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MEDIZINISCHE PRIVATUNIVERSITÄT

Karl Landsteiner Institute
of Neurorehabilitation and
Space Neurology



fMRI in Vegetative State/ Apallic Syndrome

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9th Danube Teaching Course

on Epilepsy, MS, Headache, Vertigo Child Neurology and stem cells therapies

June 20-21, 2013
Kazimierz Dolny, Poland,

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 quantitatively 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

Default Mode Network Basis for Consciousness

- General activity
- Specialized activity
 - auditive perception
 - visual perception
 - emotional perception

Awareness

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

Consciousness Cognitive Abilities - I

- Perception
- Comprehensiveness
- Recognition
- Assessment
- Processing
- Reliability

Consciousness Cognitive Abilities - II Self recognition

- Self reliability
- Responsiveness
- Conceptivity
- Accessment

- Subjectivity
(Cogito ergo sum)

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 2010, 28-29

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

- Break Down - Coma

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, Sedo Analgesia
 - 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), Sedo Analgesia

- 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.

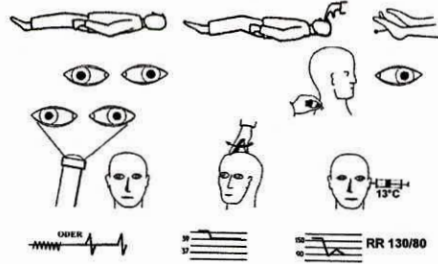
Reversible Coma Disconnection Syndromes

- 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

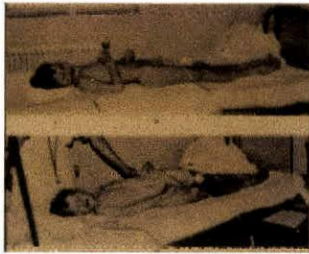
Acute Midbrain Syndrome, central, phase V



Übergangsphase zum akuten traumatischen Bulbärhirnsyndrom. 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



