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SECTION 1

Cognition and the brain: measurement, tools, and interpretation

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Introduction

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Cancer patients experience a number of adverse symptoms, including cognitive impairment, fatigue, pain, sleep disturbance, and others often in combination rather than alone. Fortunately detailed symptom assessment is becoming increasingly recognized as a part of routine patient care by physicians, allied health care providers, and accrediting agencies. Cancer treatment may only be considered successful if these symptoms are managed, but successful management is hampered by insufficient knowledge of mechanisms.

Cognitive dysfunction occurs in the majority of cancer patients on active therapy, and is not infrequently a symptom that heralds the diagnosis. In addition, it persists in a substantial number of patients long after treatment is discontinued. In some situations this type of cognitive dysfunction is popularly termed "chemobrain" or "chemofog" although cognitive impairment can be due to a large number of factors (Table 1.1), many of which are discussed in detail throughout this text.

The components of cognitive dysfunction will vary as a result of the specific etiology, but there are several core cognitive domains that appear to be differentially affected. Cancer patients with cognitive dysfunction often present with complaints of memory disturbance. However, objective testing of memory generally demonstrates a restriction of working memory capacity (e.g., the person is able to learn less information, and learning may be less efficient), and inefficient memory retrieval (e.g., spontaneous recall may be somewhat spotty). However, the ability to consolidate or store new information is generally intact, so that the memory disturbance observed in cancer patients is vastly different from that observed in neurodegenerative disorders such as Alzheimer's disease, and is often subtle and relative to the individual's pre-illness level of function. Additional common symptoms include periodic lapses of attention, distractibility, and slowed cognitive processing speed. In general, reasoning and intellectual functions are not affected, but patients often have difficulty performing their normal work due to cognitive inefficiencies.

The effect of these symptoms on daily life can be quite profound, depending upon the demands present in the individual's work and home life. Many patients observe that they can no longer multi-task, and that they may become overwhelmed when too much is happening at once. They are often easily distracted, and find that they may go from project to project without getting them done. Cognitive processing speed is generally diminished, so the person is slower to perform their usual activities. Finally, patients note that it takes increased mental effort to perform even routine tasks. This contributes to the fatigue that is often a co-existing symptom. In fact, cognitive impairment generally does not occur

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Table 1.1. Potential causes of cognitive impairment in cancer patients

- Primary or metastatic cancer in the brain
- Indirect effects of non-brain cancer
- Neurotoxic effects of treatment
- Chemotherapy
- Radiation therapy
- Immunotherapy
- Hormonal therapy
- Surgery
- Effects of adjuvant medications
- Co- or pre-existing neurologic and psychiatric illness
- Reactive mood and adjustment disorders
- Sensory impairment and general frailty
- Secondary gain

in isolation, but interacts in a negative way with fatigue, pain, sleep disturbance, etc.

The impact of cognitive dysfunction on cancer patients depends upon their developmental stage of life, the type of work they do, and their pre-illness lifestyle. For instance, the symptoms described above may not significantly impact the quality of life of an older retired person who can take things at his or her own pace. However, those symptoms may be disabling to an attorney in a court-room setting, and may necessitate changing jobs or going on disability.

Assessment of cognitive function in cancer patients is becoming more routine. For many patients, addressing cognitive problems that exist before treatment begins is important, and the underlying cause can be proactively addressed. In addition, cognitive testing is increasingly becoming an endpoint in clinical trials. In this way, the effect of new agents or treatments on brain function can be evaluated. New studies are incorporating advances in neuroimaging and biomarkers to help improve understanding of the mechanisms by which cognitive dysfunction and other symptoms develop. A number of possible mechanisms are being studied, including the inflammatory response (Lee *et al.*, 2004; Meyers *et al.*, 2005), autoimmune phenomena (Dropcho, 2005), hormonal influences (Wefel *et al.*, 2004), and direct

Table 1.2. Predictors of cognitive impairment

- Soil (host-related factors)
  - Genetic factors
  - Immune reactivity
  - Nutrition
  - Cognitive reserve
- Seed (disease-related factors)
  - Tumor genetic mutations
  - Paraneoplastic disorders
  - Cytokines
- Pesticides (treatment-related factors)
  - Cytokines
  - Poisons
  - Specific mechanisms of action
- Interactions between host-, disease-, and treatment-related factors

neurotoxicity of specific agents (Meyers *et al.*, 1997; Scheibel *et al.*, 2004). These will guide the interventions to be offered to minimize the impact of cognitive dysfunction on patients' lives.

