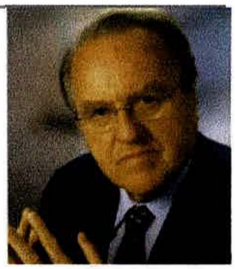
2nd EUROPEAN NEUROREHABILITATION CONGRESS



SEVERE DISORDERS IN CONSCIOUSNESS: DIAGNOSIS WITH fMRI

FRANZ GERSTENBRAND[1]

S.M. Golaszewski[1,2]
A Kunz[1,2]
M. Seidl[1,2]

1 Karl Landsteiner Institute of Neurorehabilitation and Space Neurology, Vienna, Austria

2 Department of Neurology, Paracelsus Medical University Salzburg, Austria

A detailed diagnosis of severe chronic disorders in consciousness (DOC) after Acute Brain Injury is essential for clinical and rehabilitative care and decision-making. Recent research showed, that some patients with severe chronic disorders of consciousness (SC-DOC) have partially residual brain functions and therefore a certain level of residual consciousness which cannot be assessed by clinical examination. Beside bed side examination neurobehavioral tests like Coma Recovery Scale-Revised (CRS-R) which rely on the patients' cognitive and motor ability to communicate, are the most widely used diagnostic tools. With the modern neuroimaging methods, especially functional MRI, objective physiological markers for assessing the state of consciousness are available, but till now they are not fully integrated in clinical routine.

On a group of 20 patients with an Apallic Syndrome the possibility to discover signs of consciousness shall be demonstrated. For the examination with fMRI were somatosensory, auditory and event related paradigms and evoked potentials (EP) were used. Comparing the findings of neurobehavioral diagnostic methods with the results of fMRI 3 out of 15 patients with an Apallic Syndrome, full state or early remission phase showed signs of consciousness, confirming that this patients had higher brain functions. 3 of the 5 patients with an Apallic Syndrome in a defect phase of a remission state, clinically compared with Minimally Conscious State (MCS), showed findings similar to fMRI activation in healthy subjects.

Every diagnostic modality available in each clinical setting should be performed, to minimize diagnostic error. FMRI has the potential to improve and to correct diagnosis in chronic disorders of consciousness. In Apallic patients are the findings of fMRI a great help for classification in the different states of remission or for a defect state. The use of fMRI examination would influence the diagnosis of Vegetative State, which till now is used in the American literature with the knowledge of a lack in details and ignoring generally the remission possibility. The results of fMRI can direct the neurorehabilitation program in this most severe neurological conditions. A prognostic value can be assumed.

PARACELSUS MEDIZINISCHE PRIVATUNIVERSITÄT

Karl Landsteiner Institute of Neurorehabilitation and Space Neurology

Severe Disorders in Consciousness: Diagnosis with fMRI

F. Gerstenbrand[1),2)], St. Golaszewski,[1),2)], A. Kunz[1),2)], M. Seidl[1,2)], Ch.Kurzmann[1)]

[1)] Karl Landsteiner Institute of Neurorehabilitation and Space Neurology, Vienna, Austria
[2)] Department of Neurology, Paracelsus Medical University, Salzburg, Austria

2nd European Neurorehabilitation Congress
in conjunction with
3rd European Teaching Course
on Neurorehabilitation

June 26-28, 2013
Bucharest, Romania

The Hippocratic Writings

„And men should know that from nothing else than from the brain come joys, delights, laughter and jests, and sorrows, griefs, despondency and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear and know what are foul and what are fair, what sweet und what unsavory....."

Functions of the Brain
Control centre of the body

- Responsible for consciousness
- Processing all incoming data (sensory 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
- Processing and controlling emotions
- Controlling instinct life
- Archive and memory of life experience

Consciousness
F.Plum and J.B.Posner

The limits of consciousness are hard to define satisfactorily and quantitivly and we can only interfere the selfawareness of others by their apparence and by their acts.

Consciousness

- Awareness
- Alertness
- Wakefulness
- Attention
- Arousal

- Intact Default Mode Network

Awareness

- Self awareness
- Subjective awareness
- Visual awareness
- Auditiv awareness
- Emotional awareness
- Interoceptive awareness

Basis of Brain Functions

- 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

Main Operating System in Consciousness

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

Coma
Definition after Brihaye et al, 1978

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.