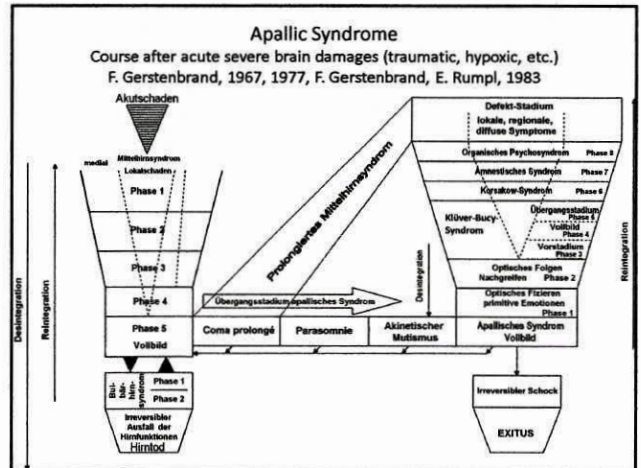
Phase IV, V

Hirnstammsyndrom: Synopsis

STADIEN DER HIRNSTAMMSCHÄDEN NACH SUPRATENTORIELLER RAUMFORDERUNG	MHS					BHS	
	II	II A	II B	III	IV	I	II
VIGILANZ	SOMNOLENZ	SOPOR	COMA	COMA	COMA	COMA	COMA
AUDITIVE REIZE	GERING VERZÖGERT MIT ZUWENDUNG	VERZÖGERT ODER ZUWENDUNG	FEHLEND	FEHLEND	FEHLEND	FEHLEND	FEHLEND
SCHMERZREIZE	FRÜHMIT GERICHTETE ABWEHR	VERZÖGERT UNGERICHTETER ABWEHR	REIZE UNGERICHTETER ABWEHR	REIZE UNGERICHTETER ABWEHR	STRECK-STRECK-GERÄHM	REIZ- STRECK- SYNERGISM.	FEHLEND
STELLUNG	NORMAL	NORMAL	BEUGENDE DIVERGENZ	DIVERGENZ	DIVERGENZ	DIVERGENZ	DIVERGENZ
BULBUS -BEWEGUNG	PENDELND	SCHWIMMEND	DYSKONTAKT	FEHLEND	FEHLEND	FEHLEND	FEHLEND
PUPILLENWEITE
LICHTREAKTION
KÖRPERHALTUNG
SPONTAN- MOTORIK	HALSEN UND WÄLZ- BEWEGUNGEN	HALSEN UND ARME STRECKBEWEG. BEINE	HALSEN UND ARME STRECKBEWEG. BEINE	BEUGE- STRECK- HALTUNG	STRECK- HALTUNG	REIZ- NACH- STRECK- HALTUNG	SCHLAFTE HALTUNG
TONUS	NORMAL	BEINE GERING ERHÖHT	BEINE ERHÖHT	ERHÖHT	STARK ERHÖHT	GERING ERHÖHT	SCHLAF
BARINSKI PHÄNOMEN
ORIGAT	ATMUNG
VEGETATIV	PULS	LEICHT ERHÖHT	NORMAL	BESCHLEUNIGT	BESCHLEUNIGT	STARK BESCHLEUNIGT	BESCHLEUNIGT
NICHT ORIGAT	RR	NORMAL	NORMAL	NORMAL	LEICHT ERHÖHT	ERHÖHT	NORMAL
KÖRPER- TEMPERATUR	NORMAL	NORMAL	LEICHT ERHÖHT	ERHÖHT	STARK ERHÖHT	ERHÖHT	NORMAL ERHÖHT

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

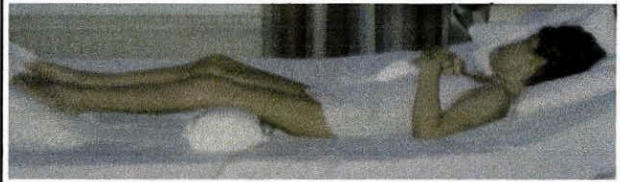
Plum, Posner The diagnosis of stupor and coma, 3rd Ed, 1982



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

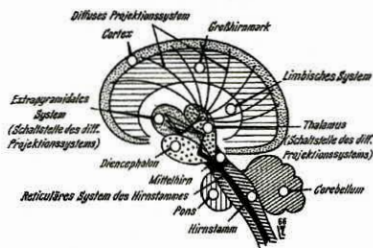
Apallic Syndrome Full stage, traumatic



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

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

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



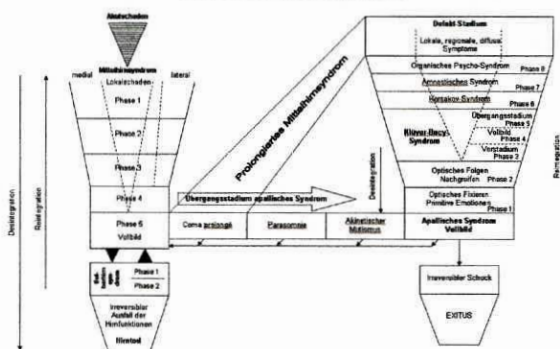
Regional, multiregional defects in different brain areas
Depending on functioning ascending reticular system

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

Apallic Syndrome

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

Entwicklung und Verlauf eines apallicen Syndroms



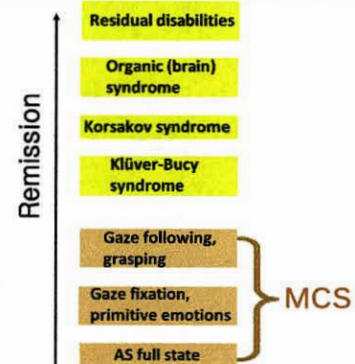
Apallic Syndrome - Remission Stages - 1 Innsbruck Remission Scale

