Chapter 7

Clinical Assessment of Brain Disorders

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Abstract

The clinical evaluation of brain diseases strictly depends on patient's complaint and observation of their behavior. The specialist, often the neurologist, chooses whether and how to assess cognition, motor system, sensory perception, and autonomic nervous system. They may also decide to request a more in-depth examination, such as neuropsychological and language assessments and imaging or laboratory tests. From the synthesis of all these results, they will be able to make a diagnosis. The neuropsychological assessment in particular is based on the collection of medical history, on the clinical observation, and on the administration of standardized cognitive tests validated in the scientific literature. It is therefore particularly useful when a neurological disease with cognitive and/or behavioral manifestation is suspected. The introduction of machine learning methods in neurology represents an important added value to the evaluation performed by the clinician to increase the diagnostic accuracy, track disease progression, and assess treatment efficacy.

Key words Clinical assessment, Neurological examination, Neuropsychology, Cognitive scores

1 Introduction

1.1 What Is a Disease? Why Are Clinical Assessments Important?

A *disease* is a specific set of processes, often biological or histological, that induce *symptoms* (subjectively felt), which negatively affect the individual's normal functioning (e.g., discomfort, pain, suffering), are often associated with a complaint, and will manifest by *signs* (objectively measured), for instance, decreased motor strength or slowed speech. Symptoms and signs taken together define a *syndrome* (e.g., headache, vomiting, stiff neck point to a meningeal syndrome), and the syndromes are contextually interpreted by physicians to hypothesize on a given disease. If, for instance, the meningeal syndrome appears brutally and is very intense, the suspected disease will be meningeal hemorrhage. If it appears subacutely over a few hours and is accompanied by a fever, the physician will rather surmise a meningitis. Box 1 introduces the main medical definitions.

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A clinical evaluation is therefore requested by the patient himself/herself or by a clinician (general practitioner, specialist, psychologist, etc.). The aim is to better characterize the symptoms and the underlying disease.

Box 1 Main Medical Definitions

Disease	Physiological (biological and/or pathological) process (es) causing pejorative clinical manifestations
Symptom	Subjective manifestation of a disease (pain, memory complaint, nausea, etc.)
Sign	Objective manifestation of a disease upon medical examination (decreased reflex, elevated blood pressure, etc.)
Syndrome	Association of symptoms and signs that can be related to a set of diseases (e.g., headache, nausea, and neck stiffness are a meningeal syndrome that can correspond to either meningitis or meningeal hemorrhage)
Clinical assessment	Stereotyped interrogation, observation, and examination of an individual by a trained healthcare provider in order to collect his/her symptoms and signs to determine a syndrome and hypothesize a main disease diagnosis and differential diagnoses

During their studies, physicians learn over a few years a large quantity of diagnostic and prognostic "decision trees" based on the co-occurrence of every set of symptoms and signs. The learning is structured so that frequent and severe diseases are more studied, while rare or orphan diseases and those considered less severe are covered more briefly. For instance, the few symptoms described above will most likely be recognized and diagnosed well by any physician as well as the degree of urgency they imply. This learning is based on aggregated knowledge at one point in time which is always susceptible to change. A clear example of such changes is Alzheimer's disease (AD) which was considered a rare form of dementia of the young from its seminal description in 1906 [1] until the 1980s when it was finally identified by numerous pathological studies to be the predominant cause of dementia in the elderly [2]. Importantly, clinical assessment requires tools to be performed, such as the famous reflex hammer used by neurologists or cognitive tests used by the neuropsychologist. Machine learning, and the decision support system that it entails, may be considered as such a tool, although it has the peculiarity of being harder to comprehend for most clinicians which may be a specific challenge for its implementation.

Every clinical assessment, whether conducted in the routine practice of medicine or in biomedical research, has to adhere to strict ethical rules that warrant the trust the patient puts in their healthcare providers. The main rules are that of beneficence; non-maleficence; respect for any individual notwithstanding their race, gender, religion, or personal beliefs; and medical confidentiality.

Finally, the current development of digital and information technologies is rapidly changing the scope of clinical assessments. Prior to consultation, auto-assessment and patient empowerment are promoted through the development of specific applications to explicitly diagnose or monitor a disease [3, 4] and patient education and access to relevant information [5]. The main issue concerning this last point is the exponential growth of these digital solutions and the risk of misinformation that can sometime lead the patient toward unethical care [6].

