The role of functional MRI in diagnosing severe chronic disorders of consciousness

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Objective:

Accurate diagnosis of severe chronic disorders of consciousness (DOC) after TBI is essential for clinical and rehabilitative care and making decisions. Neurobehavioral tests, which rely on the patient's intellectual and motor abilities to communicate, are the most widely used diagnostic tools since their advantage over clinical assessment has been validated. However, with the emergence of modern neuroimaging methods objective physiological markers for assessing the state of consciousness are available in specialized clinics. They are however not fully integrated in clinical routine, because their benefit has yet to be determined.

Participants, Materials/Methods:

15 patients in apallic syndrome (AS) and 5 patients in minimally conscious state (MCS) after TBI and other etiologies were examined with somatosensory, auditory and event related paradigms in fMRI and evoked potentials (EP). The findings were compared to the neurobehavioural diagnosis and were analyzed, if the additional information from fMRI and RP confirmed or questioned the diagnosis.

Results:

3 out of 15 patients in AS showed fMRI activation in event related paradigms, suggesting that patients are in MCS or even better.

Conclusion:

Uncertainty in diagnosis still exists even with well-established diagnostic assessment scales. As long as internationally accepted guidelines for assessing patients with chronic DOC do not exist, every single diagnostic modality available in each clinical setting should be performed to minimize diagnostic errors and to find ways to approach patients in terms of perspective channels. fMRI has the potential to bring diagnostics in chronic DOC forward to the next level.

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Motivation for the study

Patients with severe chronic disorders of consciousness of different origin (TBI, hypoxia, stroke), Apallic Syndrome AS/VS (full state, early remission state I, II - Gerstenbrand 1967), patients in minimally conscious state are misdiagnosed up to 43% (Andrews et al, 1996; Schnakers et al, 2009)

Control procedure:
B-dside testing (neurological examination, Coma Recovery Scale - revised, CRS-R)
EEG (semantic oddball paradigm - SOP, own name paradigm ONP)
fMRI (SOP, ONP)

Patient epidemiology and etiology of brain damage

Patient	Etiology	Age	Gender	DOS delay	CRS-R score R
UWS1	Hypoxia	39 years	male	634 days	4
UWS2	Hypoxia	49 years	male	204 days	3
UWS3	Hypoxia	39 years	female	73 days	4
UWS4	multiple infarctions	29 years	female	[illegible] days	4
UWS5	Hypoxia	78 years	male	37 days	3
UWS6	multiple infarctions	40 years	female	58 days	4
UWS7	Hypoxia	40 years	male	64 days	7
UWS8	SAH, multiple infarctions	38 years	female	91 days	4
UWS9	Hypoxia	55 years	female	120 days	3
UWS10	NT hemorrhage	59 years	male	120 days	3
UWS11	BS infarctions	39 years	male	1456 days	3
UWS12	T hemorrhage	65 years	male	183 days	3
UWS13	Hypoxia & astrocytoma WHO II	30 years	male	46 days	6
UWS14	T hemorrhage	28 years	male	344 days	6
UWS15	Hypoxia	52 years	female	5 years	6
MCS1	T hemorrhage	77 years	male	33 days	9
MCS2	Hypoxia	19 years	male	95 days	9
MCS3	BS infarctions	59 years	male	86 days	15
MCS4	T hemorrhage	53 years	male	181 days	14
MCS5	T hemorrhage	46 years	male	5 years	8

Coma Recovery Scale Revised (CRS-R) in bedside testing (BT)

Coma Recovery Scale Revised Score

#	auditory	visual	motor	oromotor	comm.	arousal	total
VS#1	1	0	0	1	0	1,5	3,5
VS#2	1	0	0	0	0	2	3
VS#3	1	1	1	0,5	0	1	4,5
VS#4	1,5	0	2	1	0	0	4,5
VS#5	1	0	0,5	1	0	0	2,5
VS#6	1	0	2	1	0	0	4
VS#7	2	1	2	1	0	1	7
VS#8	1	0	0	1	0	2	4
VS#9	1	0	0	1	0	1	3
VS#10	0	0	1	1	0	1	3
VS#11	0	0	1	1,5	0	0,5	3
VS#12	0,5	0	0,5	0	0	0	1
VS#13	1	1	1	1	0	2	6
VS#14	1	0	1	1	0	1	4
VS#15	1	0	2	1	0	2	6
MCS#1	1	3	1	1	0	3	9
MCS#2	1	2,5	1	1	1	2	8,5
MCS#3	4	3	3	1	1	3	15
MCS#4	2	3	4	2	1	2	14
MCS#5	1	2,5	2	1	0	1,5	8