Cognitive dysfunction in cancer patients can be thus conceptualized as a result of the interaction between the seed (cancer), the soil (the individual), and pesticides that are offered as treatment (Table 1.2). New intervention strategies are being developed, to improve patient function and quality of life as well as to provide valuable information for clinical trials. This is an exciting time for researchers who are interested in the effect of cancer and cancer treatment on brain function. Understanding the mechanisms of cognitive impairment and the development of efficacious interventions will require a multidisciplinary approach, including oncology, neuropsychology, cognitive neuroscience, genomics, proteonomics, molecular epidemiology, functional neuroimaging, neuroimmunology, animal models, and drug discovery.

This book represents the first attempt to bring together clinicians and scientists to address the effect of cancer and cancer treatment on cognitive function, and the intervention strategies that may be helpful for patients. We hope that the reader will take away our firm belief that optimizing the quality of life of cancer patients is possible, essential, and should be on equal footing with antineoplastic therapy.

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Clinical neuropsychology

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Neuropsychology is a specialized area of study within the field of psychology that focuses on brain–behavior relations, most particularly involving structural–functional connections between the nervous system and mental behavior. Outside of psychology, its closest allies are behavioral neurology, functional neuroanatomy, neuropsychiatry, speech and language pathology, and, more recently, cognitive neuroscience. A distinction may be made between clinical and experimental neuropsychology, although these branches are complementary, as evidenced by a large number of neuropsychologists who identify themselves as clinical researchers and work as true scientist practitioners. For example, neuropsychological rehabilitation generally includes diagnosis and treatment (both clinical) as well as outcome studies (research) assessing the efficacy of various interventions. *Clinical neuropsychology* refers to the practice of neuropsychological evaluation of individuals with known or suspected brain damage. Clinical neuropsychologists typically work in hospital settings or private clinics where they administer standardized, clinical neuropsychological measures to patients referred by physicians, school systems, or insurance companies. *Experimental neuropsychology* is the descriptive term for the academic branch of neuropsychology that focuses on research rather than clinical service delivery. Experimental neuropsychologists typically work in universities or teaching hospitals where they may develop their own test stimuli and procedures or administer clinical neuropsychological instruments either to healthy individuals with presumptively normal cognition or to patients with known or suspected brain damage. When experimental neuropsychologists administer clinical instruments to patients, however, it is most often to advance understanding of the cognitive processes involved in performing a particular task or for the comparison of cognitive processes in different patient groups rather than for diagnostic purposes.

This chapter focuses on the basic principles of clinical neuropsychology. Following a brief overview of the historical background that gave rise to modern clinical neuropsychology, we review the primary goals of neuropsychological evaluation and detail the procedures common to most evaluations. The remainder of the chapter provides an annotated list of frequently used neuropsychological tests organized by the behavioral domain (cognitive, motor, mood) that they are purported to assess. Our list of tests and our definitions of cognitive constructs are necessarily selective, as there are literally hundreds of published neuropsychological tests now available to clinicians. Interested readers are encouraged to consult some of the excellent compendia that describe test stimuli and administration procedures in detail (e.g., Lezak *et al.*, 2004; Strauss *et al.*, 2006). In contrast to the comprehensiveness of

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those texts, which are invaluable to actual practitioners in the field, our intent is merely to introduce health care professionals to the scope and general purposes of clinical neuropsychology. Specifically, after reading this chapter, one should have an idea of when it might be appropriate to refer a patient for a neuropsychological evaluation and be sufficiently familiar with concepts and tests to understand a neuropsychological report.

