be conceptualized as a consequence of damage to a brain region mediating whole word recognition that may be located in the medial left occipital lobe and posterior fusiform gyrus [74]. The rare syndrome of pure word deafness (Section 1.3.4) may be a form of auditory agnosia. Finger agnosia, the inability to identify which finger has been touched despite knowing that a finger has been touched, is a form of tactile agnosia, which may be seen as one feature of Gerstmann syndrome although it may occur in isolation [75]. Likewise, Braille alexia may, in some instances, be a form of tactile agnosia [76].

The existence of two visual processing pathways within the brain was first proposed by Ungerlieder and Mishkin [77]: an occipitoparietal dorsolateral ("where") visual processing stream and an occipitotemporal ventromedial ("what") stream. In rare cases, these pathways may be affected selectively; for instance, the ventral stream, specifically the lateral occipital area, in a famous patient with "visual-form agnosia" following carbon monoxide poisoning. Her perceptual identification of shape and form was lost, although she could still perceive color and the fine detail of surfaces (visual texture), and her visuomotor ("vision for action") skills were strikingly preserved [78]. Optic ataxia, impaired voluntary reaching for a visually presented target with

misdirection and dysmetria, is the sign typically evident in dorsal stream lesions. The workings of the visuomotor control system are not available to consciousness ("unconscious vision"), unlike the visual identification of objects.

A specific inability to see objects in motion, akinetopsia or cerebral visual motion blindness, despite preserved perception of other visual attributes such as color, form, and depth, has been described in association with selective lesions to area V5 of the visual cortex [79]. Although exceptionally rare, such cases suggest a distinct neuroanatomical substrate for movement vision, as do cases in which motion vision is selectively spared in a scotomatous area (Riddoch's syndrome [80]). Perception within a "blind" visual field without conscious awareness has been termed blindsight [81].

Cases of isolated progressive visual agnosia were presented by De Renzi [82], and Benson *et al.* [83] drew attention to a disorder comprising alexia, agraphia, visual agnosia, with or without components of Balint and Gerstmann syndromes, and transcortical sensory aphasia, but with relative preservation of memory until late in the course, a disorder they named posterior cortical atrophy (PCA) in the absence of neuropathological data. It is now believed that most PCA cases have AD pathology, although other pathologies have been described including dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and prion disease [84].

Various means may be used by neuropsychologists specifically to test visual perceptual and visuoconstructive functions. These may be individual tests such as Judgment of Line Orientation (thought to tap right occipital lobe function); copy of the Rey–Osterrieth Complex Figure ([85,86]; translation by Corwin and Bylsma [87]) or the Taylor Figure [88]; decoding embedded (Poppelreuter) figures [89]; or parts of test batteries, such as the WAIS-R Block Design (visuospatial construction); or dedicated batteries such as the Visual Object and Space Perception Battery (VOSP) [90].

Of the frequently used "bedside" neuropsychological test instruments, the MMSE has only perfunctory examination of visuospatial function, requiring copying a drawing of intersecting pentagons [21]. Clock Drawing is, at least in part, a visuospatial test, but requires other skills. The Addenbrooke's Cognitive Examination (ACE) adds copying a wire (Necker) cube and clock drawing [52], and ACE-R adds counting dots and identifying fragmented letters [53].

1.1.6 Praxis

The term apraxia was coined by Steinthal in 1871 but the phenomena of higher-level motor control disorders were first systematically studied by Liepmann [91], who defined apraxia as an inability to perform purposeful skilled movements as a result of neurological dysfunction, usually associated with left-sided lesions. Part of the definition of apraxia is one of exclusion, as the observed motor difficulties should not be caused by sensory loss, weakness, tremors, dystonia, optic ataxia, chorea, ballismus, athetosis, myoclonus, ataxia, or epileptic seizures. For example, deficits previously labeled as "constructional apraxia" or "dressing apraxia" are better explained as visuoperceptual and/or visuospatial deficits, as is the misdirected reaching for visual targets typical of optic ataxia. Traditionally, a distinction has been drawn between ideational and ideomotor apraxias, although both are often present in left hemisphere damage [92–95]. Ideomotor apraxia in Broca's aphasia may be conceptualized as a disconnection syndrome (Section 1.3.4).