Detailed anatomical analysis of the lesion pattern - 1

	Damage	Gray matter	White matter lesions	CSF space	BG lesion	Cerebellum	Thalamus	BS	CC	Other
UWS1	Hypoxia	severe atrophy	periventricular	severe dilatation of all ventricles, subarachnoidal		atrophy				
UWS2	Hypoxia	laminar necrosis, severe atrophy	periventricular to cortical U-Fibers	severe dilatation of all ventricles, subarachnoidal		atrophy cerebellar tonsils, vermis		severe atrophy pons, cerebral, cerebellar peduncles		
UWS3	Hypoxia	laminar necrosis, moderate atrophy, biparietal gliosis	periventricular to cortical U-Fibers	severe dilatation of all ventricles	laminar necrosis caudate nuclei, putamen					
UWS4	multiple infarctions		temporo-occipital	slight dilatation of 3rd, 4th ventricle and peripontine and cerebellomedullar cisterns		cerebellar pedunculi, left hemisphere	paramedian bilateral	complete bilateral infarction of pons including medial lemniscus, pyramidal tract, red nucleus, substantia nigra	degeneration of truncus	
UWS5	Hypoxia	laminar necrosis, slight atrophy	[illegible]	moderate dilatation of all ventricles, subarachnoidal, [illegible] CSF resorption	Caudate nuclei, putamen [illegible]			[illegible]		
UWS6	multiple infarctions		[illegible]	[illegible]		small infarctions cerebellar peduncles, right cerebellar white matter			degeneration of truncus	
UWS7	Hypoxia	bilocular biooccipital gliosis, moderate atrophy	periventricular, esp. bilat. posterior horns to cortical U-Fibers	slight dilatation of all ventricles, subarachnoidal and peripontine cisterns	caudate nuclei, putamen (l>r)					
UWS8	SAH, infarctions		left MCA territory	asymmetric, moderate dilatation of all ventricles	left putamen, pallidum	atrophy	lacunar infarctions	atrophy	degeneration of anterior third	
UWS9	Hypoxia	laminar necrosis, severe atrophy	atrophy	severe dilatation of all ventricles, subarachnoidal	laminar necrosis caudate nuclei, putamen, pallidum		bilateral laminar necrosis	atrophy cerebral peduncles, pons, medulla oblongata	slight degeneration	
UWS10	NT hemorrhage	slight frontal hygroma	periventricular	slight dilatation of all ventricles	hemorrhage residues right BG area					

Detailed anatomical analysis of the lesion pattern - 2

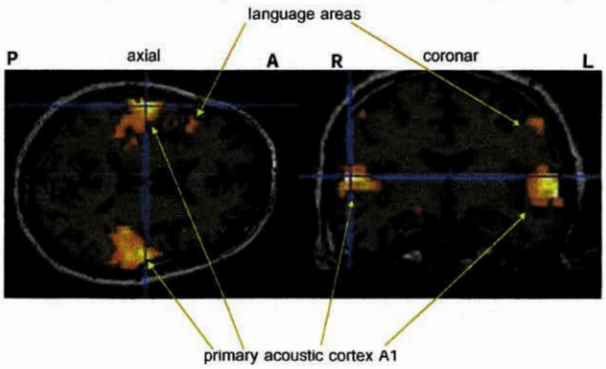
	Damage	Gray matter	White matter lesions	CSF space	BG lesion	Cerebellum	Thalamus	BS	CC	Other
UWS11	BS infarctions	slight atrophy		slight dilatation subarachnoidal, cerebellomedullar, peripontine cisterns		[illegible]	[illegible]	[illegible]		gliosis bilateral temporomesial structures
UWS12	T hemorrhage	severe atrophy, [illegible] gliosis after contusions	periventricular, [illegible]	severe dilatation of all ventricles, subarachnoidal, peripontine cisterns, transventricular CSF [illegible]				atrophy left cerebral peduncle, pyramidal tract left>right	severe degeneration	sickle shaped hygroma 4 mm right hemisphere
UWS13	Hypoxia, st.p. astrocytoma WHO II	laminar necrosis, slight atrophy, defect left temporal	transventricular CSF resorption, left temporal defect, occipital gliosis, microangiopathy	slight dilatation of all ventricles, subarachnoidal				small lacunar infarction	degeneration of truncus	gliosis left temporomesial structures
UWS14	T Hemorrhage		bifrontal, right parietal left temporal axial trauma	moderate dilatation of all ventricles, subarachnoidal	right caudate nucleus, putamen	atrophy pedunculi, hemispheres and vermis	bilateral	moderate atrophy	gliosis of anterior third and gliosis of splenium	
UWS15	Hypoxia	laminar necrosis, biooccipital gliosis after infarction (years earlier)	leukoencephalopathy both hemispheres, old infarction biooccipital	slight dilatation of all ventricles, subarachnoidal	right caudate nucleus			mild atrophy	degeneration	
MCS1	T Hemorrhage		bifrontal perifocal edema, brain passage left frontal to the right ventricle covered with hemosiderin					slight atrophy of whole BS and cerebral peduncles		
MCS2	Hypoxia	right hemisphere	right hemisphere contusions			right cerebellar hemisphere		right cerebellar pedunculi, pons, midbrain		
MCS3	BS infarctions		slight chronic vascular lesions			right SCA territory infarctions, right middle cerebellar peduncle		ventral 2/3 part of pons, mesencephalic periaqueductal lesions		
MCS4	T hemorrhage	brain prolapse left parietal, gliosis left [illegible], bifrontal, bilocular	brain prolapse left parietal, bilateral [illegible] degeneration l>r	ex vacuo dilatation of left posterior horn, severe dilatation of all ventricles l>r, no midline shift	contusions left BG	secondary atrophy		slight atrophy, degeneration of pyramidal tract	degeneration	
MCS5	T hemorrhage	contusions right frontal temporal	right frontoparietotemporal contusions, left frontal contusions	slight dilatation of all csf spaces, transventricular csf resorption	contusions right BG	secondary atrophy	right thalamus	secondary atrophy	degeneration	