1.2 Peculiarities of Clinical Assessment of Brain Disorders

The brain has functionally distinct regions, so there is a topographical correspondence between the location of the lesion in the brain and the symptom. The characterization of symptoms therefore allows to trace which brain region is affected. This helps in identifying the underlying disease. The motor and sensory cortices are perfect examples of this functional topography often depicted as homunculi [7].

Clinical evaluations for brain disorders thus follow a standardized procedure. In addition to the symptoms and signs appraisal, the physician often makes an assumption as to where the nervous system is affected. This often overlaps with the syndromic definition: "frontotemporal dementia" implies that the lesions are in the frontotemporal cortices. However, this is not always the case as some diseases and syndromes still bear the name of the physician who was the first to describe it. While most neurologists know that a parkinsonism (or Parkinson syndrome) is due to basal ganglia lesions, it is not implied in its name.

2 The Neurological Examination

2.1 General Information on the Neurological Examination

The neurological examination begins with the collection of anamnestic data, that is, the complete history recalled and recounted by a patient or their entourage, including complaint, medical history, lifestyle, concurrent treatments, etc. During the collection of anamnestic data, the clinician also carefully observes patient's behavior. The neurologist then proceeds with the examination of brain function, which is oriented by the complaint, and often includes cognitive screening tests and examination of motor system, sensitivity, and autonomic nervous system. Usually, this examination has more formal and structured parts (this can be, for example, a systematic evaluation of reflexes always in the same order or the use of a specific scale to assess sensory or cognitive function) and other

more informal ones. In fact, the clinician chooses case by case on the basis of what is required and what is available to the physician at the time of the said assessment. For example, they may use a lay journal in their office to ask a patient to describe a complex photograph in order to get a general idea of their visuospatial perception skills. This is quite time-consuming, and, depending on the patient's case, presence of entourage, and thoroughness of the clinician, an initial visit can take from 0.5 h to 2 h to capture the essential features necessary to formulate a diagnosis, prognosis, and care plan. If the neurologists deem it necessary, they may request additional tests or examinations, such as a neuropsychological evaluation, language assessment, laboratory tests, imaging tests, etc.

For applying machine learning techniques, the results of formal exams are usually more adequate because they offer quantitative measures. However, this may change over the coming years as solutions are being developed to analyze informal material. This may include clinical reports or videos of patient examinations. Another example is natural language processing tools that may help in identifying semantic deficits in patients suffering from incipient dementia [8]. The context of data acquisition is very important and can greatly impact its quality. Among the different contexts, we can cite "routine clinical practice," "retrospective or prospective observational studies," and "clinical trials" that have increasing levels of quality due to the level of standardization of data acquisition and monitoring.

2.2 Clinical Interview

A clinical interview precedes any objective assessment. It is adapted to the patient's complaint and as standardized as possible so as not to forget any question. It consists of:

- Personal and family history with, if necessary, a family tree.
- Lifestyle (including alcohol intake and smoking).
- Past or current treatments.
- As accurate as possible description of the illness made by the patient and/or their informant. It is important to know the intensity of the symptoms, their frequency, the chronological order of their appearance, the explorations already carried out, and the treatments undertaken as well as their effectiveness.

In a formal evaluation, especially in cohort studies and clinical trials, symptoms can be assessed thanks to different scales, some of which will be presented in this chapter, depending on the clinical variable of interest. These scales' results will also be used to monitor the disease evolution, notably in order to test new treatments.

The interview process is probably the most important part of the whole clinical assessment. It will allow delineating the patient's medical issue, which in turn will determine the next steps of the examination and management plan. It also creates a relation of trust that is essential for the future adhesion of the patient to the physician's propositions.

2.3 Evaluation of Cognition and Behavior

The assessment of cognition and behavior can be carried out by the neurologist using more or less in-depth tests depending on the situation, or a complete neuropsychological assessment can be requested and carried out separately by a neuropsychologist (*see* Subheading 3 of this chapter). The assessment of cognition is guided by the cognitive complaint of the patient and/or the informant [9]. However, on the one hand, it is possible that the patient is not fully aware of their deficits. This is a symptom called *anosognosia* (which literally means *lack of knowledge of the disease*) and is typical of various forms of dementia, including AD and frontotemporal dementia, but also brain damage due, for example, to stroke in certain regions of the brain. On the other hand, a cognitive complaint can be due to anxiety, depression, and personality traits and may have no neurological basis. The medical doctor can use simple tests in their daily practice such as the Mini-Mental State Examination (MMSE) [10]. For a more detailed description of the MMSE, please refer to Subheading 3 of this chapter.