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

Apallic Syndrome - Remission Stages - 2 Innsbruck Remission-Scale

- 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: Psycho-organic syndrome – normal consciousness, aware

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

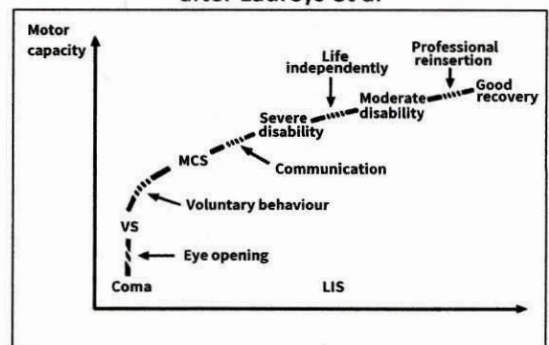


Minimally Conscious States

(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

Restoration of a Coma State after Laureys et al



Acute coma, 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 MRI Stimulation of Brain Functions

- Silent stimulation (no stimulation)
- Sensoric Stimulation
 - Vibro stimulation
 - Acoustic stimulation
 - Visual stimulation
 - Pain stimulation
- Cognitive Stimulation
 - Language stimulation
 - Imaginary stimulation via memory

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).

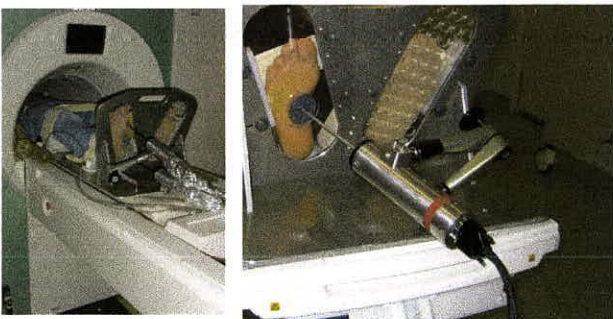
Paradigms in fMRI

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

Hierarchy in fMRI Paradigmas (Kotchoubey, Schwarzbauer)

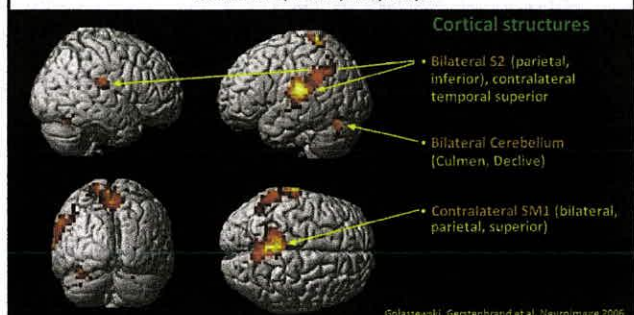
- Silent Paradigma (no stimulation)
- Vibro Stimulation
- Emotional Paradigma (cry/laughing, face)
- Language Paradigma (semantic discrimination)
- Memory Paradigma (Warrington Test)
- Mental Immagary

