L1. The offline brain, does it exist? An attempt at modern terminology and classification

F. Gerstenbrand, Vienna, Austria, H. Binder, Vienna, Austria, S. Golaszewski, Salzburg, Austria
Karl Landsteiner Institute for Neurorehabilitation and Space Neurology, Vienna/Austria

Coma Vigile (Wachkoma), a special form of a coma, is the leading symptom of the Apallic Syndrome/Vegetative State. The patient is conscious, but without higher and highest brain functions and shows more or less uniform neurological symptoms). Pathophysiologically the Apallic Syndrome can be compared with the physiological brain functions of a new born or a young child. An Apallic Syndrome after an acute severe brain damage shows a typical course passing from an initial state to a full state. In a great number of patients a remission is following (Gerstenbrand, 1967). In the remission state the disturbed consciousness in form of a coma vigile shows a reintegration, the motor deficits and the sensory dysfunctions are restored, together with the redevelopment of the higher and highest brain functions, the cognitive abilities. The Apallic Syndrome after a progressive brain process (Alzheimer Disease etc.) shows a disintegration of all brain functions to the end stage of an Apallic Syndrome (Vegetative State).

The Apallic Syndrome/Vegetative State is not to be equated with an Off-Line Brain, but can be compared with a partly On-Line Brain. The irreversible Off-Line Brain corresponds with the Brain Death Syndrome. The term Coma is pathophysiologically not to be equated with an Off-Line Brain because of the various accompanying symptoms, which are not recognized.

In contrast to the Apallic Syndrome/Vegetative the classical Locked-In Syndrome shows only a loss of the motor functions. The patients are conscious with sleep/wake rhythm and full active sensory functions. The extended Locked-In Syndrome based on an enlarged lesion to the mesodiencephalic region, sometimes including parts of the thalamus, symptoms of a stupor, parasomnia, hypersomnia, acinetic mutism and thalamic symptoms can be found.

Only the irreversible Brain Death, the total Brain Break Down, can be called Off-Line Brain.

L2. Heterogenous Mechanisms of Mild Cognitive Impairment in Parkinson Disease

Kurt A. Jellinger
Institute of Clinical Neurobiology, Vienna, Austria

Cognitive deficits are common in Parkinson disease (PD), but the range of clinical deficits and their structural backgrounds is variable. Mild cognitive impairment (MCI), representing the earliest clinical features of cognitive disorders, according to current criteria include the amnestic and non-amnestic phenotypes (aMCI and naMCI), the latter with multiple-domain and single domain naMCI. These are heterogenous populations, with prodromal Alzheimer disease (AD) and other dementing disorders represented in both groups. Patients with PD have an increased risk to develop MCI and dementia, the frequency of PD-MCI varying between 21and 62%, single domain being more common than multiple domain impairment. A recent multicenter analysis of 1,346 PD patients revealed an incidence of MCI in 25.8%, affecting various cognitive domains, most frequently memory, visuospatial and attention-executive abilities (1). Neuroimaging methods show hypometabolism in posterior cortical regions, widespread dopaminergic and cholinergic dysfunctions as well as increased cortical amyloid burden(2).The neuropathology of PD-MCI,

9th International Congress on current treatment and therapeutic perspectives in Alzheimer's, Parkinson's disease, MS and Epilepsy 27-30 January 2011 Athens King George Palace

Program

THURSDAY 27th of January 2011

Opening Ceremony
Addresses

Opening Lecture
Democracy, Philosophy and Medicine

Recital for traditional musical instruments and Chorus

Welcome Reception

FRIDAY 28th of January 2011

9.00-9.30 Lecture
Chaipersons: K.Jellinger, S.Baloyannis

The offline brain-is there such a think?
Apallic Syndrome and Locked-in Syndrome
F. Gerstenbrand, H.Binder,S. Golaszewski

9:30-10:00 Lecture
Chairpersons: F. Gerstenbrand, D.Vassilopoulos

Heterogenous mechanisms of mild cognitive impairment in Parkinson's disease
K. Jellinger

10.00-10.30 Coffee break and poster viewing

10:30-13:00 Lectures
Chairpersons: Th. Wisniewski, A. Papademetriou

10:30-11.00 Immunomodulation as a therapeutic a Therapeutic approach for Alzheimer's disease and prion diseases
Th. Wisniewski

11:00-11.30 Screening the metabolic causes of dementia: bedside Alzheimer's disease
A.Federico

