Handbook of Schizophrenia

Edited by H.A. NASRALLAH

VOLUME 1

The Neurology of Schizophrenia

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Henry A. NASRALLAH

Chairman, Department of Psychiatry,
The Ohio State University,
Columbus, OH, U.S.A.

Daniel R. WEINBERGER

Chief, Section on Clinical Neuropsychiatry and Neurobehavior,
Intramural Research Program, National Institute of Mental Health,
Director, Behavioral Neurology Service, Saint Elizabeth's Hospital,
Washington, DC, U.S.A.

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Contributors

K.F. BERMAN
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

J.L. CADET
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

J.A. COFFMAN
Department of Psychiatry, The Ohio State University, College of Medicine, 473 West 12th Avenue, Columbus, OH 43210, U.S.A.

L.E. DELISI
Clinical Neurogenetics Branch, The National Institute of Mental Health, Room 3N/220, Building 10, The National Institutes of Health, Bethesda, MD 20205, U.S.A.

T.E. GOLDBERG
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

J.A. GREBB
Nathan Kline Institute, Orangeburg, NY 10962, and Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, NY 10016, U.S.A.

D.V. JESTE
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

Ch.A. KAUFMANN
Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032, U.S.A.

D.G. KIRCH
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, D.C. 20032, U.S.A.

J.E. KLEINMAN
Section on Clinical Brain Studies, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

J.B. LOHR
Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

T.C. MANSCHRECK
Laboratory for Clinical and Experimental Psychopathology, Department of Psychiatry, Massachusetts General Hospital, Erich Lindemann Mental Health Center, Boston, MA 02114, U.S.A.

J.M. MORIHISA
Department of Psychiatry, Georgetown University School of Medicine, and Department of Psychiatry, VAMC, Washington, DC 20422, U.S.A.

H.A. NASRALLAH
Department of Psychiatry, The Ohio State University College of Medicine, 473 West 12th Avenue, Columbus, OH 43210-1228, U.S.A.

K.C. RICKLER
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

R.C. SHELTON
Department of Psychiatry, Vanderbilt University School of Medicine, Medical Center North, Room A-2215, Nashville, TN 37232, U.S.A.

E.F. TORREY
Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, Washington, DC 20032, U.S.A.

D.R. WEINBERGER
Section on Clinical Neuropsychiatry and Neurobehavior, Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health; Behavioral Neurology Service, Saint Elizabeth's Hospital, William A. White Building; and Department of Neurology and Psychiatry, George Washington University School of Medicine, Washington, DC 20032, U.S.A.

A. WISNIEWSKI
Neuropsychiatry Branch, Intramural Research Program, National Institute of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington, DC 20032, U.S.A.

R.F. ZEC
Department of Psychiatry, Andrew McFarland Mental Health Center, Southern Illinois University School of Medicine, Springfield, IL 62708, U.S.A.

Introduction

The objective of the *Handbook of Schizophrenia* series is to provide a comprehensive overview of all aspects of schizophrenia, the most serious and disabling psychiatric disorder. The authors are investigators who are directly involved in basic and clinical schizophrenia research, biological as well as psychosocial.

The first volume in this series is, appropriately, devoted to the *Neurology of Schizophrenia.* Following the psychodynamic and the pharmacological eras earlier in this century, psychiatry is currently undergoing what may be considered its third major phase in less than 100 years: the neuroscience revolution. There are few scientific disciplines or medical specialties that are evolving as rapidly as psychiatry, with its almost breathtaking rate of new discoveries and insights.

Schizophrenia has been at the center of brain research over the past two decades. The discovery of effective antipsychotic medications in the 1950s triggered a vigorous search for the neurochemical basis of schizophrenia, which has led to numerous other discoveries along the way. However, it was the technological revolution which has provided the necessary impetus for the current momentum of brain research and its future promise in psychiatry. The quantum leap in computer technology has facilitated the development of brain imaging techniques which now allow, for the first time, the in vivo assessment of the brain's structures and functions. In less than a decade several types of brain imaging techniques have been developed and implemented, providing remarkable new insights into the last biological frontier, the brain.