Cases of isolated progressive apraxia were presented by De Renzi [82]. Apraxia may be a feature of neurodegenerative disease, classically CBD (Section 2.4.4), although AD can present with a similar phenotype (biparietal atrophy; Section 2.1), even with alien limb behavior.

Praxic difficulties may be tested for in various ways, including gesture naming, decision and recognition; gesture to verbal command, to visual or tactile tools; imitation of real or nonsense gestures; and tool selection. There are also test batteries for apraxia assessment [95].

1.1.7 Executive function

The term executive function is used to encompass various cognitive abilities, including the formulation of goals; organization, planning, execution, and monitoring of a sequence of actions; problem solving; and abstract thinking. It also overlaps with sustained attention. The term "dysexecutive syndrome" may be used to describe dysfunction in any or all of these areas, which is most often associated with pathological processes in the frontal lobes [96,97]. Because of the heterogeneity of these functions, some authors dislike the umbrella term of "executive function," and prefer to describe the specific function impaired. Moreover, frontal lobe damage may result in various clinical phenotypes, in which behavioral change is often the most salient feature. Orbitofrontal injury may result in disinhibition, as described in Phineas Gage, one of the most famous patients in the annals of clinical neuropsychology, who sustained marked behavioral change following traumatic frontal lobe injury [98], although other patterns of clinical and cognitive change may be observed with frontal lobe injury; for example, apathetic (frontal convexity) and akinetic (medial frontal) syndromes are also described. Because most tests of executive function probe planning and strategy, mediated by dorsolateral prefrontal cortex, some patients with exclusive orbitofrontal damage, for example with behavioral (frontal) variant frontotemporal dementia (Section 2.2.1), may complete these tests without conspicuous errors.

Because of the overarching nature of the construct of "executive function," no single test is adequate to assess its integrity [99]. Many tests known to be sensitive to aspects of executive dysfunction are available. Perhaps the most frequently used are the Stroop Test and the Modified Wisconsin Card Sorting Test (MWCST). In the Stroop Test, patients are required to read a list of color names, printed in colors that differ from the name, followed by reading the colors in which each name is printed, thus having to inhibit the reading of each color name (i.e., inhibition of inappropriate responses) [100]. MWCST uses a set of cards marked with symbols of different shape, color, and number, which may be sorted in various ways. Sorting rules are changed by the examiner without informing the subject, requiring problem solving skills. Difficulty switching category is typical of frontal lobe damage, leading to perseveration with previous categories [101]. Clearly MWCST, unlike the Stroop Test, calls for novel responses. MWCST may not be specific to frontal lobe dysfunction, as patients with hippocampal lesions may commit perseverative errors [102].

Oral tests of verbal fluency, or controlled oral word association tests (COWAT), may be divided into those testing phonological, letter, or lexical fluency (naming to letter), such as the FAS test (name as many words beginning with the letters *F*, *A*, or *S* as possible in one minute each), and those testing semantic or category fluency (naming to set; in one minute name as many animals, fruits, or musical instruments as possible). Letter fluency has been characterized as a test of mental flexibility (as well as of expressive language) probing executive function, which is particularly impaired ("defective exemplification" [103]) with left frontal lesions (without aphasia), whereas category fluency examines the integrity of the semantic network. Design fluency, a visual analog of verbal fluency, may be more impaired with right frontal lesions [104]. Verbal fluency tasks are attractive because they are brief (one minute each) and require no special equipment, but account may need to be taken of patient age and education when considering test norms [105].

There are many other tests available to neuropsychologists to probe executive functions, sometimes along with other domains. These include Raven's Progressive Matrices, the Porteus Mazes, Tower tests (London, Hanoi), Trail-Making Test (especially Part B), the Halstead–Reitan Category Test, the Weigl Color Form Sorting Test [106], the Cognitive Estimates Test [107], and the Verbal Switching Test [108]. The Hayling and Brixton Tests for sentence completion and spatial anticipation are tests of rule following and