Coma I

- Reversible (temporary)
  - Artificial Coma, Sedoanalgesia
  - Metabolic Coma
  - Toxic Coma
  - Cortical Disconnection Coma
    - Acute Midbrain Syndrome/Upper Pons Syndrom
    - Brain Stem Disconnection Syndrome
  - Subacute Cortical Disconnection Coma
    - Apallic Syndrome /Vegetative State

Coma II

- Irreversible Coma
  - Brain Death
  - Permanent Apallic Syndrome/Vegetative State
  - Defect State of Apallic Syndrome/Vegetative State (Wachkoma)

Brain Death

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

Source: Encyclopedia of Death and Dying

Temporary Coma,
"Artificial Coma" (General Anesthesia),
Sedoanalgesia

- 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.

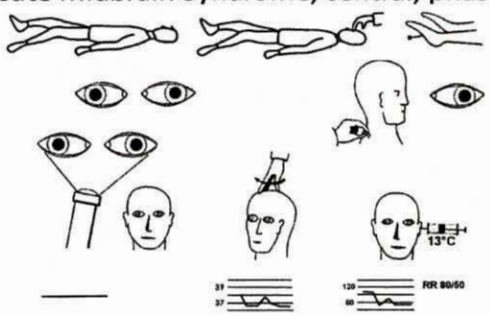
Reversible Coma
Disconnection Syndromes

- Acute Disconnection Syndrome
  - Mid Brain Syndrome- Upper Pons Syndrome
- Sub Acute Disconnection Syndrome
  - Apallic Syndrome/Vegetative State (AS/VS)
- Locked In Plus Syndrome
- Remission Phase of Apallic Syndrome/ Vegetative State
  - Eight remission phases (AS)

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

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

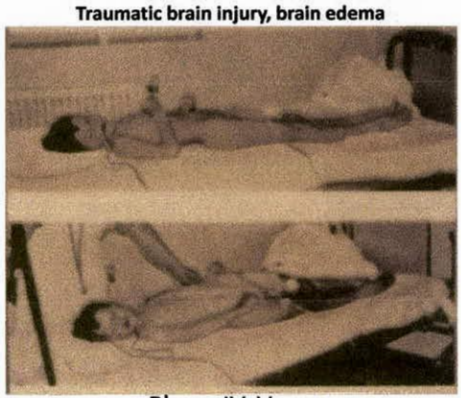
Acute Midbrain Syndrome, central, phase V



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

Phase V, Stretch position, disinhibition of autonomic system

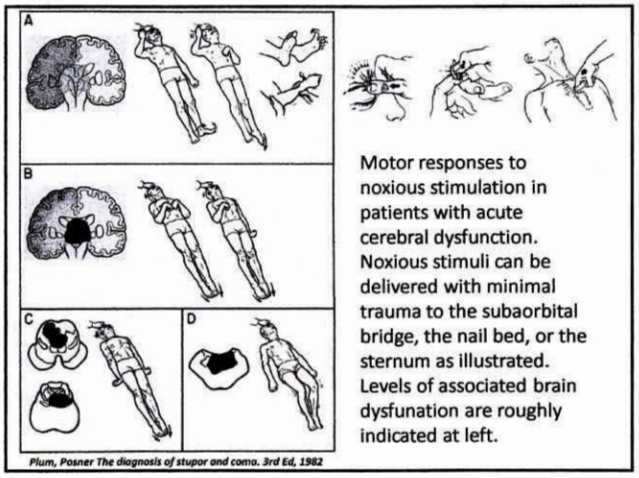
Acute Secondary Midbrain Syndrome
Traumatic brain injury, brain edema



Phase IV, V

Hirnstammsyndrom: Synopsis

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-STEIGERGISMEN	REST-STRECK-SYNERGISM.	FEHLEND
OPTOMOTORIK	STELLUNG BULBUS BEWEGUNG	NORMAL PENDELND	NORMAL SCHWIMMEND	BEGINNENDE DIVERGENZ DYSKUNUGIERT	DIVERGENZ FEHLEND	DIVERGENZ FEHLEND	DIVERGENZ FIXIERT FEHLEND	DIVERGENZ FIXIERT FEHLEND
	PUPILLENWEITE							
	LICHTREAKTION							
KÖRPERMOTORIK	KÖRPERHALTUNG							
	SPONTANMOTORIK	MASSEN- UND WÄLZBEWEGUNGEN	MASSENBEWEG. ARME STRECKBEWEG. BEINE	MASSENBEWEG. ARME STRECKBEWEG. BEINE	BEUGESTRECKHALTUNG	STRECKHALTUNG	REST-; NACHSTRECKHALTUNG	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