The future course of psychiatry is obviously linked to advances in brain research and the unraveling of the brain-behavior link at the biopsychosocial levels. Significant progress is expected to shed new light, not only on schizophrenia but probably on many normative brain functions as well. Over the next few years, psychiatry is expected to undergo significant growth spurts of knowledge that will carry it into legitimate maturity as a scientific discipline.

This volume presents the impressive scientific evidence for the neurological basis of the schizophrenic syndrome. It provides not only facts, but also many conceptual frameworks for defining subtypes of schizophrenia and relating clinical phenomenological findings to disorders of brain structure and function. The first several chapters follow roughly the same sequence as does a neurologist's clinical examination of a schizophrenic patient (history, physical examination, differential diagnosis, laboratory tests, EEG evoked potentials, neuropsychological testing, etc.). Chapters 9 through 13 cover the state of the art in brain imaging findings in schizophrenia with the use of computerized tomography, magnetic resonance imaging, computerized mapping of electrophysiological data, cerebral blood flow studies and positron emission tomography. Finally, several chapters propose various

theoretical models of schizophrenia based on current neuropathophysiological findings and provide a framework for future directions in research.

This book is intended to be a useful resource for clinicians, teachers and researchers who are interested in schizophrenia as a neurological syndrome. Psychiatrists, neuroscientists, physicians in general, as well as psychologists, neurologists, educators and rehabilitation specialists will find this book of particular value in their work. Future volumes in the series will provide overviews of advances in other areas of brain dysfunction and biopsychosocial treatment in schizophrenia.

HENRY A. NASRALLAH

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CHAPTER 1

The clinical neurologic examination in schizophrenia

JEAN LUD CADET, KENNETH C. RICKLER AND DANIEL R. WEINBERGER

Recent advances in clinical neuroscience and in neurological technology have led to a reevaluation of the early literature on the neuropathology of schizophrenia and have stimulated a more rigorous neurological approach to the study of this group of disorders. Schizophrenia has traditionally challenged clinicians and basic scientists and both groups have profited from renewed efforts to define its neural substrates.

These efforts reflect a wider resurgence of interest in neuropsychiatry, an orphaned discipline that at times has proved frustrating for both psychiatrists and neurologists. Many psychiatrists are uncomfortable with the medical concepts and techniques involved in neurological diagnosis; their neurological colleagues may feel ill-equipped to examine the difficult psychiatric patient or to deal with the complex psychosocial issues which surround even organically based behavioral disorders. As a result, relevant subtle aspects of the neurological exam may be neglected, resulting in a declaration of 'no acute neurological disorder' or 'no localizing signs.' In a similar fashion, the traditional mental status examination in psychiatry often fails to detect the presence of organic dysfunction. These deficits have the ability to impact negatively upon clinical care as well as to inhibit the potential for significant clinical collaboration in the further investigation of schizophrenia.

In this chapter, a selective formulation of the neurological examination will be presented. Whenever possible, the techniques of the examination will be interwoven with the available data relating to schizophrenia. When relevant, differential diagnosis and underlying pathogenic mechanisms will be discussed. For the sake of clarity and convention we have chosen to use the traditional format for the neurological examination. A number of standard neurological texts use the same format and afford the interested reader further opportunity to review these matters in greater detail (1, 2).

The process of neurological diagnosis involves a systematic attempt to examine anatomy in relation to function. The application of this process to schizophrenic patients presumes that their symptoms and behavior(s) have some type of anatomic and physiologic substrate. Such a presumption does not ignore theoretical concepts which accord a role to psychodynamic processes or environmental stressors; rather,

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these processes and stressors are seen as resulting from and/or impacting upon a state of brain dysfunction.