HELLENIC SOCIETY FOR AMELIORATION
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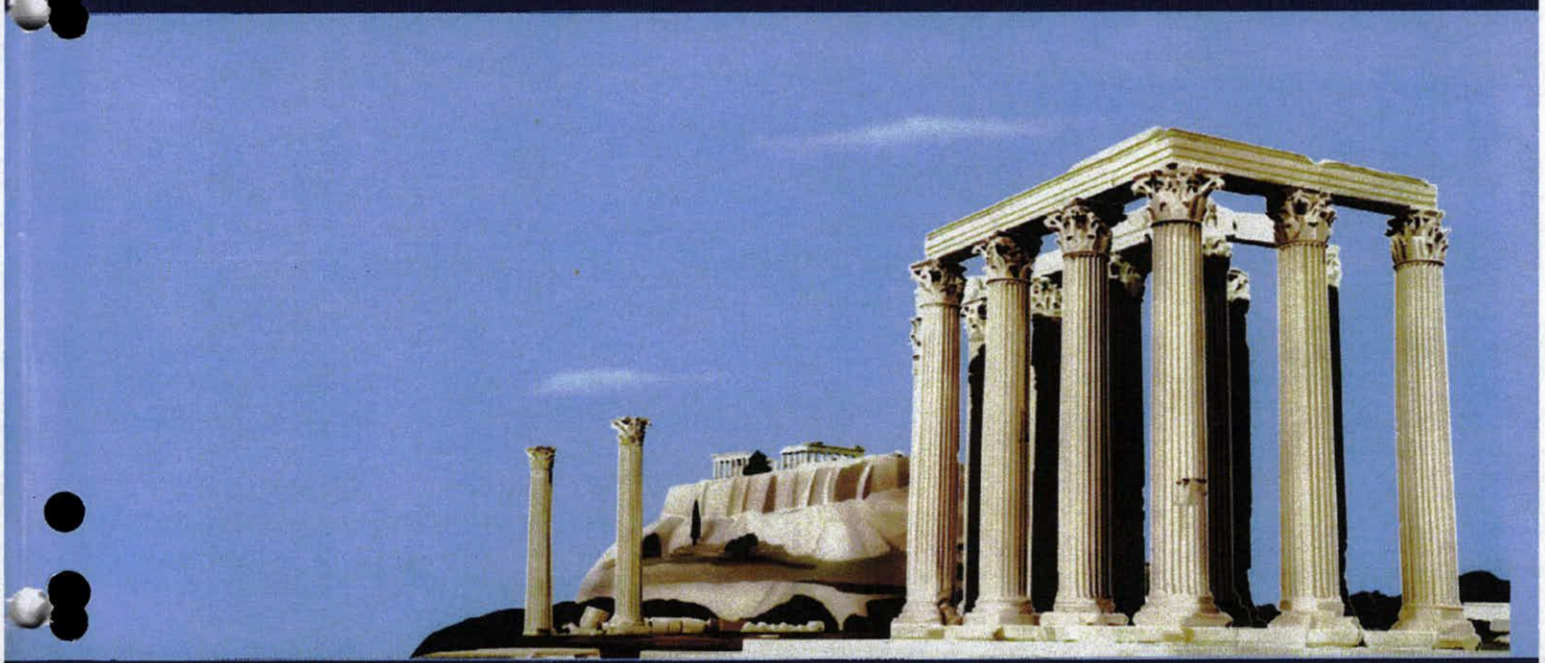

27 - 30 January 2011, Athens - Greece
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1077

Karl Landsteiner Institute
of Neurorehabilitation and
Space Neurology

The Offline Brain, does it exist?

An attempt at modern terminology and classification

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„The Online Brain"
Functions of the Brain

- Control center of the body
- Responsible for consciousness
- Processing all incoming data, sensory feelings, etc.
- Acts as an operator by sending messages from all over the body to their proper destination
- Controlling of outgoing messages
- Operating all body movements
- Archive and memory of life experience

Consciousness - medical overview
Brain activity in the default network

- Awareness
- Alertness
- Wakefulness
- Attention
- Arousal
- Responsiveness
- Subjectivity

Definition of „ Subjectivity"

Subjectivity is based on establishing a relationship between the organism and any object that becomes conscious.

Source: A. Damasio in Richard Robinson: Neuroscientists Make Inroads in Insights into Consciousness and Empathy. Neurology Today, 4th of February, 2010, Vol 10, Issue 3, p. 28-29

Offline Brain

- Loss of all brain functions
  - totally
  - partially
  - temporarily
    - course of remission
  - permanent

Offline Brain – total

- Coma
  - reversible
  - irreversible (brain death)
- Artificial coma
  - general anesthesia, in principle reversible
  - sedoanalgesia in sick patients

Coma

Definition after Plum and Posner

Deep unarousable unconsciousness

Plum, F, Posner J.B., The Diagnosis of Stupor and Coma. F.A. Davis Company, Philadelphia, 3rd Edition, 1980,

Coma

Definition after Brihaye et al.