Historical background

Neuropsychology has a long history but only a short past as a formalized field of study. The Edwin Smith Surgical Papyrus, which has been dated to around 2500 BC, documents 48 cases of individuals suffering from traumatic lesions of the head, neck, and other parts of the body, contains the first known record of a word for "brain," and is the first written record demonstrating an awareness of localization of function (Walsh, 1978). Around 2000 years later in Classical Greece, Hippocrates and other physicians observed an association between damage on one side of the brain and spasms or convulsions on the other. By 200 AD, the Greeks and Romans recorded atheoretical observations about aphasias, alexias, and other types of functional loss following head injuries but with no analysis of the underlying cognitive schema. The 1500s brought descriptions of focal symptoms and syndromes involving speech loss following brain damage, unlike previous reports, which had been limited to diffuse problems such as dementia, anoxia, or clouding of consciousness. Building on these observations, clinical descriptions of nearly all the major neuropsychological syndromes appeared over the next 300 years (see Benton, 2000; Gibson, 1969). However, prior to 1800, there was very little theory and virtually no attempt to correlate these syndromes with particular brain regions.

The late nineteenth century brought significant advances in brain–behavior relations. Arguably, the most significant contribution was the French neurologist Paul Broca's demonstration in 1861 of the importance of the "anterior lobe" to the faculty of articulate speech (Benton, 2000). Although Broca himself acknowledged the much earlier work of Bouillaud (1825) for the identification of this association, the year 1861 has been heralded as the beginning of modern neuropsychology as a formalized field of study (Benton & Joynt, 1960). Further advances came in short order, including works on receptive aphasia by Wernicke in 1874, a model of sensory and perceptual processing (the agnosias) by Lissauer in 1889, Dejerine's reports of alexia with and without agraphia in 1891 and 1892, and Liepmann's distinction between apraxia and agnosia in 1900. Thus, the neuropsychological disorders with the longest history of systematic observation and taxonomic categorization are generally characterized by loss of specific functions following cerebrovascular accidents.

The Second World War produced an unfortunate boon to neuropsychology as large numbers of head-injured veterans returned to society. In the intervening years leading up to the present, neuropsychologists have moved away from discrete mapping of isolated brain structures with simple or complex behaviors in favor of seeking patterns of interconnections in distributed systems or networks. For example, amnesia has been associated with three general brain regions: diencephalon [(Korsakoff's syndrome), mesial temporal lobe damage (as represented by the patient HM (Scoville & Milner, 1957) who developed a permanent anterograde amnesia following bilateral surgical resection of the medial temporal lobes for intractable epileptic seizures], and posterior cerebral artery stroke (which serves the hippocampus). More complex disorders, including dementia, schizophrenia, closed-head injuries (i.e., non-penetrating injuries caused by rotational forces of the brain as occur in motor vehicle accidents), and those with undetected (or undetectable) brain damage (which is sometimes the case with irradiation or chemotherapy), are even less localizable. In sum, the history of neuropsychology may be traced from mentioning the brain in an ancient Egyptian papyrus to documentation of associations between a localized brain lesion and loss of a specific cognitive function, to the identification and expectation of the involvement of complex brain systems and networks in complex behaviors and syndromes.

Goals of assessment

The original goal of assessment was *localization of function* for its own sake. Tests were designed to assess the functional integrity of specific anatomical regions. Thus, the inability to identify shapes when palpated with one's right hand while blindfolded would lead to a "diagnosis" of left parietal brain damage, specifically in the "hand" region of the left postcentral gyrus or somatosensory strip. With the advent of brain imaging, of course, neuropsychologists have been called upon less and less to identify the presence and localization of brain lesions that can routinely be obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scanning. Nevertheless, neuropsychology continues to play this role when imaging is contraindicated or otherwise not available and for lesions that are difficult to discern with imaging. For example, a neurosurgeon may refer an epileptic patient for evaluation of language and memory functions prior to surgical resection of a suspected seizure focus in the left mesial temporal lobe. In such cases, the specific seizure focus may be unknown.

