Aubinet C, Chatelle C, Gosseries O,
Carrière M, Laureys S, Majerus S.

LIÈGE université
GIGA

Residual implicit versus explicit language recovery in post-comatose patients

25/11/2022

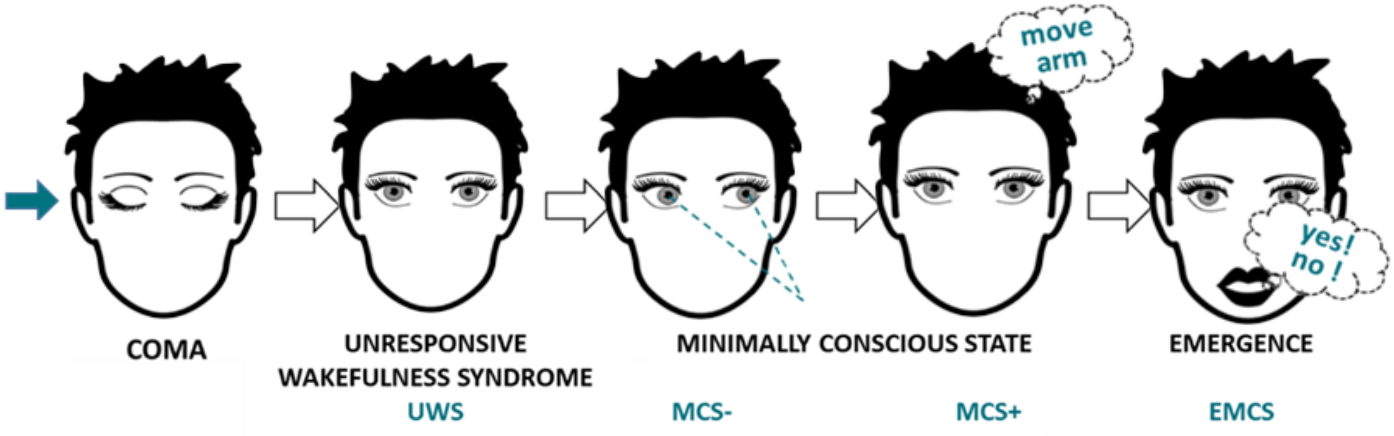
GCPN 2022 meeting
Université de Mons

COMA SCIENCE GROUP

Psychologie & Neuroscience Cognitives
PsyNCog
Psychology & Neuroscience of Cognition

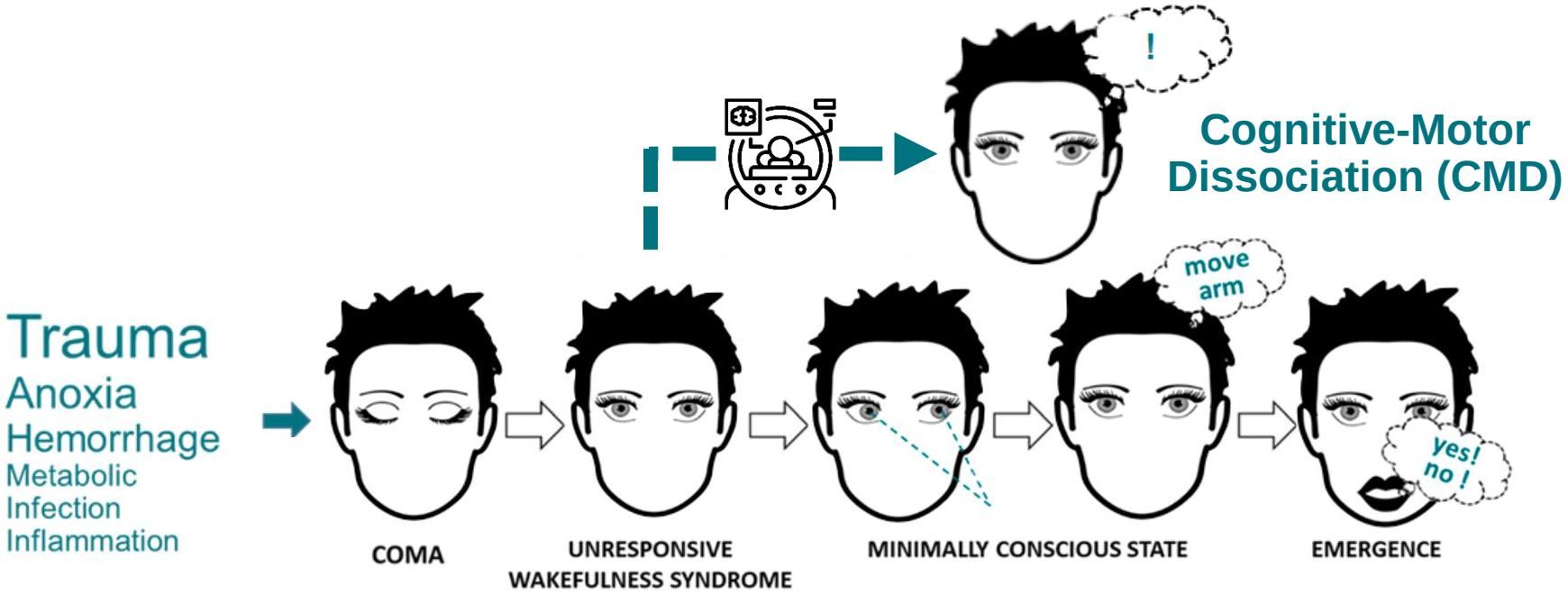
Post-comatose disorders of consciousness (DoC)