Coma is defined as the pathological status of a patient who cannot be aroused to a wakeful state and whose eyes are continuously closed and do not open on command or on receipt of nociceptive stimuli.

Brihaye J, Frowein RA, Lidgren S, et al. Report of the meeting of the WFNS Neuro-traumatology Committee, 1. Coma-Scaling. Acta Neurochir 1978;40:181.

„Irreversible Offline Brain" Brain Death

The term *brain death* is defined as "irreversible unconsciousness with complete loss of brain functions," including the brain stem, although the heartbeat may continue

Source: Encyclopedia of Death and Dying
http://www.deathreference.com/Bl-Ce/Brain-Death.html

Brainstem Death

Irreversible loss of all brain stem function

– rest of brain function possible

– as brain death syndrome accepted in UK

Brain Death

Description after Shewmon

Brain Death is stated in patients where continuing treatment of a patient is without any hope of regaining any level of brain function. A continuation of therapeutic measures in brain death is neither in the interest of the patient nor ethically permissable. To treat a living corpse is unethical, it reduces a human being „ to a mere collection of organs" Shewmon (1998).

„Chronic Brain Death": 56 Brain Death patients"living" for more than 1 month, 7 patients more than 6 months , for more than 1 year, 1 patient 14,5 years
Shewmon (1998)

Brain Death Differential diagnoses

- apallic syndrome / vegetative state
- Locked-in Syndrome
- extended Locked-in Syndrome

Temporary Coma
General Anesthesia/„Artificial Coma"

- Stable administration of anesthetic drugs
- Arousal not possible, unresponsive; eyes closed, with reactive pupils
- Analgesia, akinesia
- Drug-controlled blood pressure and heart rate
- Mechanically controlled ventilation
- EEG patterns ranging from delta and alpha activity to burst suppression

Source: E.N. Brown, R.Lydic, Ph.D., N.D. Schiff: General Anesthesia, Sleep, and Coma, N Engl J Med 2010;363:2638-50.

Recovery of General Anesthesia
Artificial Coma

- **Emergence, phase 1**
  - Cessation of anesthetic drugs
  - Reversal of peripheral muscle relaxation (akinesia)
  - Transition from apnea to irregular breathing to regular breathing
  - Increased alpha and beta activity on EEG

Source: E.N. Brown, R.Lydic, Ph.D., N.D. Schiff: General Anesthesia, Sleep, and Coma, N Engl J Med 2010;363:2638-50.

Recovery of General Anesthesia, Artificial Coma

- **Emergence, phase 2**
  - Increased heart rate and blood pressure
  - Return of autonomic responsiveness
  - Responsiveness to painful stimulation
  - Grimaces (5th and 7th cranial nerve nuclei)
  - Swallowing, choking, coughing (9th and 10th cranial nerve nuclei)
  - Return of muscle tone (spinal cord, reticulospinal tract, basal ganglia, and primary motor tracts)
  - Defensive posturing
  - Further increase in alpha and beta activity on EEG

Source: E.N. Brown, R.Lydic, Ph.D., N.D. Schiff: General Anesthesia, Sleep, and Coma, N Engl J Med 2010;363:2638-50.

Recovery of General Anaesthesia, Artificial Coma

- **Emergence, phase 3**
  - Eye opening
  - Responses to some oral commands
  - Awake patterns on EEG
  - Extubating possible

Source: E.N. Brown, R.Lydic, Ph.D., N.D. Schiff: General Anesthesia, Sleep, and Coma, N Engl J Med 2010;363:2638-50.

Reversible Coma
Partial Coma, Partial Offline Brain

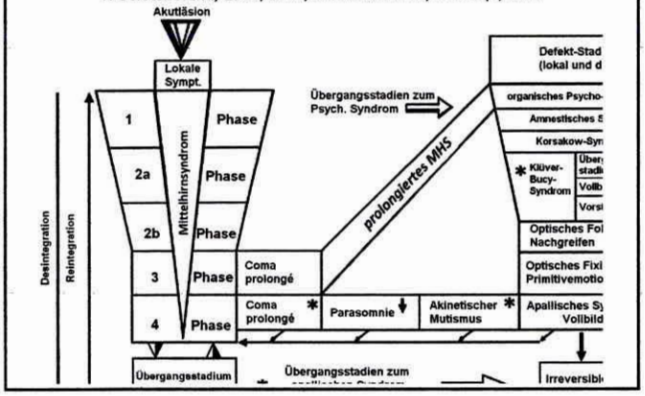
- Apallic syndrome/vegetative state
- Extended Locked-In Syndrome
- Remission state of apallic syndrome/ vegetative state (AS/VS)
  - Eight remission phases
- Minimally conscious state
  - Clinically comparable with different stages of remission state of AS/VS