More typically, however, neuropsychological evaluations are requested for other purposes, most of which vary according to the clinical setting. The goal for any particular evaluation may be determined on the basis of a mutual understanding arising from an established relationship between the physician and neuropsychologist, by a specified request in the written referral, or, when the referral question is unclear, by contacting the physician to determine the purpose of the referral. In other words, the neuropsychologist requires a contextual framework in order to design the evaluation and report the results. Some of the more common evaluation goals are discussed below.

Differential diagnosis is one of the most common goals of neuropsychological evaluation in cases where the underlying disease is unknown. In memory clinics and some general hospital settings the primary referrals come from neurologists or geriatricians to assist in differential diagnosis of dementia for elderly patients with reported memory problems. The evaluation can determine whether the patient has dementia (or mild cognitive impairment or normal aging or amnesia, for example), and, if so, what the most likely cause may be (Alzheimer's disease, frontal lobar degeneration, subcortical vascular disease, alcoholism, or a potentially reversible dementia syndrome of depression). A very different type of diagnosis may be sought with younger populations, especially in university or other academic settings where neuropsychologists may be called upon to assess individuals with poor academic achievement. In these cases, the objective may be to help determine whether the learning difficulties are primarily attributable to a learning disability as opposed to environmental circumstances. Neuropsychological evaluations are also frequently requested following closed-head injuries sustained in motor vehicle accidents. Even when there is a documented concussion, it may be unclear whether the person has sustained structural brain damage. A thorough neuropsychological evaluation including assessment of both cognitive and personality variables can help determine whether poor concentration and attention following the accident, for example, are likely due to brain damage, psychological factors, or even the medications that the person may be taking for physical injuries sustained in the accident.

When the diagnosis is not in question, such as with a genetic disorder (Huntington's disease, Wilson's disease), medical disorder [infection with human immunodeficiency virus (HIV), epilepsy, multiple sclerosis, Parkinson's disease], documented brain lesion (neoplasm, aneurysm, arteriovenous malformation), or trauma (closed- or open-head injury, electrical injury), an evaluation may nevertheless be requested to provide a *descriptive report* of the patient's cognitive strengths and weaknesses. This evaluative purpose can serve a variety of goals, including treatment planning, workers' compensation and other employment issues requiring vocational guidance, long-term care planning, or documentation of a baseline against which to gauge future abilities. Importantly, many diseases have widely varying behavioral expressions, much as there are multiple phenotypes of a single genotype. Thus, two individuals with the same type of brain tumor may have completely non-overlapping symptoms or may have similar symptoms with differing magnitudes that leave one person functionally intact and the other compromised. Individual differences in pre-existing abilities and different occupational or social demands also lead to different functional outcomes among individuals with the same disease. Neuropsychological evaluation in these cases may be helpful in contextualizing the impact of the brain disease in that person's life.

Neuropsychologists are also called upon to conduct *serial assessments* to document changes over time in response to behavioral or drug interventions (in the case of clinical trials) or when naturalistic changes may be expected that would affect care needs, such as degenerative dementias, chronic progressive disease (e.g., multiple sclerosis), or rapidly growing tumors. Many neuropsychological measures are highly sensitive to practice effects. In fact, stable performance (i.e., with no practice-associated improvement) from initial to repeated administration on some measures may actually indicate the progression of a disease or a decline in function. Practice effects make the selection of tests and interpretation of performance particularly important for serial assessments. Among the armamentarium of tests outlined below are a number of measures with alternate versions of equivalent difficulty specifically designed for serial testing (e.g., Hopkins Verbal Learning Test-Revised; Brandt & Benedict, 2001).