Since this presumption draws our focus to the nervous system, some organizing principles must be applied to the interpretation of data derived from a systematic neurological examination. The absence of demonstrable neurological abnormality does not necessarily exclude organic dysfunction. Like other efforts at physical diagnosis, the neurological examination suffers from limitations; however, recent advances in other clinical tools such as brain imaging techniques, evoked potential and electroencephalography (EEG) have broadened and enriched the clinical neurological data base about schizophrenia beyond these limitations. Conversely, the demonstration of an abnormal finding on neurological examination does not always have clinical relevance or significance. Nonetheless, from a research viewpoint it remains important to continue to document the nature and extent of neurological abnormalities in schizophrenia with the hope that the relevance of findings will eventually unfold.

The neurological examination in schizophrenia also serves another important function: the opportunity to diagnose illnesses which may appear at first glance to be schizophrenia but, in fact, are not. The performance of a thorough neuropsychiatric evaluation both addresses differential diagnosis and leads to a more accurate characterization of the psychiatric symptomatology. For example, in its early stages Wilson's disease may mimic schizophrenia, the detection of Kayser-Fleischer rings during the performance of a thorough examination will help to make the diagnosis.

General approach to the patient

The neuropsychiatric history

Medical diagnosis relies heavily on the patient's history. This anamnesis, in part, depends on the clinician's skills at directing the interview in an empathic and productive way. The schizophrenic patient may task these skills heavily and in most cases it is imperative to carry out follow-up interviews. In all cases, it is felt that close relatives or significant others should participate to some degree in that process. The medical history of the schizophrenic patient is essential to the formulation of a differential diagnosis and in characterizing nervous system dysfunction. Standard textbooks of psychiatry have dealt with this issue at length (3).

The interview begins by eliciting the chief complaint. This is usually followed by inquiring about the date of onset, nature, and severity of presenting signs and symptoms; associated symptomatology; provoking and alleviating stimuli; treatment modalities and their effects; and the course of the illness.

In order to form a neurological differential diagnosis, it is important for the clinician to obtain answers to questions regarding the location and the nature of the disease process. Are the symptoms related to the cerebral cortex, the basal ganglionic structures, long white matter tracts, the brainstem, the cerebellum,

peripheral nerves, or other structures of the neuraxis? Inquiries about language and speech disturbances, disturbances of state of consciousness, involuntary movements, gait difficulty, weakness, or pain may help in directing the flow of the interview and localizing lesions. Those neurological disorders that may simulate schizophrenia often have symptoms referable to the cortex (e.g. memory, and language impairment), the basal ganglia (e.g. rigidity, slowness of movement, and extra movements), and/or cerebellum (e.g. coordination).

The tempo of the illness whether episodic, cyclic, or progressive may suggest its nature. Seizure disorders, vascular lesions, syncope, intoxications, and certain sleep disorders (e.g. narcolepsy) produce symptoms that are relatively sudden in onset. Brain tumors, neurodegenerative diseases, and viral encephalitides are progressive. In pursuing a history suggestive of a seizure, the examiner inquires about disturbances of sleep; persistent daytime sleepiness; and periods of intermittent confusion, restlessness, or incoherence. History of loss of consciousness should stimulate questions about the frequency and length of attacks; sequence of events including premonitory symptoms (anxiety, lightheadedness or malaise); specific auras (e.g. hallucinations, autonomic sensations, fear, embarrassment, etc.) and presence or absence of urinary or fecal incontinence. Differentiating syncope from a seizure may be difficult. Patients with true syncope may suffer from myoclonic jerks of the arms and legs or from tonic extension of the whole body. In a small number of cases there may be a tonic-clonic attack. The presence of incontinence does not rule out syncope and depends on the rapidity with which consciousness is regained. Postictal confusion is common and may be prolonged; post-syncopal confusion is rare and brief. It is important to elicit the presence of associated symptoms, drug history, and family history. Cerebral ischemia may be secondary to cerebrovascular disease, to vasovagal syncope, carotid sensitivity, central autonomic failure (Shy-Drager syndrome, some cases of parkinsonism), drugs (phenothiazine, levodopa), and cardiac diseases.