2.4 Evaluation of Motor System

The examination of motor function starts as soon as the physician greets their patient in the waiting room. They will immediately observe the patient's walk and their bodily movements. Then, in their office, the observation will continue to search, for example, for a muscular atrophy or fascicules (i.e., muscular shudder detected by looking at the skin of the patient). This purely observational phase is followed by a formal examination, provoking objective signs.

One goal of motor assessment is to assess muscle strength. This is done segmentally, that is, carried out by evaluating the function of muscle groups that perform the same action, for example, the muscles that allow the elbow to flex. The neurologist gives a score ranging from 0 to 5, where 0 indicates that they did not detect any movement and 5 indicates normal movement strength.

A second aspect which is assessed is muscle tone. It is explored by passively mobilizing the patient joints. Hypertonia, or rigidity, is an increase in the tone. When the neurologist moves the joint, it may remain rigidly in that position (*plastic* or *parkinsonian* hypertonia), or the limb may immediately return to the resting position as soon as the neurologist stops manipulating it (*spastic* or *elastic* hypertonia). Hypotonia is a reduction of muscle tone, i.e., lack of tension or resistance to passive movement. This is observed in cerebellar lesions and chorea.

Another goal of motor assessment is evaluating deep tendon reflexes. Using a reflex hammer, the neurologist taps the tendons (e.g., Achilles' tendon for the Achillean reflex). The deep tendon reflexes will be categorized as (1) normal, (2) increased and polykinetic (i.e., a single tap provokes more than one movement), (3) diminished or abolished (as in peripheral nervous system diseases), and (4) pendular (as in cerebellar syndrome). Often evidenced in case of increased reflexes, Babinski's sign is the lazy and

majestic extension of the big toe followed by the other toes in response to the scraping of the outer part of the foot plant. It is pathognomonic (i.e., totally specific) of a pyramidal syndrome, which is named after the axonal fiber tract that is altered: the pyramidal fasciculus. Motor assessment also includes evaluation of tremors and posture.

Once again, specific scales exist to robustly and homogeneously assess some of these signs such as the Unified Parkinson's disease rating scale (UPDRS) in Parkinson's disease [11]. For more information, the Movement Disorder Society UPDRS Revision Task Force has made the questionnaire available [12]. We report MDS-UPDRS items in Box 2. There are 65 items, 60 of which with a score from 0 to 4 (0, normal; 1, slight; 2, mild; 3, moderate; and 4, severe) and 5 with yes/no responses.

Box 2 MDS-UPDRS Structures

Part I: Non-motor experiences of daily living

13 items. Less than 10 min

1. Cognitive impairment
2. Hallucinations and psychosis
3. Depressed mood
4. Anxious mood
5. Apathy
6. Features of dopamine dysregulation syndrome
7. Nighttime sleep problems
8. Daytime sleepiness
9. Pain and other sensations
10. Urinary problems
11. Constipation problems
12. Lightheadedness on standing
13. Fatigue

Part II: Motor experiences of daily living

13 items. It does not involve examiner time; items are answered by the patient or caregiver independently.

1. Speech
2. Salivation and drooling
3. Chewing and swallowing
4. Eating tasks
5. Dressing
6. Hygiene
7. Handwriting
8. Doing hobbies and other activities
9. Turning in bed
10. Tremor
11. Getting out of bed, car, or deep chair
12. Walking and balance
13. Freezing

Part III: Motor examination

33 items (18 items with different duplicates corresponding to the right or left side or to different body parts). 15 min

1. Speech
2. Facial expression
3. Rigidity of neck and four extremities
4. Finger taps
5. Hand movements

Part IV: Motor complications

Six items. 5 min

1. Time spent with dyskinesia
2. Functional impact of dyskinesias
3. Time spent in the OFF state
4. Functional impact of fluctuations
5. Complexity of motor fluctuations
6. Painful OFF-state dystonia

(continued)

Box 2 (continued)

6. Pronation/supination
7. Toe tapping
8. Leg agility
9. Arising from chair
10. Gait
11. Freezing of gait
12. Postural stability
13. Posture
14. Global spontaneity of movement
15. Postural tremor of hands
16. Kinetic tremor of hands
17. Rest tremor amplitude
18. Constancy of rest tremor

2.5 Evaluation of Sensitivity

Sensitivity is the ability to feel different tactile sensations: normal (or crude) tact, pain, hot, or cold. Once again, it depends on the anatomical regions and tracts affected by a pathological process. The anterior spinothalamic tract carries information about crude touch. The lateral spinothalamic tract conveys pain and temperature. Assessment includes measuring:

- Epicritic sensitivity: test the patient's ability to discriminate two very close stimuli.
- Deep sensitivity: test the direction of position of the joints by the blind prehension. The doctor can also ask the patient if the vibrations of a diapason on joint bones (knee, elbow) are felt.
- Discrimination of hot and cold; sensitivity to pain.