Neuropsychological evaluations are also sought to help *clarify the outcome of a surgical intervention.* Many neurosurgeons routinely refer their patients for neuropsychological evaluations both pre- and post-operatively to assess comparative outcomes from surgical and cognitive perspectives. This is particularly true for surgeries with high morbidity rates or in vulnerable brain regions, where the potential for adverse cognitive outcomes would add to the "cost" in a risk-benefit analysis of whether to perform the surgery (e.g., carotid endarterectomy, pallidotomy for Parkinson's disease, certain brain tumors, shunt placement for normal pressure hydrocephalus in elderly patients or those with severe dementia).

There are a number of situations in which neuropsychological evaluation may be particularly useful or relevant *for the care of cancer patients.* The actual cognitive profiles associated with various brain cancers and the cognitive effects of various cancer treatments are described in subsequent chapters. Below, we briefly sketch some of the circumstances that might lead an oncologist to refer a cancer patient for a neuropsychological evaluation:

- When there are subjective complaints from the patient of (1) cognitive declines, such as poor concentration, slowed thinking, word-finding difficulties, trouble making decisions, right-left confusion, short-term memory problems, difficulty performing calculations, becoming lost in familiar areas; (2) sensory or perceptual changes, such as visual field cuts, anosmia (loss of sense of smell), inability to recognize faces or some other class of objects (cars, buildings); (3) motor changes, such as a change in handwriting, difficulties with balance, gait, or fine-motor skill; or (4) psychological changes, such as irritability, depression, excessive anxiety.
- When there are external reports from friends or family members of any of the above symptoms or of any of the following symptoms that may indicate compromised integrity of the frontal lobes (and which may be unnoticed or denied by the patient): (1) abrupt changes in personality (e.g., lack of empathy, depression, becoming enraged easily); (2) uncharacteristic behaviors, such as making inappropriate sexual remarks, spending

large sums of money, engaging in strange or ritualistic eating habits; (3) declines in self-care or hygiene; or (4) hypersomnolence or insomnia.

- In cases where the primary tumor is rapidly changing.
- To determine potential cognitive or mood effects of radiation treatment.
- To determine potential cognitive or mood effects of chemotherapy.
- To document possible neuropsychological sequelae that may have been incurred from destruction of healthy tissue during neurosurgical tumor resection.

Standard neuropsychological evaluation procedures

The clinical neuropsychological evaluation comprises several discrete sections, including history taking, test selection, the clinical interview, test administration (also called the assessment), interpretation of results, and the dissemination of findings and conclusions. The *history taking* begins with the referral question. In many cases, the referral itself may include several reports, such as a neurological examination, radiological reports from brain imaging, bloodwork results, other medical reports, or even an entire hospital record. This part of the history review takes place before the assessment and may be done several days or weeks in advance. If the patient has undergone a previous evaluation, as is often the case for patients referred by insurance companies and/or involving a legal claim, reports from those evaluations are typically reviewed as part of the history. This is particularly important when the prior assessment was conducted within the past year (or even within the past month, such as when evaluating a patient pre- and post-surgically), as it will likely affect the selection of tests for the current evaluation.

Historically, clinical neuropsychologists could be divided into two camps in terms of *test selection*: those who used fixed batteries and those who opted for a flexible approach. The most widely known and commonly used battery of tests is the Halstead–Reitan Battery (Reitan & Wolfson, 1993), which was originally developed as a sensitive diagnostic measure of patients with frontal lobe or lateralized brain lesions. Currently, many neuropsychologists use a "core" battery of tests to tap functions in several key functional domains, including general mental status or intelligence, attention, visual perception, construction, language, memory, executive function, and mood, personality, or emotional status. This core battery is then supplemented by additional measures as warranted by the referral question, the patient's capacity for testing, the patient's abilities as ascertained throughout the assessment, and the clinical setting. For example, even "Halstead–Reitanners" who use the current version of the original Halstead–Reitan Battery generally supplement their assessment with one of the Wechsler scales of intelligence as well as tests of memory and other specific functional domains. Some brief evaluations of very elderly patients or those with severe brain damage may include only a single mental status examination that encompasses a minimal sample of several of the domains listed above (e.g., Mattis Dementia Rating Scale; Mattis, 2001). Other general-purpose batteries (e.g., Kaplan–Baycrest Neurocognitive Assessment; Leach *et al.*, 2000; The Repeatable Battery for the Assessment of Neuropsychological Status; Randolph *et al.*, 1998) have been developed for use as contained measures when a brief assessment is appropriate. However, these same measures, as well as brief screening instruments such as the Mini-Mental State Examination (Folstein *et al.*, 1975), may be used in longer assessments as a preliminary measure to guide the selection of tests for subsequent evaluation of specific functional domains (many of which are listed below).