Semantic Oddball paradigm (meaningful versus non-meaningful sentences)

e.g. The sun is hot

e.g. With the ears one can speak

SOP/fMRI: 44 y. old Patient, Locked-In-Syndrome plus severe hypersomnie post Basilar thrombosis 3 years ago



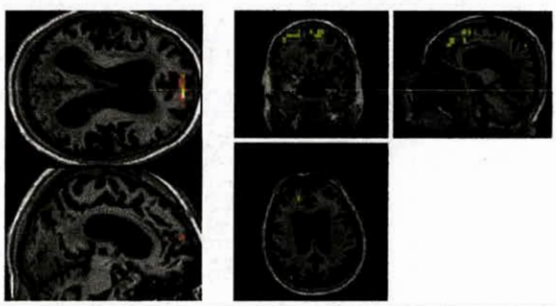
Own name paradigm (own versus other first name)

e.g. Markus, hello Markus ...

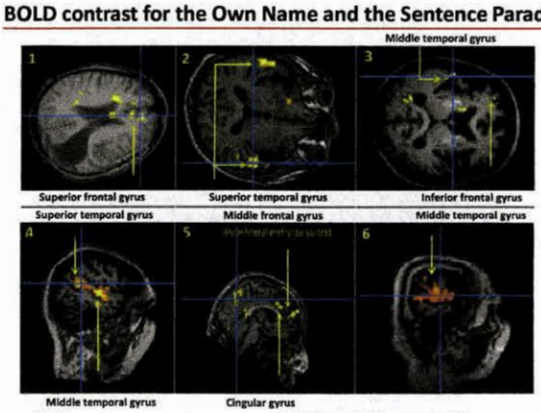
ONP/fMRI: patients

- Patient: 45 y. old
- Basilaris thrombosis 6 mo ago
- No response in bedside testing

- Patient: 50 y. old
- Hypoxic Encephalopathy post cardiac arrest 3 mo ago
- No response in bedside testing



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 3: sentences > silence
4) UWS 6: meaningful > non-meaningful
5) MCS 3: own name > silence
6) UWS 7: sentences > silence

Functional MRI paradigms: specific responses in 7 patients

Patient	Paradigm	GTs prim L	GTs prim R	GTs Wernicke's L	GTs Wernicke's R	GFi L	GFi R	GFm DLPFC L	GFm DLPFC R	GFs L	GFs R
UWS3	S>R	+				+					
	M>NM										
	O>R										
	O>NO										
UWS4	S>R	+	+		+						
	M>NM		+		+						
	O>R										
	O>NO							+	+	+	+	+
UWS6	S>R	+	+	+	+	+					
	M>NM		+		+		+				
	O>R	+	+	+	+						
	O>NO					+					
UWS11	S>R	+	+	+							
	M>NM										
	O>R	+	+								
	O>NO										
MCS1	S>R	+	+	+	+						+
	M>NM										
	O>R										
	O>NO	+	+	+	+						
MCS2	S>R										
	M>NM										
	O>R	+	+			+					
	O>NO					+	+				
MCS3	S>R	+									
	M>NM										
	O>R	+	+	+	+						
	O>NO										