2.6 Other Evaluations

The physician evaluation will also assess the autonomic nervous system which, when impaired, can induce tensile disorders: hypo−/hypertension, orthostatic hypotension (without compensatory acceleration of pulse), diarrhea, sweating disorders, accommodation disorders, and sexual disorders. They will also evaluate cerebellar functions: balance, coordination (which when impaired causes ataxia), and tremor.

Finally, clinicians will assess cranial nerves' functions. Cranial nerves are those coming out of the brainstem and have various functions including olfaction, vision, eye movements, face sensorimotricity, and swallowing. They are tested once again in a standardized way from the first one to the twelfth.

2.7 Summary of the Neurological Evaluation

At the end of this examination, the signs and symptoms are described in the report, and the physician specifies:

- A syndromic group of signs and symptoms
- The presumed location of brain damage

- A main diagnostic hypothesis
- Possibly, secondary hypotheses (differential diagnosis)
- Additional examination strategy through neuroimaging or additional examinations to refine disease diagnosis
- A therapeutic program

3 Neuropsychological Assessment

3.1 Generalities on Neuropsychological Assessment

Neuropsychology is concerned with how cognitive functions (*see* Box 3) and behavior are correlated with anatomo-physiological brain mechanisms. Thanks to the scientific-technological advances made in recent decades and the advent of increasingly sensitive structural and functional imaging techniques, we have discovered that human cognition has a modular architecture in which each module—whose operationalization depends on the reference framework—corresponds to a specific function [13]. This allowed us to understand which brain regions or structures we expect to be damaged when we observe a certain cognitive deficit [14–17]. The role of the neuropsychologist can be summarized in two core activities: assessment and intervention. In this chapter, we will focus on neuropsychological assessment, which produces data that is typically used by machine learning algorithms.

Neuropsychological assessment includes a clinical interview, followed by the measurement of cognitive functions using standardized tests and finally the interpretation of the results. This is applicable in diagnostic settings, to monitor disease progression if the diagnosis has previously been made or to measure the effectiveness of a treatment.

Box 3 Main Cognitive Functions

Memory	Short-term memory or working memory temporarily retains few pieces of information for the time needed to perform a certain task, using mechanisms such as mental repetition Episodic memory allows long-term conscious memory of a potentially infinite number of events (episodes) and contexts (time and place) in which they occurred Semantic memory allows the long-term conscious memory of a potentially infinite number of facts, concepts, and vocabulary, which constitute the knowledge that the individual has of the world Procedural memory is the memory of how things are done (e.g., tying shoelaces) and how objects are used

(continued)

Box 3 (continued)

Attention	Selective attention is the ability to select relevant information from the environment Sustained attention is the ability to persist for a relatively long time on a certain task
Visuospatial abilities	Estimation of spatial relationships between the individual and the objects and between the objects themselves and identification of visual characteristics of a stimulus such as its orientation
Language	Oral and written production and comprehension, at a phonological, morphological, syntactic, semantic, and pragmatic level
Executive functions	Superior cognitive functions such as planning, organization, performance monitoring, decision-making, mental flexibility, etc.
Social cognition	Using information previously learned more or less explicitly to explain and predict one's own behavior and that of others in social situations

Neuropsychology is therefore an interdisciplinary discipline. It is first and foremost a branch of psychology. The clinical interview that precedes the administration of tests is typical of psychological disciplines. The clinician collects anamnestic information (i.e., regarding medical history, lifestyle, and familiarity), observes patient behavior, and builds a relationship of trust and collaboration with him/her. All of these are crucial aspects in any type of psychological interview. In addition, the neuropsychologist must also be able to understand whether the cognitive complaint or the deficits detected are linked to brain damage or whether they are psychogenic. To do this, they assess, qualitatively or quantitatively depending on the situation, the mood of the patient and the presence of any anxiety syndromes, psychotic symptoms, etc.