Remission Course of Reversible Coma
Vigouroux et al. 1964
Coma prolongé, three stages

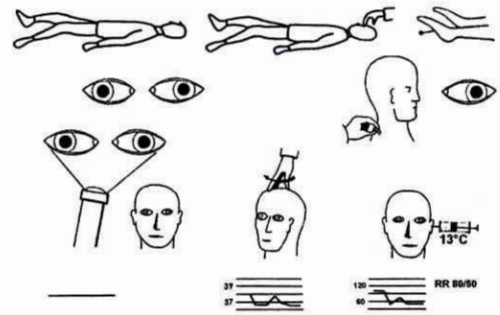
- Coma carus:
  - Acute midbrain syndrome — Gerstenbrand,
  - Acute bulbar brain syndrome — Lücking, 1971
  - Upper pons stage — Plum, Posner, 1972
  - Medullary stage
- Coma avec stabilisation des phénomènes végétatifs
  - Apallic syndrome, full stage — Kretschmer, 1940 Gerstenbrand, 1967
  - Vegetative state — Jennett, Plum, 1972
- Coma phase sortie de l'état comateux
  - AS, remission stage — Gerstenbrand, 1967

Apallic Syndrome

Course after acute severe brain damages (traumatic, hypoxic, etc.)
F. Gerstenbrand, 1967, 1977, F. Gerstenbrand, E. Rumpl, 1983



Acute Midbrain Syndrome, central, phase V

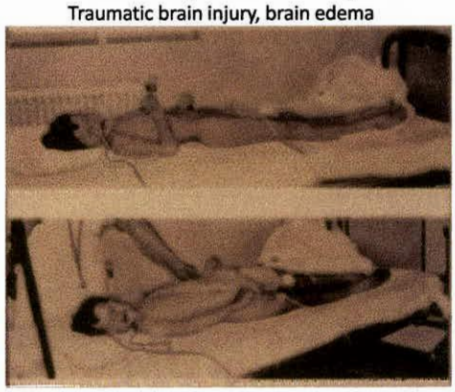


Vollbild des akuten traumatischen Bulbärhirnsyndroms. Schematische Darstellung. Nähere Erläuterung und Text s. Abb. 2.