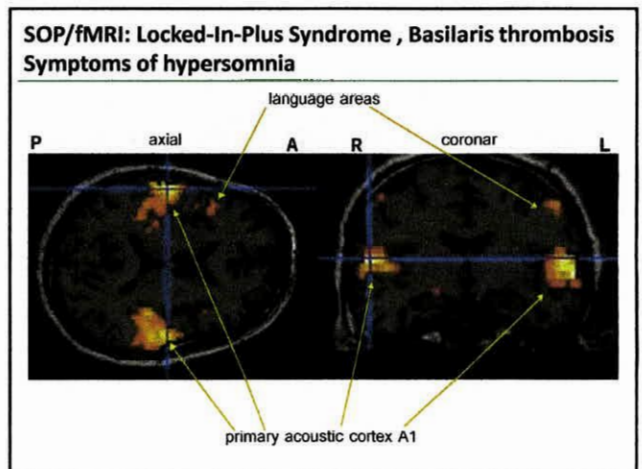
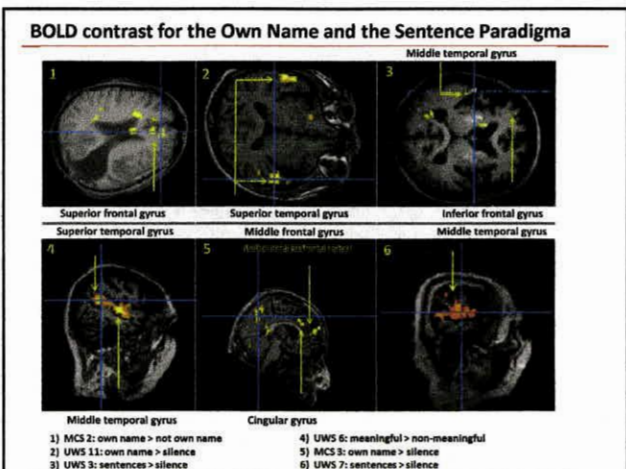
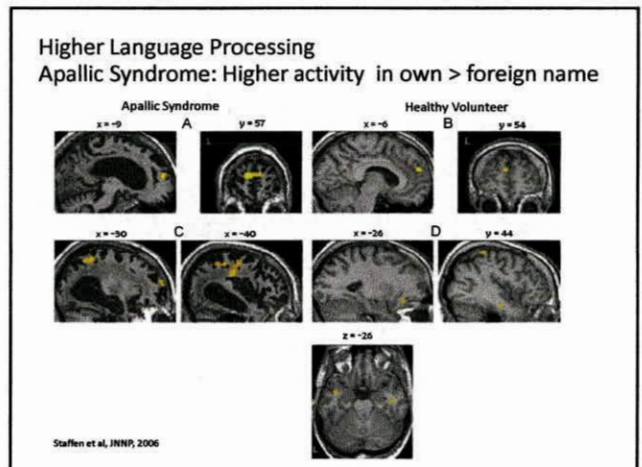
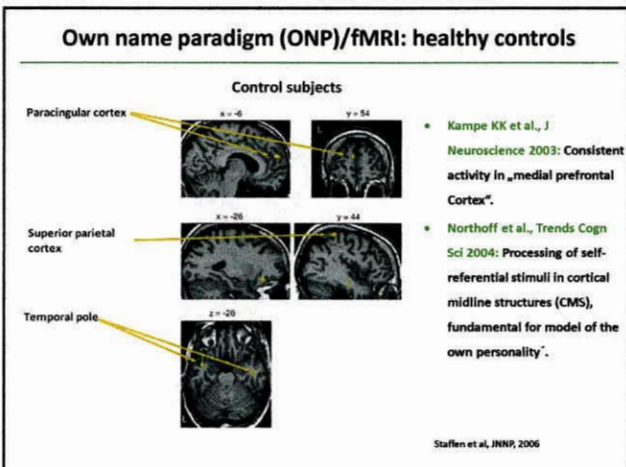
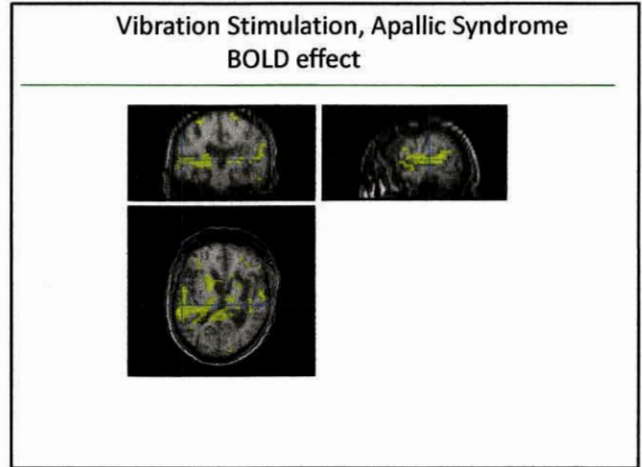
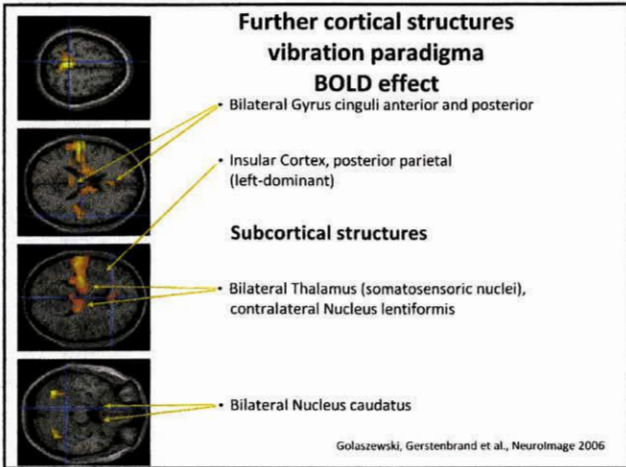
Vibration to the foot sole: amplitude 1 mm,
frequency 50 Hz