Neuropsychology also has obvious points in common with neurology, since it is interested in the evaluation and intervention on the cognitive-behavioral manifestation of pathologies of the central nervous system. Over the past decades, much knowledge has been gained on the relationship between cognition and brain, and many tests have been developed. As a result, neuropsychological assessment has split off from neurological examination, assuming a separate role [18].

3.2 Psychometric Properties of Neuropsychological Tests

The use of cognitive tests is the specificity of the neuropsychological assessment.

Each new test is developed according to a rigid and rigorous methodology, trying to minimize all possible sources of error or bias, and based on scientific evidence. For example, a test that aims to assess learning skills might include a list of words for the participant to memorize and then recall. These words will not be randomly selected but carefully chosen based on characteristics such as frequency of use, length, phonology, etc. The procedures for administering neuropsychological tests are also standardized. The situation (i.e., materials, instructions, test conditions, etc.) is the same for all individuals and dictated by the administration manuals provided with each test.

All tests, before being published, are validated for their psychometric properties and normed. A normative sample is selected according to certain criteria which may change depending on the situation [19]. In most cases, these are large samples of healthy individuals from the general population, stratified by age, sex, and/or level of education. In other cases, more specific samples are preferred. The goal is to identify how the score is distributed in the normative sample. In this way, we can determine if the score obtained by a hypothetical patient is normal (i.e., around the average of the normative distribution) or pathological (i.e., far from the average). Establishing how far from the average an observation must be in order to be considered abnormal is a real matter of debate [20]. Many neuropsychological scores, as well as many biological or physical attributes, follow a normal distribution in the general population. The most used metrics to determine pathology thresholds are z scores and percentiles. For a given patient, the neuropsychologist usually computes the z score by subtracting the mean of the normative sample from the raw score obtained by the patient and then dividing the result by the standard deviation (SD) of the normative sample. The distribution of z scores will have a mean of 0 and a SD of 1. We can also easily find the percentile corresponding to the z score. Most often, a score below the fifth percentile (or z score $= -1.65$) or the second percentile (or z-score $= -2$) is considered pathological. As an example, intelligence, or intelligence quotient (IQ), is an attribute that follows a normal distribution. It is conventionally measured with the Wechsler Adult Intelligence Scale, also known as WAIS [21], or the Wechsler Intelligence Scale for Children, also known as WISC [22]. The distribution of IQs has a mean of 100 and a SD of 15 points. Around 68% of individuals in the general population achieve an IQ of 100 ± 15 points. Scores between 85 and 115 are therefore considered to be average IQs (therefore normal). Ninety-five percent of individuals are in a range within 30 points of 100, thus

between 70 and 130. Scores between 70 and 85 and those between 115 and 130 indicate borderline intelligence and medium-to-higher intelligence, respectively. Finally, only a little more than 2% of people are located in the two tails, respectively. An IQ below 70 is therefore considered pathological and indicative of intellectual disability. An IQ above 130 is indicative of superior intelligence.

Another reason a new test is administered to a normative sample is to evaluate its psychometric properties to understand whether it is suitable for clinical or research use [23]. The two main properties worth mentioning are reliability and validity [24].

Reliability indicates the consistency of a measure or in other words the proportion of variance in the observed scores attributable to the actual variance of the measured function, and not to measurement errors [25]. Reliability may be assessed in various ways. Internal consistency, for example, indicates whether the items of a test all measure the same cognitive function. A common procedure to evaluate it is to randomly divide the test into two halves and calculate the correlation between them. Test–retest reliability indicates the ability of a test to provide the same score consistently over time. No undesirable event, such as a pathological event, should have occurred between the two assessments and cause the patient to score worse (or better) on the second one. Another bias that could undermine test–retest reliability is practice effect, which refers to a gain in scores that occurs when the respondent is retested with the same cognitive test. This gain does not reflect a real improvement in the function assessed [26]. Parallel forms of the same test are often used to avoid these problems. Another measure of reliability is the consistency between different examiners (inter-rater reliability). In fact, despite the standardization described above, some degree of variance may remain between examiners [27].