In general, headache is a frequent complaint in patients who visit their physician but may be ignored in the evaluation of the neuropsychiatric patient. It requires careful analysis because it may be the only clue to underlying pathologies. These include brain tumors, ophthalmic and nasopharyngeal diseases or systemic disorders. Headache occurring in the morning suggests hypertension, migraine, and neoplasms. Migraine is unilateral, recurrent, throbbing, and often associated with blurriness of vision, migrating scotomas, and fortification spectrum. It tends to be familial. Complicated migraine (migraine associée) may be accompanied by transient neurologic deficits including hemiplegia and aphasia. Muscle contraction headaches are usually bilateral, dull, and often unremitting. Cluster headaches are nocturnal and usually awaken the patient. Posterior fossa tumors may produce pain in the occipital nuchal area, whereas supratentorial lesions cause frontal or parietal pain. Consistent unilateral headache suggests an intracranial lesion. So-called 'psychotic headache' is characterized as bizarre in nature and usually unremitting, but the possibility of psychotic elaboration of bona fide cephalalgia must be considered.

Abnormal involuntary movements or dyskinesias may be seen in a variety of neuropsychiatric and systemic illnesses, such as Huntington's chorea, Wilson's disease, systemic lupus erythematosus (SLE), thyrotoxicosis, Sydenham's chorea, as well as in pregnancy. They may also be associated with drugs including anticonvulsants, neuroleptics, and stimulants. The presence of these abnormalities at rest, during action, or maintenance of posture is determined. History of other associated symptoms including subjective restlessness and loss of function is also elicited. The drug history prior to the development of the illness is crucial to the differential diagnosis of these disorders. Abnormalities of gait, lack of control of extremities, history of dystonic posturing or myoclonus, and of localized or generalized weakness are documented in the initial assessment.

Peripheral nervous system disorders may be associated with impotence and/or incontinence. Diabetes mellitus (DM) is the most common cause of autonomic polyneuropathy. Impotence may be the presenting symptom in DM. Other neurological causes of impotence include pandysautonomia, Shy-Drager syndrome, familial dysautonomia, amyloidosis, alcoholic polyneuritis, and Guillain-Barré syndrome. The history of associated symptoms such as sweating irregularities and incontinence may be very helpful in distinguishing neurologic from psychiatric impotence. Inquiry about nocturnal erections is also helpful. Patients with temporal lobe tumors or epilepsy may also be hyposexual. Drugs such as the phenothiazines and anticholinergic agents, endocrine abnormalities (e.g. hypothyroidism, Addison's disease, and Cushing's syndrome) may all be associated with sexual impotence.

The neurodevelopmental history

The neurodevelopmental history is one of the most significant aspects of the neuropsychiatric patient's history because it provides clues to premorbid neurological dysfunction and/or injury. It includes specific drug intake, presence of infections, and other difficulties that might have occurred during the pregnancy. The clinician also inquires about premature delivery, induction and length of labor, neonatal infections, seizures or hypoxia, icterus, twin or multiple births, and APGAR score. The physician asks about nutrition; the presence of delayed milestones, hyperactivity, pervasive reading, speaking, learning, or communicating difficulties; and the appearance of choreiform movements, (e.g. Sydenham's chorea), hemiparesis, abnormal tone, gait abnormalities as well as difficulties in acquiring motor skills. It is important to inquire about febrile seizures, central nervous system (CNS) infections, and head traumas.

History of past illness and review of symptoms

This usually consists of a checklist that can be used to take a detailed but focused review of systems. Particular attention is paid to those conditions with neuropsychiatric implications. SLE, vasculitides, endocrine abnormalities, exposure to neurotoxic substances, seizures, and vitamin deficiencies etc., are to be considered.