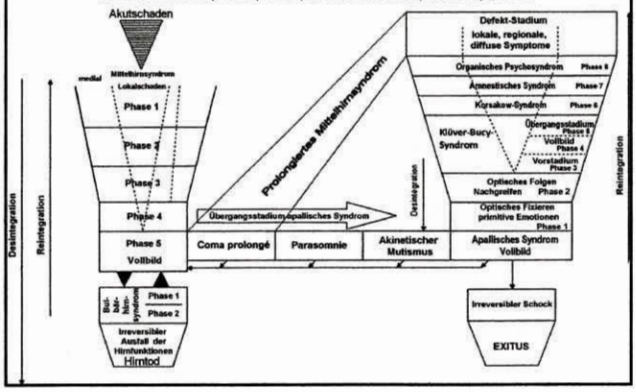


Plum, Posner The diagnosis of stupor and coma. 3rd Ed, 1982

Motor responses to noxious stimulation in patients with acute cerebral dysfunction. Noxious stimuli can be delivered with minimal trauma to the subaorbital bridge, the nail bed, or the sternum as illustrated. Levels of associated brain dysfunation are roughly indicated at left.

Apallic Syndrome

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



Symptoms of Apallic Syndrome

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

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

Apallic Syndrome
Full stage, traumatic

Abb. 20 Abb. 21

Abb. 20. Vollstadium des traumatischen apallischen Syndroms (Fall 2), tonisches Greifen.
Abb. 21. Vollstadium des traumatischen apallischen Syndroms (Fall 10/40), phasisches Greifen.

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

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

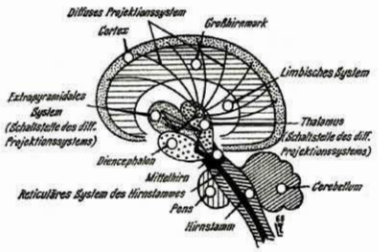


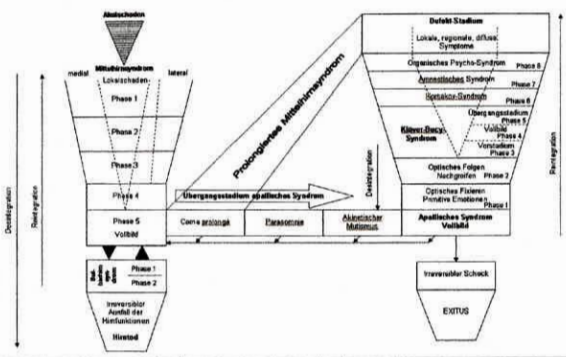
Abb. 67. Schematische Darstellung der verschiedenen Hirnformationen durch deren Ausfall das Symptomenbild des apallischen Syndroms entstehen kann. Einzeichnung des reticulären Systems im Hirnstamm und des diffusen Projektionssystems.

Regional, multiregional defects in different brain areas

Depending on functioning ascending reticular system

Apallic Syndrome

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



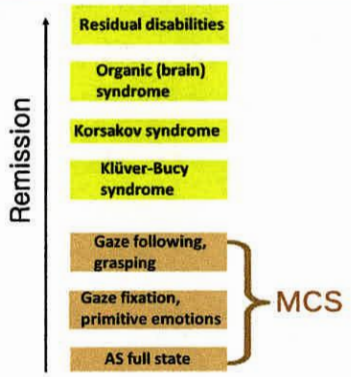
Apallic Syndrome - Remission Stages
Innsbruck Remission Scale - 1

- Phase I: Optic fixation – reduction of Coma vigile, sopor
- Phase II: Optic tracking – sleep-wake-rhythm nomalizing, stupor
- Phase III: Pre-Klüver-Bucy-Phase – combination in primitive motor reflexes, hyper-somnia – wakeful
- Phase IV: Klüver-Bucy-Phase – typical Klüver-Bucy reflexes, obnubilation

Apallic Syndrome - Remission Stages
Innsbruck Remission-Scale - 2

- Phase V: Post-Klüver-Bucy-Phase – hyper-somnia, 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, aware

Remission States of postraumatic Apallic Syndrome (Innsbruck scale, Gerstenbrand 1977)