Specific brain areas:

GTs prim: transvers temporal gyrus

GTs: Wernicke's superior temporal gyrus

GFi: Inferior frontal gyrus

GFm DLPFC: middle frontal gyrus, dorsolateral prefrontal cortex

GFs: superior frontal gyrus

GTm: medial temporal gyrus

Contrasts:

S > R: sentences vs rest

M > NM: meaningful vs non meaningful sentences

O > R: own name vs rest

O > NO: own name vs not own name

Funktionelle Neuroanatomie des SP und ONP - 1

fMRI passive listening	Paradigm	GTs prim L	GTs prim R	GTs Wernicke's L	GTs Wernicke's R	Gfi L	Gfi R	GFm DLPFC L	GFm DLPFC R	GFs L	GFs R	Other
UWS2	S>R											
	M>NM					+						
	O>R											
	O>NO											
UWS3	S>R	+				+						
	M>NM											
	O>R											
	O>NO											
UWS4	S>R	+	+		+							
	M>NM		+		+							
	O>R	+	+	+	+							
	O>NO					+		+	+	+	+	left precuneus, left BA 17, left insula
UWS5	S>R	+	+	+	+							
	M>NM											
	O>R	+	+	+	+							
	O>NO											
UWS6	S>R	+	+	+	+	+						right precentral gyrus
	M>NM		+		+		+					
	O>R	+	+	+	+							precuneus, cingular gyrus, BA 17
	O>NO					+						superior parietal lobule, precuneus
UWS7	S>R											
	M>NM											
	O>R	+	+					+	+		+	precuneus, cingular gyrus
	O>NO											
UWS8	S>R		+									
	M>NM											right inferior temporal gyrus
	O>R		+									
	O>NO									+		

Funktionelle Neuroanatomie des SP und ONP - 2

fMRI passive listening	Paradigm	GTs prim L	GTs prim R	GTs Wernicke's L	GTs Wernicke's R	Gfi L	Gfi R	GFm DLPFC L	GFm DLPFC R	GFs L	GFs R	Other
UWS11	S>R	+	+	+								
	M>NM											
	O>R	+	+									
	O>NO											
UWS13	S>R	+										
	M>NM											
	O>R											
	O>NO											
UWS14	S>R	+	+	+	+							
	M>NM											
	O>R	+	+	+	+							BA 17, fusiforme gyrus
	O>NO									+		
MCS1	S>R	+	+	+	+							
	M>NM											
	O>R											left GTm
	O>NO	+	+	+	+							
MCS2	S>R											
	M>NM											
	O>R	+	+			+						
	O>NO					+	+					bilateral medial prefrontal cortex
MCS3	S>R	+										
	M>NM											
	O>R	+	+	+	+							
	O>NO											
MCS4	S>R	+	+	+	+							
	M>NM											
	O>R	+	+	+	+							
	O>NO											
MCS5	S>R	+	+	+	+							
	M>NM											
	O>R	+		+								
	O>NO											

Results I: fMRI/EEG, AS patients in bedside testing

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: fMRI/EEG, MCS patients in bedside testing

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 BT diagnosis did show higher order speech processing and cortical response to a self-referential stimulus in fMRI

Discussion

The best possible diagnoses and prognoses as accurate as possible are essential for the justification of medical, legal and ethical reasons for rehabilitation measures as follows:

- Improvement of the rehabilitation result (identification of programs for a possible rehabilitation)
- To give the patient the opportunity to express their condition (e.g. pain, state of mind)
- Give patients the opportunity to express their will (e.g. last will, end of life decisions, etc.)

Conclusion

Brain trauma fMRI shows specific brain activity in language regions and regions of self-awareness in unresponsive patients diagnosed as Apallic Syndrome (AS/VS). EEG shows a differentiated response to sentences and names. It can be concluded that the diagnosis of AS in brain trauma has to be revised, patients are able for the processing of language, memory and self-referential stimuli at a higher cortical level.

fMRI and EEG showed consistent results.

Knowledge about the perception of language and self-referential stimuli in patients with severe disorders of consciousness is very important for individual planning of neurorehabilitation program and for relatives, caregivers and therapists to improve outcome.

Up to now, we do not have any data for the prognostic value of the detected specific brain activity in fMRI and EEG. Thus, long-term assessments for AS and MCS patients in brain trauma are needed.


Thank you for your attention!

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