Family and genetic history

Many neuropsychiatric diseases of the CNS are familial. These include Huntington's chorea (4), neurofibromatosis (5), Wilson's disease (6), tuberous sclerosis (7), metachromatic leukodystrophies (MLD) (8), Kufs' disease, idiopathic cerebral ferrocalcinosis (Fahr's disease) Alzheimer's disease etc. This is reviewed in detail elsewhere (9).

Clinical neurological examination

General physical examination

The general physical examination is an integral part of the neurological evaluation. It is discussed at length in standard physical diagnostic books (10). However, certain aspects of the exam need to be re-emphasized because of their potential importance in the neuropsychiatric population. For example, changes in skin texture, color, or moisture may be a sign of an endocrinologic and metabolic disorder (10). Patients who have postencephalitic Parkinson's disease may be especially seborrheic (11). The neurocutaneous syndromes show characteristic skin abnormalities: sebaceous adenomas and hypopigmental patches in tuberous sclerosis (7); neurofibromas and café-au-lait spots in Von Recklinghausen's syndrome (5); portwine facial nevus flammeus in Sturge-Weber-Dimitri syndrome; and conjunctival telangiectasias in ataxia-telangiectasia (12). Hypertrophy of gingiva might reveal chronic treatment with dilantin. In nicotinic acid deficiency, there may be glossitis and angular fissuring of the tongue (13). Vitamin deficiencies may be associated with various neuropsychiatric symptoms including irritability, depression, psychosis and cognitive disturbances (13). Dysmorphic facial appearance, epicanthal folds, bone and joint irregularities, hypertelorism, torso and spinal malformations, and abnormalities of hands and feet such as coarse skin, clinodactyly and syndactyly may be associated with neurodevelopmental disorders including autism, attention deficit disorder with hyperactivity and learning disabilities (14, 15). These signs are thought to be related to first trimester insults (14). Head size (macro- or microcephaly), the presence of bruit on auscultation (arterio-venous malformation), or any area of unilateral protuberance of the skull (meningiomas) should be documented.

Mental status

A complete mental status examination should be carried out in all neuropsychiatric patients. The 'mini mental state' may be used as a screening device (16). The examination is carried out in a non-confronting, conversational manner. During the anamnesis, observation is made of the patient's mental abilities and of his use of language. Disturbances in these functions may be related to diffuse or localized involvement of the brain. The cognitively oriented mental status exam can assist in differentiating diffuse from focal cerebral disease. While it is possible to formulate

hypotheses about possible brain dysfunction on the basis of the patient's history, it is nonetheless imper tive to test the subject's performance on specific subcategories of the exam. Interpreting the mental status exam in neurological terms is particularly challenging in patients with schizophrenia. Aspects of the exam may suggest diagnosable focal or diffuse disease of the CNS. Nevertheless, diagnostically important associated findings will usually be absent.

Level of consciousness

The level of consciousness is evaluated first. This term embodies an amalgamation of processes that allow the organism to be aware of itself and its environment. The degree of awareness will affect the rest of the examination. Several terms which describe the degree of arousal have been used. They include alertness, clouding of consciousness, lethargy or somnolence, delirium, stupor, and coma (17).

The *alert* patient appears awake and is able to cooperate fully except in cases of aphasia, paralysis, or malingering. Patients with the locked-in syndrome, which is usually secondary to bilateral ventral pontine lesions, are usually alert, but because of paralysis of bulbar and limb musculature they are mute and only able to communicate through vertical eye movements (18).

Clouding of consciousness refers to patients who show reduced awareness of their environment. They may show hyperexcitability, irritability, or belligerence. Excitement may alternate with marked drowsiness, with subsequent progression to lethargy or somnolence. In these states, the patient is unable to sustain arousal, which prohibits full participation in the rest of the neurological evaluation.