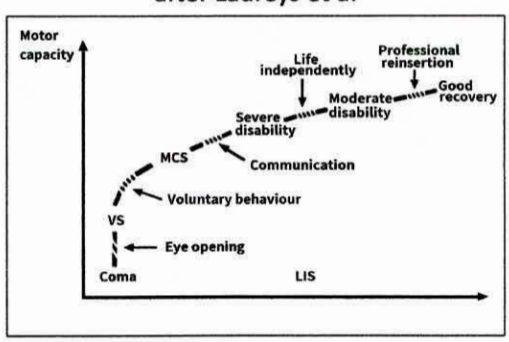
Minimally Conscious States

(Giacino et al, 1997)

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

- Critics:
  - No detailed neurological symptomatology
  - Phenomenological description
  - Etiology generally open
  - Comparable with different remission phases of AS/VS

Restauration of a Coma State after Laureys et al



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

Locked-In Plus Syndrome
Basilaris Thrombosis
LIS Additional Symptoms

- 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

Examination for Disorders of Consciousness

- Neurological bed side examination
- Coma recovery scale revised (CRS-R)
- EEG (event related potentials)
  - semantic oddball paradigm - SOP
  - own name paradigm - ONP)
- fMRI (event related potentials)
  - semantic oddball paradigm - SOP
  - own name paradigm - ONP)

Functional Magnetic Resonance Imaging (fMRI)

- Method to registrate incoming stimulations in different brain regions
- Using the BOLD effect (Blood Oxygenation Level Depend)
- More blood in the region

Functional MRI
Stimulation of Brain Functions

- Silent stimulation (no stimulation)
- Sensoric Stimulation
  - Vibrating stimulation
  - Acustic stimulation
  - Visual stimulation
  - Pain stimulation
- Cognitive Stimulation
  - Language stimulation
  - Imaginary stimulation

Functional Neuroimaging
Apallic Syndrome

Functional neuroimaging studies suggest that specific brain activity in response to speech and hearing the own first name can remain in patients in the vegetative state or in early remission

(e.g. Coleman, Brain, 2007; Davis, PNAS, 2007; Di, Neurology, 2007; Schiff, Neurology 2005; Kampe, The Journal of Neuroscience, 2003; Owen, Neurocase, 2002).

Paradigms in fMRI

- Stimulus related paradigms
  - Sensoric paradigma
    - Reaction on sensible stimulation (vibro stimulation)
    - Reaction on pain (electric medianus stimulation)
    - Visual stimulation, acustic stimulation
  - Cognitive paradigma
    - Language paradigma (semantic discrimination)
    - Own name paradigma (self awareness)
    - Emotional paradigma (reaction on crying/ laughing face)
    - Memory paradigma (Warrington Test)
    - Motor-Imagination (play tennis, mental navigation)
- Stimulation non-indepent paradigma (silent paradigma)
  - Default Mode Network

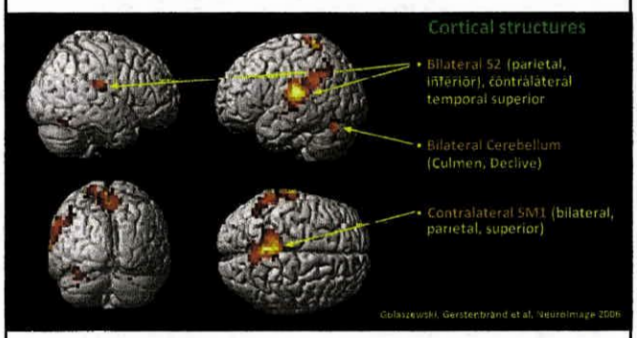
Hierarchy in fMRI Paradigms
(Kotchoubey, Schwarzbauer)

- Silent Paradigma (no stimulation)
- Vibro Stimulation
- Emotional Paradigma (cry/laughing, face)
- Language Paradigma (semantic discrimination)
- Memory Paradigma (Warrington Test)
- Mental Imagination

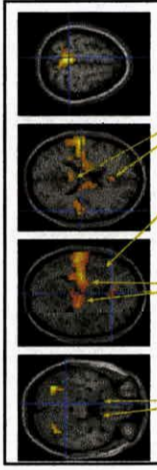
Vibration to the foot sole: amplitude 1 mm, frequency 50 Hz

Foot Sole Vibration

Stimulus: 50 Hz, A=1mm / Group analysis



Further cortical structures vibration paradigma BOLD effect



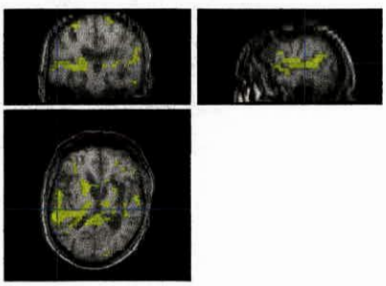
- Bilateral Gyrus cinguli anterior and posterior
- Insular Cortex, posterior parietal (left-dominant)