The *clinical interview* is typically conducted with the patient alone, especially for inpatients, although permission may be requested to contact a spouse or caregiver separately by phone. When secondary sources are present, as is often the case with outpatients, they may be interviewed together with the patient, especially when the patient may be an unreliable historian, or separately (with the patient's permission in most settings). When a child is being tested, he or she is typically interviewed briefly, though the parents are often asked to report such things as the timing of developmental milestones in addition to current symptoms or problems. Depending on the setting and availability of ancillary records, the clinical interview can take from 10 min to an hour or more. At a minimum, the neuropsychologist ascertains critical demographic variables that may affect test interpretation, such as the patient's age, education, native language, and handedness, as well as social variables, such as highest and most recent occupational attainment, current living situation (including language spoken at home), medical history and current medical status, and the patient's understanding of the reason for the referral.

In general, even when the patient suffers from dementia, the interview will provide useful information, such as whether the patient is aware of his or her deficits and other aspects of insight. It also provides an opportunity to assess spontaneous or conversational speech, including length and appropriateness of responses to open-ended questions. Behavioral observations, such as eye contact, impulsivity, distractibility, and inattention are made during the interview and throughout the assessment. Although there are specific tests to assess for malingering (used frequently in medicolegal contexts), the examiner also tries to gauge the patient's motivation level and fatigue to determine whether the results obtained represent the patient's true abilities.

The actual *neuropsychological assessment* entails the test administration component of the evaluation. This may be done by the neuropsychologist, but more typically the assessment is carried out by a psychometrist (trained technician) or clinical trainee (such as a predoctoral intern or postdoctoral fellow). In the latter cases, the neuropsychologist makes or approves of the test selection and supervises the test administration and scoring accuracy. Commonly used tests for various functional domains are listed in the next section.

Published tests include strict guidelines for standardized test administration, and this is critical for subsequent *interpretation of results*. For example, inexperienced examiners may "coach" patients or give extra cues in an effort to help them get the right answer. Alternatively, the overly rigid examiner may refuse to repeat a question that the patient didn't hear because of poor auditory acuity, a competing public address announcement, or a sneeze. Either of these approaches could yield unrepresentative test results. Among the data to be interpreted are the summary scores obtained on the various tests administered, the qualitative responses that led to those scores, the consistency of performance on multiple measures of the same domain, relative strengths and weaknesses observed across domains, the degree to which the test environment conformed to or deviated from optimal conditions, the patient's co-operation with the test procedures, normative expectations for individuals with similar demographic and social backgrounds, and any motor, visual, auditory, comprehension, or verbal expressive difficulties that may have impacted the patient's ability to perform the presented tasks. Qualitative interpretation of quantitative data is essential. Consider, for example, the many ways in which a score of 0 may be obtained on a single item, such as the identification of a line drawing: (1) no response; (2) identification of the item at the superordinate level of taxonomic categorization (animal for rhinoceros); (3) identification of an exemplar from the same class (hippopotamus for rhinoceros); (4) phonemic paraphasic response (rhinosteros); (5) neologism (pinder); (6) misperception of gestalt, with focus on a single detail (horn for rhinoceros); or (7) correct response after the time limit. These responses have differing interpretive significance, which is why a test score in isolation may be misleading.

Following test selection appropriate to the specified purpose, accurate test administration and scoring, and interpretation of the obtained results in the context of the history, presenting symptoms, and testing circumstances, the final step in the evaluation is *dissemination of the findings*. This