Validity is the capacity of a test to measure what it actually proposes to measure and not similar constructs [28]. The validity of a test can be assessed by calculating the correlation between the score of interest with another measure that is theoretically supposed to be correlated. The following are some types of validity commonly assessed when developing or validating a new neuropsychological test: content validity (i.e., the test only measures what it is supposed to measure), substantive validity (i.e., the test is developed on the basis of theoretical knowledge and empirical evidence), convergent validity (i.e., individuals belonging to a certain homogeneous group have a similar score on the same test), and divergent validity (i.e., individuals belonging to two different groups have different scores on the same test, e.g., patients versus controls).

3.3 Realization of a Neuropsychological Assessment and Interpretation of Its Results

During an assessment, the neuropsychologist chooses the most appropriate tests for the patient, ensures that they are performed correctly, and interprets their results. Indeed, each neuropsychological assessment is tailored to the patient's needs. To assess a certain cognitive function, the clinician can choose a specific test depending on the patient's level of education, the presence of any sensory deficits (e.g., tests involving verbal material will be proposed to a visually impaired patient), as well as the diagnostic hypothesis.

Once anamnestic data has been collected and the cognitive scores have been obtained, the goal is to interpret these results and define the patient's cognitive profile. Defining a cognitive profile means identifying which cognitive functions are preserved and which are impaired. In the event that one or more impaired cognitive deficits are detected, it is necessary to specify at what level the deficit is located and its severity. For example, a patient may have a memory disorder whose severity can be identified by comparing their score to normative data as described above. Depending on the test used, the neuropsychologist will be able to define whether this memory disorder is due to difficulties in creating new memory traces (linked to the medial temporal lobe [14]), or to difficulties in retrieving existing traces (linked to the prefrontal lobe [16]), and so on. By describing the impaired and preserved cognitive mechanisms and by referring to what we know about brain correlates of cognitive function, the neuropsychologist will be able to detect a pattern. This may be a cortical syndrome, such as in the event of alteration of language or visuospatial functions [29]; a subcortico-frontal profile, involving, for example, impaired executive functions [30]; a subcortical profile, often involving slow information processing [31]; etc.

It is important to clarify that the aim of the neuropsychological assessment is not to diagnose a disease, but to describe a cognitive profile. This is only one of the elements taken into account by a physician, often a neurologist, to make the diagnosis. The physician will determine which disease or pathological condition underlies the cognitive impairment, by combining the evidence from other tests, such as laboratory tests, imaging, and neurological examination, as described above.

3.4 The Example of a Cognitive Test: The Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination, also known as MMSE, is one of the most widely used tools in both clinical practice and research, validated in many languages and adapted to administration in many countries. It is a screening tool for adults, which allows assessing global cognition quickly and easily through a paper–pencil test lasting 5–10 min.

Box 4 MMSE Questions and Scoring System
Temporal orientation [5 points, 1 per item] The respondent is asked to say the day of the week, the day of the month, the month, the year, and the season
Spatial orientation [5 points, 1 per item] The respondent is asked to say the floor and the name of the hospital or practice, district, town, and country.
Short-term memory [3 points, 1 per word] The examiner names three objects (apple, table, and penny in the English version), and the respondent repeats them immediately
Attention [5 points, 1 per subtraction] The respondent subtracts 7 from 100 five times
Verbal learning [3 points, 1 per word] The respondent recalls the three previously learned words
Denomination [2 points, 1 per object] The respondent names two objects indicated by the examiner, often a pen and a watch
Repetition [1 point] The respondent repeats the sentence "No ifs, ands, or buts"
Listening comprehension [3 points, 1 per task] The respondent is asked to take a sheet with their right hand, fold it in half, and throw it on the ground
Written comprehension [1 point] The respondent executes a written command, often "Close your eyes"
Writing [1 point] The respondent writes a sentence that contains a verb and a subject
Praxico-constructive and visuospatial skills [1 point] Copy of two intersecting pentagons showed by the examiner

The MMSE includes 30 questions, each with a binary score (0 for wrong answer and 1 for correct answer). More details are presented in Box 4. The total score ranges from 0 to 30. An MMSE score of 18 or less indicates severe impairment of cognitive functions. A score between 18 and 24 indicates moderate to mild impairment. A score of 25 is considered borderline. And a score of 26–30 indicates cognitive normality. Different diagnostic thresholds have been proposed as they depend—mainly—on age, education, and setting [32]. In clinical settings, a score below 24 is commonly considered pathological [33]. In research contexts, it is more common to use a cut-off of 26 (pathological if <26) [34]. The MMSE is therefore very useful for getting an idea of the patient's cognitive functioning, also facilitating effective communication between professionals.