Subcortical structures

- Bilateral Thalamus (somatosensoric nuclei), contralateral Nucleus lentiformis
- Bilateral Nucleus caudatus

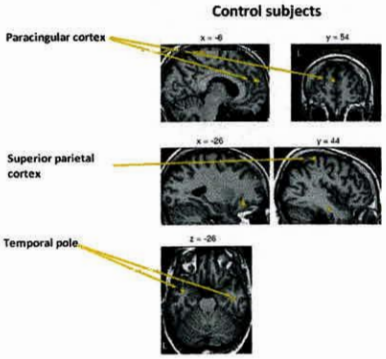
Golaszewski, Gerstenbrand et al., Neuroimage 2006

Vibration Stimulation, Apallic Syndrome BOLD effect



Own name paradigm (ONP)/fMRI: healthy controls

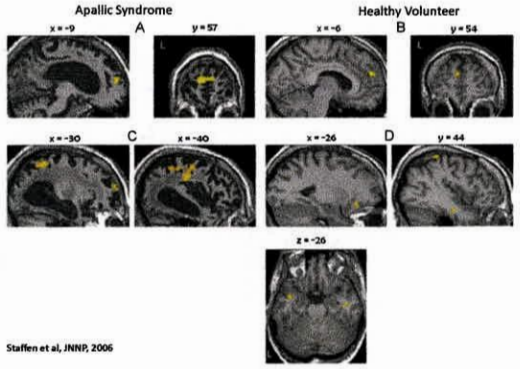
Control subjects



- Kampe KK et al., J Neuroscience 2003: **Consistent activity in „medial prefrontal Cortex".**
- Northoff et al., Trends Cogn Sci 2004: **Processing of self-referential stimuli in cortical midline structures (CMS), fundamental for model of the own personality´.**

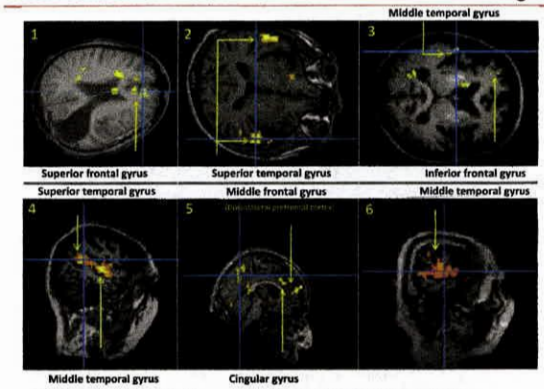
Staffen et al, JNNP, 2006

Higher Language Processing
Apallic Syndrome: Higher activity in own > foreign name



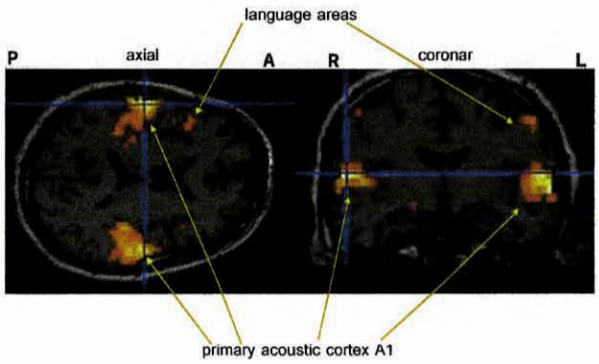
Staffen et al, JNNP, 2006

BOLD contrast for the Own Name and the Sentence Paradigma



1) MCS 2: own name > not own name
2) UWS 11: own name > silence
3) UWS 9: sentences > silence
4) UWS 6: meaningful > non-meaningful
5) MCS 3: own name > silence
6) UWS 7: sentences > silence