Foot Sole Vibration BOLD effect

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





Results I: specific fMRI response in AS/VS

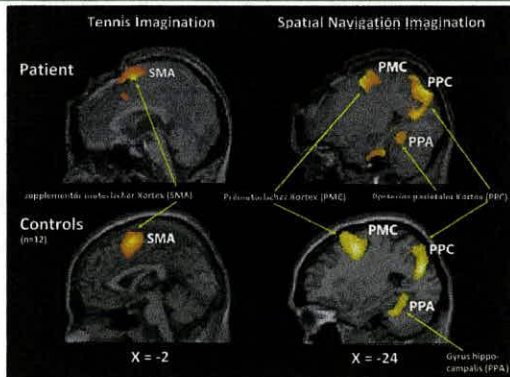
patient number	vibrotactile stimulation	silence vs name	own name vs foreign name	silence vs sentence	semantic oddball
VS#1	no	no	no	no	no
VS#2	no	no	yes	yes	no
VS#3	no	no	no	yes	no
VS#4	yes	yes	yes	yes	yes
VS#5	no	yes	no	yes	no
VS#6	yes	yes	yes	yes	yes
VS#7	no	yes	no	no	no
VS#8	no	yes	yes	yes	yes
VS#9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

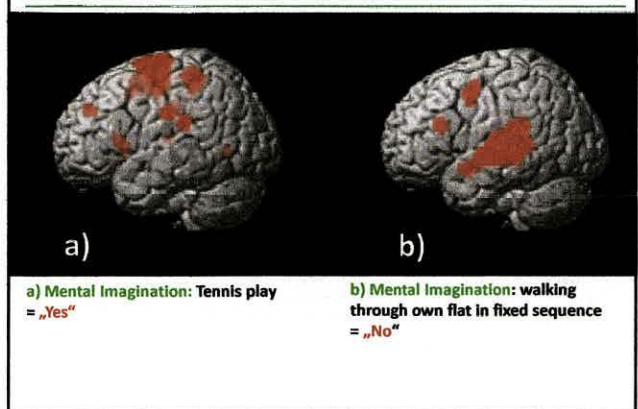
patient number	vibrotactile stimulation	silence vs name	own name vs foreign name	silence vs sentence	semantic oddball
MCS#1	no	yes	yes	yes	no
MCS#2	no	yes	yes	yes	yes
MCS#3	no	yes	no	yes	no
MCS#4	on	yes	no	yes	yes
MCS#5	no	yes	yes	yes	no

⇒ 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



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



Default Mode Network Raichle 2001

Function:

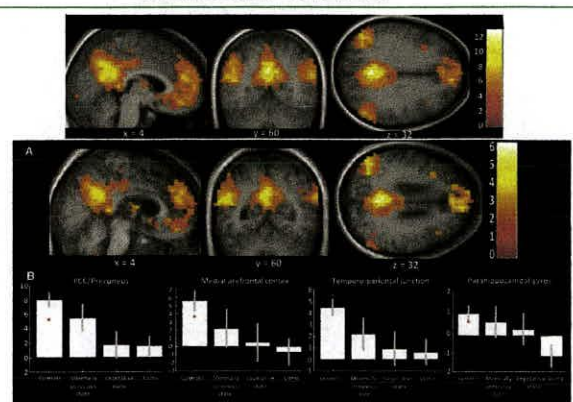
Attention-demanding cognitive task
 Cognitive processes (day dreaming, mind wandering, stimulus, independent source, self related source)

Anatomical basis:

Precuneus bilateral
 Temporo-parietal junctions
 Medial prefrontal cortex

Level of consciousness, paraclinical brain marker

Default Mode Net Work



fMRI examination for detailed diagnosis in patients with 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.

International Danube Symposium Neurological Sciences and Continuing Education

in collaboration with

Lublin Branch of Polish Neurological Society

Department of Neurology
Medical University of Lublin



**IX MIĘDZYNARODOWE
WARSZTATY SZKOLENIOWO-NAUKOWE**
STWARDNIENIE ROZSIANE, PADACZKA, BÓLE I ZAWROTY GŁOWY,
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9TH INTERNATIONAL TEACHING COURSE
MULTIPLE SCLEROSIS, EPILEPSY, HEADACHE AND VERTIGO,
CHILD NEUROLOGY, STEM CELLS THERAPIES

June 19-21, 2013

Kazimierz Dolny, Poland

**PROGRAM
FINAL PROGRAMME**

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PROGRAM NAUKOWY / SCIENTIFIC PROGRAMME

Środa, 19 czerwca 2013 / Wednesday, June 19, 2013

Przyjazd uczestników / Participants arrival

Czwartek, 20 czerwca 2013 / Thursday, June 20, 2013

SALA GŁÓWNA B-D / Main Hall B-D

9.00 – 9.15 **Otwarcie / Opening Ceremony**

Z. Stelmasiak, F. Gerstenbrand, L. Vecsei

9.15 – 10.15 Danube Lectures

Przewodniczący / Chairperson: Z. Stelmasiak

F. Gerstenbrand – *fMRI in Vegetative State / Apallic Syndrome*

L. Vecsei – *Excitotoxin receptors antagonist in the treatment of Parkinson disease*

10.15 – 10.40 *Przerwa / Break*

10.40 – 12.10 **Komórki macierzyste w leczeniu chorób układu nerwowego**

/ Stem Cells in the Treatment of the Nervous System Diseases

Przewodniczący / Chairperson: K. Rejda

K. Domańska-Janik – *Postępy w leczeniu komórkami macierzystymi / Advances in stem cell therapy*

Bogusław Machaliński, Monika Gołąb-Janowska, Bartłomiej Baumert, Przemysław Nowacki - *Efekty troficzne po dokanalowym zastosowaniu komórek macierzystych/progenitorowych u chorych z SLA / Trophic effects after intrathecal administration of stem/progenitor cells in ALS patients*

M. Świderek-Matysiak, K. Selmaj – *Mezenchymalne komórki macierzyste w leczeniu stwardnienia rozsianego / Mesenchymal stem cells in MS therapy*

12.10 – 12.30 *Przerwa na kawę / Coffee-break*

12.30 – 13.30 **Sesja satelitarna Sponsora Biogen Idec Poland**

/ Sponsor's Satellite Session Biogen Idec Poland

13.30 – 14.30 *Przerwa na posiłek / Lunch-break*