Phase V, Stretch position, disinhibition of autonomic system

Acute Secondary Midbrain Syndrome

Traumatic brain injury, brain edema

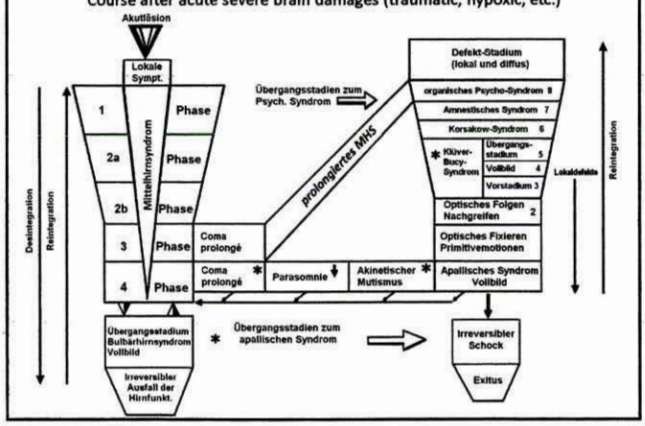


Phase IV, V

STADIEN DER HIRNSTAMMSCHÄDEN NACH SUPRATENTORIELLER RAUMFORDERUNG ZENTR. HERNIATION		MHS					BHS	
		I	II A	II B	III	IV	I	II
VIGILITÄT		SOMNOLENZ	SOPOR	COMA	COMA	COMA	COMA	COMA
REAKTION	AKUSTISCHE REIZE	GERING VERZÖGERT MIT ZUWENDUNG	VERZÖGERT OHNE ZUWENDUNG	FEHLEND	FEHLEND	FEHLEND	FEHLEND	FEHLEND
	SCHMERZREIZE	PROMPT GERICHTETE ABWEHR	VERZÖGERT UNGERICHTETE ABWEHR	RESTE UNGERICHTETER ABWEHR	BEUGE-STRECK-STELLUNG	STRECK-SYNERGISMEN	REST-STRECK-SYNERGISM.	FEHLEND
OPTOMOTORIK	-STELLUNG BULBUS -BEWEGUNG	NORMAL PENDELND	NORMAL SCHWIMMEND	BEGINNENDE DIVERGENZ DYSKUNJUGIERT	DIVERGENZ FEHLEND	DIVERGENZ FEHLEND	DIVERGENZ FIXIERT FEHLEND	DIVERGENZ FIXIERT FEHLEND
	PUPILLENWEITE							
	LICHTREAKTION							
KÖRPERMOTORIK	KÖRPERHALTUNG							
	SPONTANMOTORIK	MASSEN- UND WELLBEWEGUNGEN	MASSENBEWEG. ARME STRECKBEWEG. BEINE	MASSENBEWEG. ARME STRECKBEWEG. BEINE	BEUGE-STRECK-HALTUNG	STRECK-HALTUNG	REST-; NACH-STRECK-HALTUNG	SCHLAFFE HALTUNG
	TONUS	NORMAL	BEINE GERING ERHÖHT	BEINE ERHÖHT	ERHÖHT	STARK ERHÖHT	GERING ERHÖHT	SCHLAFF
	BABINSKI PHÄNOMEN	↓ ↓	↑ ↓	↑ ↓	↑ ↑	↑ ↑	↑ ↑	—
OBLIGAT	ATMUNG							—
VEGETATIV	PULS	LEICHT ERHÖHT	NORMAL	BESCHLEUNIGT	BESCHLEUNIGT	STARK BESCHLEUNIGT	BESCHLEUNIGT	VERLANGSAMT
NICHT OBLIGAT	RR	NORMAL	NORMAL	NORMAL	LEICHT ERHÖHT	ERHÖHT	NORMAL	ERNIEDRIGT
	KÖRPERTEMPERATUR	NORMAL	NORMAL	LEICHT ERHÖHT	ERHÖHT	STARK ERHÖHT	ERHÖHT	NORMAL ERNIEDRIGT

Apallic Syndrome

Course after acute severe brain damages (traumatic, hypoxic, etc.)



Symptoms of Apallic Syndrome „Partial coma“

- Coma vigile
- No recognition of the surrounding
- No contact to the surrounding
- No reaction to external stimuli
- Sleep-wake-rhythm fatigue regulated
- Optomotoric disturbances
- Flex-stretch position of the extremities and trunk
- Rigidospasticity
- Primitive motor patterns (oral, grasping, etc.)
- Dysregulation of the vegetative system

Etiology of Apallic Syndrome

1. After acute, severe brain injuries
   TBI, encephalitis, hypoxia, malignant stroke etc.
   - *Possibility of remission*
2. After progredient, diffuse brain processes
   CJD, M. Alzheimer, M. Pick, Chorea Huntington, etc.
   Final stage
   - *Remission not possible*
3. Intoxication
   3a Acute
   Exogenous (neuroleptics etc.)
   Endogenous (hepatic, uremic etc.)
   - *Full remission possible*

   3b Chronic
   Exogenous (Minamata disease etc.)
   Endogenous (hepatic, thyreotoxic etc.)
   - *Partial remission possible*

Apallic Syndrome
Attempt of a neurophysiological explanation
F. Gerstenbrand, 1967

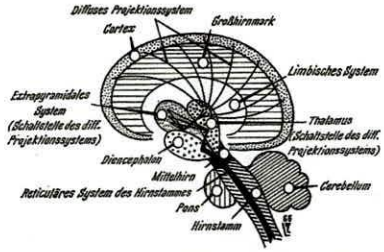


Abb. 67. Schematische Darstellung der verschiedenen Hirnformationen durch deren Ausfall das Symptomenbild des apallischen Syndroms entstehen kann. Einzeichnung des reticulären Systems im Hirnstamm und des diffusen Projektionssystems.

Regional, multi-regional defects in different brain areas

Depending on functioning ascending reticular system

Apallic Syndrome
Comparison with Anencephalus

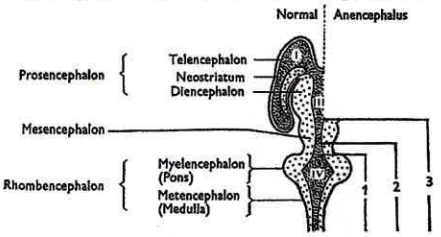
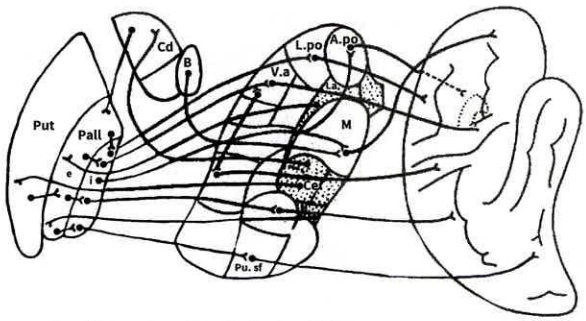


Abb. 69. Schematische Darstellung der 3 Typen des Anencephalus. 1. Rhombencephaler, 2. mesorhombencephaler, 3. mesencephaler Anencephalus (aus *M. Monnier*, Die Regulierung des Bewußtseins und ihre Störungen, in Bewußtseinsstörungen, Symp. vom 10. bis 12. I. 1961, St. Moritz, Schweiz, G. Thieme-Verlag, Stuttgart, S. 25).