Concerning psychometric properties, internal consistency is reported to vary significantly according to the setting. Alpha coefficient was around 0.30 in the general population [35] and 0.96 in a clinical setting [36]. Lower coefficients may be related to lower variability in community-based samples where the majority of participants are healthy and often highly educated. Regarding test–retest reliability, healthy individuals scored better at retest (about one point higher) when they repeated the MMSE about 3 months after the first assessment. Patients with cognitive impairment, on the contrary, did not show such learning. In [10], the MMSE also had good validity in discriminating patients with Alzheimer's dementia, depression, and schizophrenia.

4 Clinical Examination by Pathology

Neurology is a broad branch of medicine that deals with all pathologies affecting the central and peripheral nervous system, also including blood vessels and muscles, such as neurodegenerative diseases, epilepsy, sleep disorders, vascular diseases, headaches, movement disorders, neuro-oncology, etc. Clinical evaluation is therefore tailored to the complaint and symptoms. The purpose is to propose a treatment or follow the evolution of the disease. There is therefore a need for sensitive clinical tests that allow for early detection of abnormalities, so that treatment can be administered more promptly.

4.1 Diversity of Brain Disorders and Clinical Evaluation

As science advances, medicine is getting increasingly specialized. Although "general neurologists" are the majority in the domain, the field is segmented in different subspecialties in university hospitals, each with their topic and diseases of interest, and dedicated tools for innovative studies. We briefly describe these subspecialties below (*see* Box 5).

Box 5 Non-exhaustive List of the Main Neurological Diseases

Neurodegenerative disorders affecting mostly cognition or behavior	Alzheimer's disease Frontotemporal dementia Lewy body dementia Primary progressive aphasia
Movement disorders	Parkinson's disease Essential tremor Dystonia

(continued)

Epilepsy	Generalized idiopathic epilepsy Absence Partial idiopathic epilepsy Secondary epilepsy (post-traumatic, post-stroke, etc.)
Stroke or neurovascular diseases	Ischemic stroke Brain hemorrhage Cerebral venous thrombosis
Neuro-oncology	Meningioma Oligodendroglioma Astrocytoma Glioblastoma Brain metastasis
Peripheral nerve diseases	Mononeuropathy Polyneuropathy Radiculopathy Plexopathy
Headaches	Migraine Tension-type headache
Sleep disorders	Sleep apnea Narcolepsy
Inflammatory and demyelinating brain diseases	Multiple sclerosis Sarcoidosis
Neurogenetic diseases	Huntington's chorea Spinocerebellar ataxia
Neuromuscular disorders	Amyotrophic lateral sclerosis Myasthenia Myopathies

4.1.1 Neurodegenerative Disorders Affecting Mostly Cognition or Behavior

They include Alzheimer's disease, Lewy body and frontotemporal dementias, as well rarer conditions such as primary progressive aphasias. This field relies heavily on neuropsychological evaluation. Although progress has been achieved in diagnosis of these conditions (especially Alzheimer's disease) these last decades, therapeutic unmet needs remain high.

4.1.2 Movement Disorders

These include Parkinson's disease but also dystonia, myoclonus, tics, and tremors. Different treatment options have emerged for this group of diseases in the last years. These include drugs based on the dopamine levels in the brain (one of the main neurotransmitters for movement) and deep brain stimulation which requires the implantation of electrodes to stimulate or inhibit specific regions of the basal ganglia.

4.1.3 Epilepsy

This broad term refers to the abnormal electric activity of neurons in brain regions or in the whole brain inducing seizures. They are defined by the co-occurrence of symptoms or signs, and these electric abnormalities are detected by electroencephalography (EEG). Many anti-epileptic drugs exist to decrease the seizure frequency in these patients. Some patients present with pharmacoresistant epilepsy. For such patients, surgery, which aims at resecting part of the brain in order to suppress seizures, can be a treatment option.

4.1.4 Stroke or Neurovascular Diseases

Acute stroke is managed in stroke emergency units. A stroke can be either a brain infarction or a hemorrhage. They are not primary diseases of the brain tissue but of the arteries, capillaries, and veins that irrigate it. Treatment options range from rapid clot removal in ischemia (whether by thrombolysis or neuroradiological intervention), anti-aggregating or anticoagulation therapy, and physical or speech rehabilitation.