SOP/fMRI: Locked-In-Plus Syndrome , Basilaris thrombosis
Symptoms of hypersomnia



Results I: specific fMRI response in AS/VS

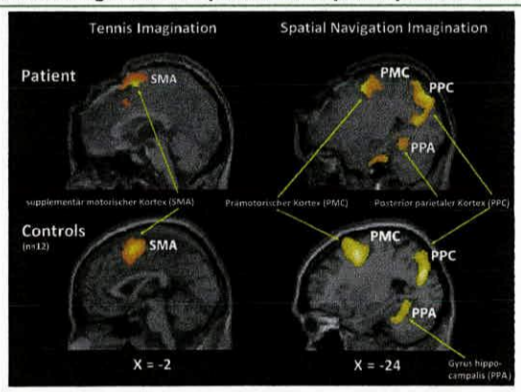
patient number	vibrotactile stimulation	silence vs name	own name vs foreign name	silence vs sentence	semantic oddball
VS#1	no	no	no	no	no
VS#2	no	no	yes	yes	no
VS#3	no	no	no	yes	no
VS#4	yes	yes	yes	yes	yes
VS#5	no	yes	no	yes	no
VS#6	yes	yes	yes	yes	yes
VS#7	no	yes	no	no	no
VS#8	no	yes	yes	yes	yes
VS#9	yes	no	no	no	no
VS#10	yes	no	no	no	no
VS#11	no	yes	no	yes	no
VS#12	yes	no	no	no	no
VS#13	yes	no	no	yes	no
VS#14	no	yes	yes	yes	no
VS#15	no	no	no	no	no

Results II: specific fMRI response in MCS patients

patient number	vibrotactile stimulation	silence vs name	own name vs foreign name	silence vs sentence	semantic oddball
MCS#1	no	yes	yes	yes	no
MCS#2	no	yes	yes	yes	yes
MCS#3	no	yes	no	yes	no
MCS#4	on	yes	no	yes	yes
MCS#5	no	yes	yes	yes	no

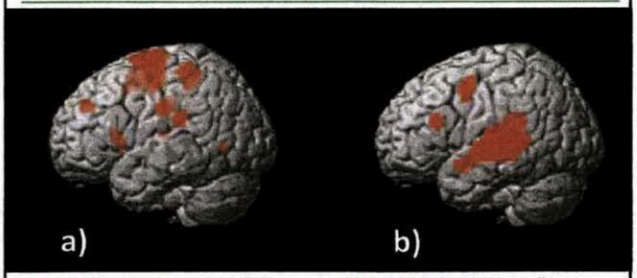
⇒ 8 out of the 15 AS patients in the CRCS-r did show higher order speech processing and cortical response to a self-referential stimulus in fMRI

Mental Imagination of a patient with Apallic Syndrome in fMRI



(Owen et al, Science 2006)

Mental Imagination in fMRT: healthy volonteer, 25a, f



a) Mental Imagination: Tennis play = „Yes"

b) Mental Imagination: walking through own flat in fixed sequence = „No"

Default Mode Network

Raichle 2001

Function:

Attention-demanding cognitive task

Cognitive processes (day dreaming, mind wandering, stimulus, independent source, self related source)

Anatomical basis:

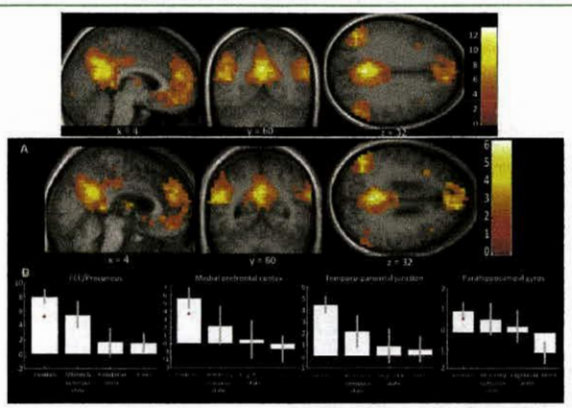
Precuneus bilateral

Temporo-parietal junctions

Medial prefrontal cortex

Level of consciousness, paraclinical brain marker

Default Mode Net Work



(Vanhaudenhuyse et al, Brain, 2010)

Misdiagnosis in disorders of consciousness

Patients with severe chronic disorders of consciousness of different origin (TBI, hypoxia, stroke), in an Apallic Syndrome, full state or early remission state and patients in minimally conscious state are misdiagnosed up to 43%.

(Andrews et al,1996; Schnakers et al, 2009)

Conclusion

- In unresponsive patients diagnosed as Apallic Syndrome/Vegetative State the fMRI shows brain activity in language regions and regions of self- awareness, the diagnosis has to be revised. Patients are able for processing of language, memory differentiation and self-referential stimuli at a higher cortical level.
- Knowledge about the perception of language and self-referential stimuli in patients with severe disorders of consciousness is very important for planning of an individual neurorehabilitation program, also for relatives, for therapists and for caregivers to improve the outcome.
- Up to now, there are no data for a prognostic value of the detected specific brain activity in fMRI.