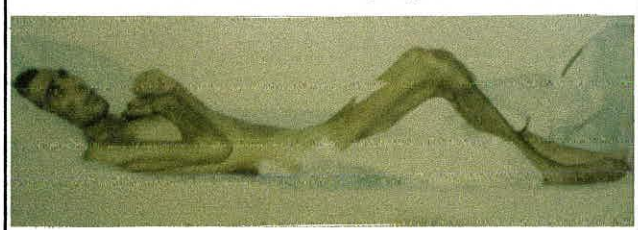
Different forms of anencephalus, after Monnier, 1961)

Unspecific Projection System of the Thalamus to the Cortex



ganglia and the cortex. After: R. Hassler, 1964

Apallic syndrome, pat. G.B., 36ª
traumatic brain injury, 1975



No modern treatment

Irreversible tertiary lesions, complications

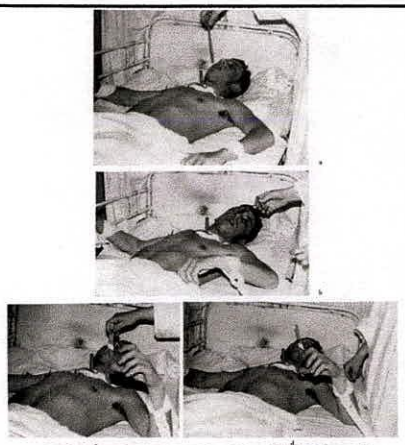
Exitus after 14 months

Apallic syndrome, pat. E.S., 19ª
traumatic brain injury, 1992

Modern treatment program in special center for apallic syndrome patients

No tertiary lesions, minimal complications

Remission after 5 months to minimal defect state

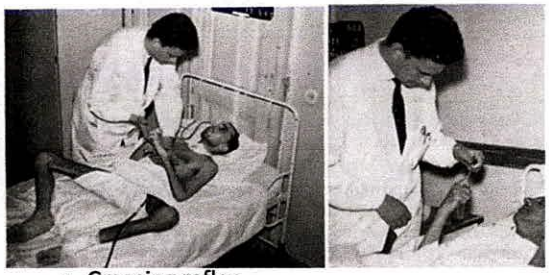


Pat. G.N., 39a

Full stage, traumatic apallic syndrome

Optic oral mechanism, Bulldogg-reflex

Apallic Syndrome
Full stage, traumatic



- Grasping reflex
  - Abb. 20: tonic
  - Abb. 21: phasic

Apallic Syndrome, traumatic, full stage

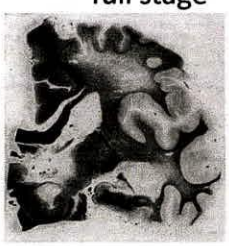
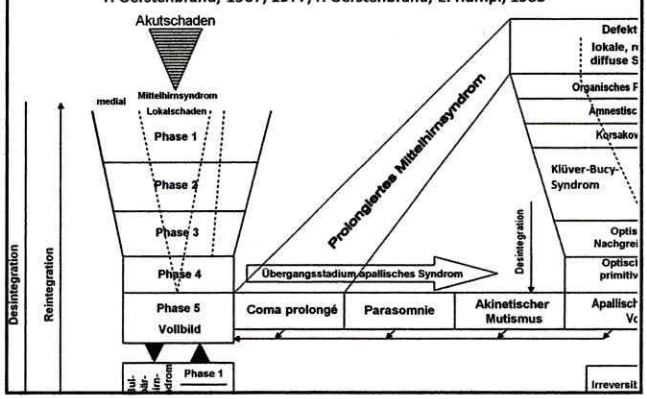


Abb. 58. Großhirn mit Hirnstamm, Frontalschnitt (Färbung nach *Heidenhain*). Fall 1 (N. I. 145/63). Diffuse fronto-temporale Markläsion, cystische Herdnekrosen, Kompressionsnekrose im Thalamus, Cysten im periaquäduktalen Grau.