4.1.5 Neuro-oncology

This specialty deals with brain tumors, which may be malignant or benign. There are close connections with neurosurgery units and neuropathology which play a valuable role in analyzing the microstructure of the tumor in order to achieve a precise diagnosis. Treatments typically rely on a combination of surgery, radiotherapy, and chemotherapy.

4.1.6 Peripheral Nerve Diseases

They include all the diseases of the nerves outside of the brain, brainstem, or spine. These diseases induce motor, sensory, and autonomous impairments and are diagnosed through a combination of medical examination and electromyographic (EMG) recordings. Treatment options are very dependent on the cause of the disease which can range from simple mechanic compression of a nerve requiring mild surgery (carpal syndrome) to hepatic graft in some rare conditions (TTR mutation causing familial transthyretin amyloidosis).

4.1.7 Headaches

Although headaches are highly prevalent, specialists are rare in university hospital as these conditions (including migraine) are often cared for in private practice offices, except for the most urgent causes which are managed by emergency units. Treatments aim to decrease the frequency of the crisis (preventative treatments) for the most severe cases or the pain during a given crisis.

4.1.8 Sleep Disorders

Sleep disorders are sometimes managed by neurologists for some diseases (like narcolepsy) or pneumologists (since sleep apneas are among the most frequent cause of sleep impairment) or psychiatrists (tackling insomnia, often associated with psychiatric comorbidities). A sleep recording called polysomnography is sometimes

required to assess the most complex problems. Physicians can prescribe continuous positive airway pressure devices which keep the airways opened during sleep.

4.1.9 Inflammatory and Demyelinating Brain Diseases

The most emblematic of this group is multiple sclerosis in which the autoimmune system turns against the individual, penetrates the blood–brain barrier, and attacks the myelin which allows the rapid diffusion of the neuronal electric signal along the axons. This is one of the most advanced fields of neurology regarding treatment. Since the start of the twenty-first century, specific therapies preventing the crossing of the blood–brain barrier of lymphocytes revolutionized the management of multiple sclerosis [37].

4.1.10 Neurogenetic Diseases

Neurogenetic diseases are a group of rare diseases (like Huntington's chorea) due to a genetic mutation. These diseases usually follow a Mendelian mode of inheritance. They have the particularity to be detectable (through genetic testing after a specific counseling) which gives the opportunity to study them in their premorbid phase (i.e., before the onset of typical symptoms in a group of mutation carriers). Innovative gene therapies are actually being developed in some of these neurogenetic conditions [38]. Note that there also exist genetic forms of diseases which are in majority sporadic (e.g., familial forms of Alzheimer's disease).

4.1.11 Neuromuscular Disorders

These are diseases affecting the motor neurons such as amyotrophic lateral sclerosis, the neuromuscular synapse like myasthenia, or specifically the muscles in myopathies. To the exception of myasthenia, few treatment options exist in this particular field of neurology.

4.2 Importance of a Correct and Timely Diagnostic Classification

Neurologists have a saying: "time is brain." The correct and timely identification of a neurological disease is indeed crucial to be able to mitigate and sometimes reverse the signs and symptoms. As such, machine learning techniques may be very useful tools both in the context of slow-paced diseases such as Alzheimer's which are often diagnosed quite late or not at all [39] and to optimize the patient flow in emergency care, in case of stroke, for instance. This framework is theoretical as in practice some diseases can interact to induce symptoms. For instance, dementia is often of mixed origin, due to the association of degenerative (Alzheimer's disease) and vascular alterations. A walking deficit can be due to Parkinson's disease but also in part to arthrosis, etc. The correct identification of a disease is in part probabilistic, and this can lead to heterogeneity in the collected data from the clinical assessment.

5 Conclusion

Clinical assessment is central in neurology for the assessment of the patient because it is the direct reflection of what he/she feels and experiences. Indeed, according to regulatory agencies, a treatment is deemed effective if it has an effect on the clinical expression of the disease (e.g., on cognition, motor skills, sensitivity, autonomy, and survival) and not on intermediate markers such as imaging, biology, or others.

Machine learning is bringing clinical evaluation into a new era because it allows to go beyond the intuitions of the individual physician and could associate signs that were previously not seen as part of a disease type or subtype. However, the researcher should always remember that the best algorithm is only as good as the data it runs on, which depends on the clinician's understanding of how and why these particular data are collected and will be used for. So, for discovery, validation, and clinical implementation of new machine learning techniques, basic knowledge of the possible discrepancies and biases one may experience going from research setting to clinical practice is paramount.

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