In *delirium,* the patient is disoriented and fearful. He misperceives sensory stimuli and hallucinates. There may be periods of lucidity that alternate with those of agitation and suspiciousness. These states usually last less than 2 weeks; but there may be lingering and intermittent hallucinatory experiences.

In *stupor,* the patient looks like he is asleep, but he responds to vigorous stimulation. After arousal, the patient is unable to maintain alertness if the stimulus is stopped. He usually groans, moves somewhat restlessly in bed, and may progress to coma. Stupor has to be differentiated from catatonia (19, 20). In *catatonia* the patient looks awake and typically manifests catalepsy, grimacing, mutism, posturing, and rigidity. It is significant that catatonia may be secondary to a multitude of factors which include affective disorders, schizophrenia, encephalitis, or drug-induced psychosis (19). The eyes of the catatonic patients are usually open, the skin is greasy, the pulse is rapid, the temperature may be elevated, but the respiration pattern is regular. Although they may not respond to visual threats and even painful stimuli, caloric tests of vestibular functions show normal oculomotor response.

Coma is a state of complete unarousability. Comatose patients show no response to any external stimuli including deep pain. When one encounters a patient with an altered level of consciousness, a description of the patient's actual behavioral responses should be recorded instead of a non-informative label (e.g. coma). This allows for more objective criteria by which to follow the subject's progress.

Although schizophrenic patients are usually alert, their level of consciousness may at times resemble the various symptoms listed above. Even when alert, they may have difficulty cooperating because of intrusion of psychotic thoughts or hallucinations. The presentation may be similar to an acute confusional state. The differential diagnosis, is made on the basis of a lack of other associated signs and symptoms. Other ancillary tests, including EEG, do not show evidence of other causes for a disturbance in consciousness.

Attention

After assessing the level of consciousness, the clinician needs to evaluate the patient's ability to initiate, sustain, and shift attention. This is done early in the examination because attention and concentration will affect other higher intellectual functions as well as cooperation. Four quantifiable tests may be used to evaluate attention: the digit span, subtraction of serial sevens, reverse spelling, and the 'A' test.

In the *digit span test,* the patient is asked to listen carefully to a list of numbers and to repeat them after the examiner. The digits are repeated at a rate of one per second. The average individual is able to repeat five to seven digits. The subjects also may be asked to repeat a number of given digits in reverse order. Three to five correct reverse digits is normal. It should be noted that this test is not a test of memory.

The *serial 7 subtraction* is presented in the following manner: 'Start with 100 and subtract 7, take 7 from the answer and keep on subtracting sevens. If I were doing it with 5, it would be 100, 95, 90, etc'. The time taken to accomplish the test and the number of errors are noted. The patient is then asked to spell 'earth' or 'world' forwards and backwards. If the patient fails, shorter words may be tried: 'hand', 'hold', 'cat', or 'bat'. Bender suggested that defects in *reverse spelling* are a sign of brain dysfunction implicating the dominant hemisphere or of diffuse cerebral abnormality (21). Interpretation of these tests depends on the age, level of education, and the social history of the subject. Patients who have had little verbal education or who calculate poorly may be asked to perform serial 3 subtractions and to recite the months of the year backwards as substitutes. Since virtually everyone knows the months of the year forwards, inability to recite them backward may indicate an attentional deficit.

The *'A' test* is made up of a random number of letters among which the letter 'A' appears frequently (see appendix to this chapter). The patient is asked to indicate by tapping or raising a finger whenever 'A' appears in the sequence. Abnormal responses include errors of omission, commission, or perseveration.

It is also very important to observe the patient for any signs of hemi-inattention or neglect as they may suggest parietal lobe dysfunction. Denial of hemiparesis is the best known and most often described (22). In that disorder the examiner is unable to convince the patient of the existence of his hemiplegia even though the patient is unable to execute any task with the affected limbs. Other disorders of the