L.G., 32a, full stage, died 9 months after accident,
Diffuse lesion of the white matter fronto-temporal with local cystic necrosis, arterial compression necrosis in thalamus, cystic lesions peri-aquaeductal. (Heidenhain staining)

Apallic Syndrome

Course after acute severe brain damages (traumatic, hypoxic, etc.)
F. Gerstenbrand, 1967, 1977, F. Gerstenbrand, E. Rumpl, 1983



Transitory stage of apallic syndrome, development of detailed symptoms
schematische Darstellung des Aufbaus der S

	Akutes Mittelhirnsyndrom	Übergangsstadium		
		Coma prolongé	Parasomnie	Akin. Mutismu
Vigilanz, Coma vigile				
Bewusstsein				
Muskeltonus, Rigidospastizität				
Position der Extremitäten				
Sehnenreflexe, gesteigert				
Motorische Primitivschablonen oral, Greifen, spontan				
Motorische Primitivschablonen auslösbar durch Reize				
Störung der Pupillenregulation				
Oculocephaler Reflex				

Apallic Syndrome after progredient, diffuse brain processes to a final stage

F. Gerstenbrand, 1967, 1977, F. Gerstenbrand, E. Rumpl, 1983

- Desintegration of higher and highest brain functions
  Diffuse organic psychosyndrome
- Multilocular cerebral Symptoms
  Aphasia, Apraxia, motor disabilities, etc.
- Klüver-Bucy Phase
  3 different stages
- Preapallic Phase
  „Dementia", motoric primitive patterns, mass movements, decerebrale rigidity, etc.
- Apallic Syndrome, Full Stage
  No remission signs

Apallic Syndrome - Remission Stages
Innsbruck Remission-Scale - 1

- Phase I: Optic fixation – reduce of Coma vigile, sopor
- Phase II: Optic tracking – sleep-wake-rhythm nomalizing, stupor
- Phase III: Pre-Klüver-Bucy-Phase – combination in the primitive motor reflexes, hypersomnia – wakeful
- Phase IV: Klüver-Bucy-Phase – typical Klüver-Bucy reflexes, obsfuscated mind

Apallic Syndrome - Remission Stages
Innsbruck Remission-Scale - 2

- Phase V: Post-Klüver-Bucy-Phase – hypersomnia, communication possible
- Phase VI: Korsakov syndrome – voluntary behavior, disorientation, confusional state
- Phase VII: Amnestic phase – emotional irritation, flat emotions
- Phase VIII: Psychoorganic syndrome – normal consciousness, awareness

Symptoms of Locked-in syndrome
No real coma state

- No possibility to communicate with surrounding except for blinking morse code
- Consciousness and perception fully maintained
- Total paralysis of all extremities, trunk, neck and motor brain nerves
- Eye opening and vertical eye movements possible
- Impairment of swallowing
- Spontaneous respiration possible
- Alpha-EEG

Etiology of Locked-In Syndrome
Lesion in Pons

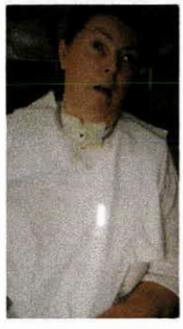
- Infarction caused by basilar thrombosis
- Hemorrhage
- Encephalitis
- Tumor
- Traumatic lesion

- Disconnection of the motor system, sensory connections undisturbed

Different Types of LIS
(after Bauer et al, 1979)

- According to neurological symptoms
  - Classical Locked-In syndrome
  - Incomplete Locked-In syndrome
  - Total Locked-In syndrome
- According to to time course
  - Chronic Locked-In syndrome
  - Transient Locked-In syndrome

Patient L.I.S , 45ª, female



Post traumatic etiology

Defect state

Profound differences between apallic syndrome and locked-in syndrome

- Apallic syndrome
  Loss of all brain functions, reduction to the midbrain-level (coma vigile, no voluntary motor action, primitive motor patterns)

  temporary or permanent

- Locked-in syndrome
  Loss of all motor abilities, except rest in optomotor functions, undisturbed vigilance, full contact to the surrounding, normal body sensation

  temporary or permanent

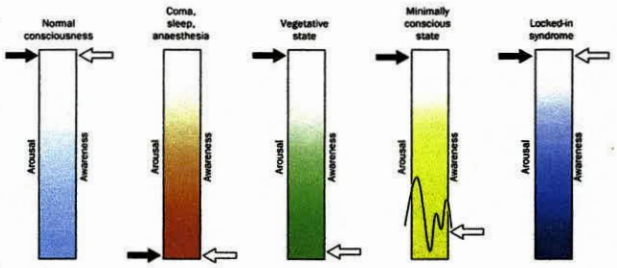
Partial Coma, Partial Offline Brain Minimally Conscious States

(Giacino et al, 1997)

- Rough consciousness: awareness
- Phenomenal consciousness: registration of external and internal phenomena
- Access consciousness: directed attention, cognitive awareness, decision making

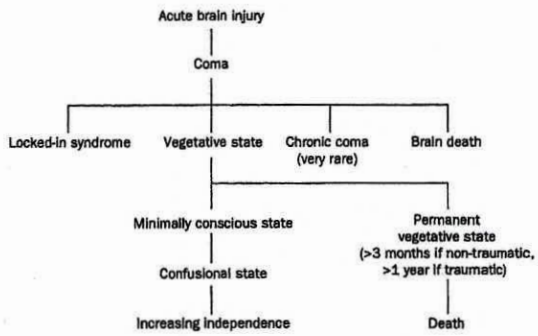
- Critics:
  - No detailed neurological symptomatology
  - Only phenomenological description
  - Etiology generally open
  - Generally comparable with different remission phases of AS/VS

Remission of a Coma State after Laureys et al

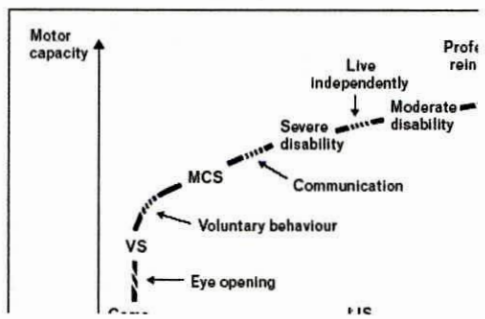


Arousal and awareness, the 2 components of consciousness in coma, vegetative state, minimally consciousness state and Locked-In syndrome

Severe acute brain injury after Laureys et al., 2004



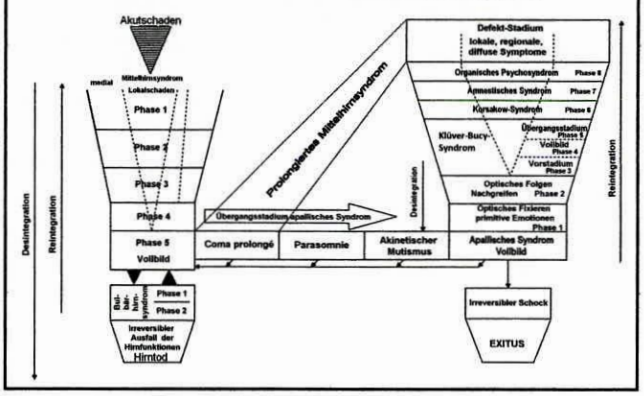
Restauration of a Coma State after Laureys et al.



Acute coma, passing, vegetative state, minimally consciousness state, good recovery

Apallic Syndrome

Course after acute severe brain damages (traumatic, hypoxic, etc.)
F. Gerstenbrand, 1967, 1977, F. Gerstenbrand, E. Rumpl, 1983



Partly „Offline" Brain States

- Acinetic mutism (Cairns et al., Skultety)
  - Lesion region 3rd ventricle, periaqueductal
- Sopor
- Stupor (Plum, Posner)
  - Lesion intralaminar nucleus thalami
- Hypersomnia (Jefferson)
  - Lesions mesodiencephal
- Parasomnia (Facon et al.)
  - Lesion periaqueductal

Changement in Consciousness in partly offline brain

- Acinetic mutism (Cairns et al, Skultety)
  - Disturbance in the initiation of spontaneous and intentional movement
  - Awareness undisturbed
- Sopor
  - Abnormal deep sleep not to get rid
- Stupor (Plum, Posner)
  - Deep sleep, unresponsiveness, temporarily arousable
- Hypersomnia (Jefferson)
  - Dormancy, continuously, not arousable
- Parasomnia (Facon et al)
  - Permanent dormancy, awakes by himself after months
  - Not identical with description/classification of sleep disorders

Offline – Online
Which structures have to be disposed?

- Cortical network for the different brain functions
- Activation system of the cortical network (ascending reticular system)
- Functioning working system to accept and evaluate incoming stimuli as well as control of outgoing messages
- Access to the archive of memories and ability to add new experiences

Offline – Online
„Main Operating System"

- Ascending reticular system
  - Functioning
    - undisturbed
  - Activation with different methods
    - Stimulation with all incoming sensory stimuli
      - Optic and acoustic stimulation, etc.
      - Stimulation of proprioceptive system
    - Medication
- Functional, biochemical, physical activation
  - Function like a "joy stick"
- "Switcher" unknown