Trauma
Anoxia
Hemorrhage
Metabolic
Infection
Inflammation



Thibaut et al., *Ann. Neurol.*, 2021
Sanz et al., *Rev. Neuropsychol.*, 2018
Giacino et al., *Neurology*, 2002

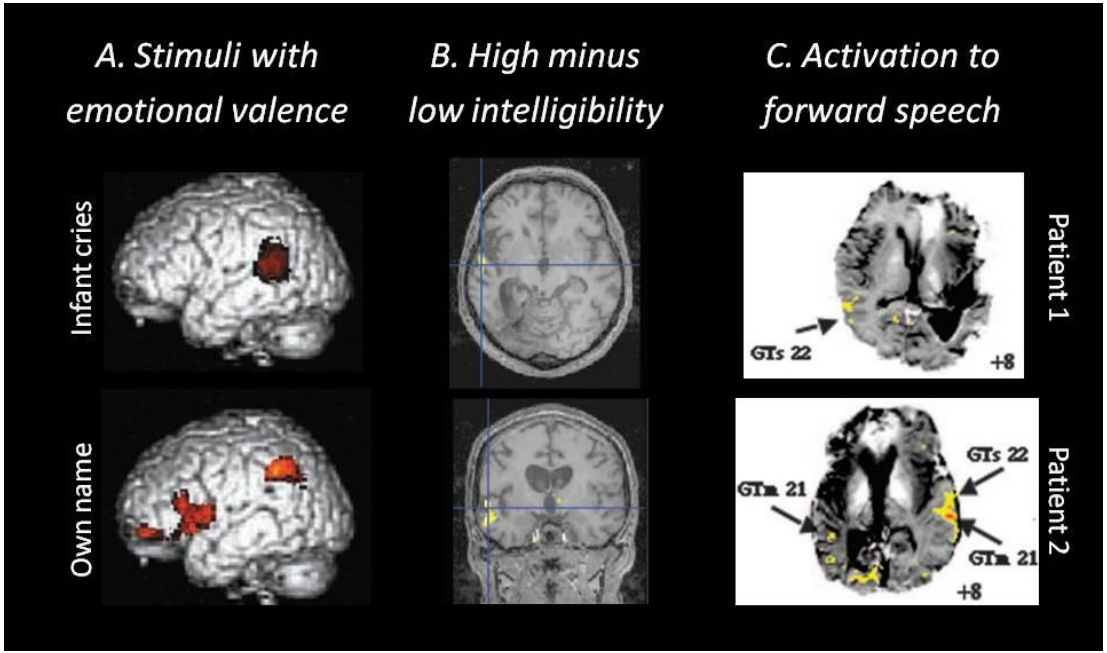
Post-comatose disorders of consciousness (DoC)



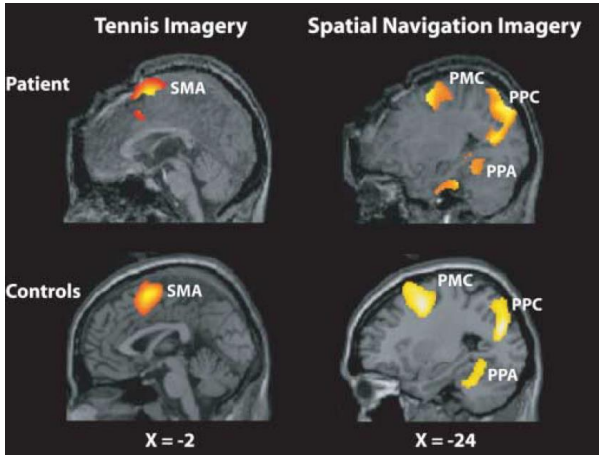
Thibaut et al., *Ann. Neurol.*, 2021
Sanz et al., *Rev. Neuropsychol.*, 2018

Insights of residual language abilities in DoC

Passive tasks



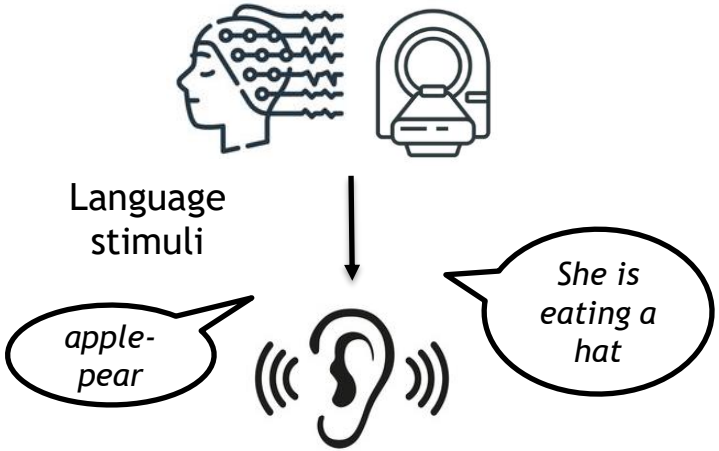
Active tasks



Laureys et al., *Neurology*, 2004
Owen et al., *Neuropsychol. Rehabil.*, 2005
Schiff et al., *Neurology*, 2005

Implicit vs. explicit language abilities in DoC patients

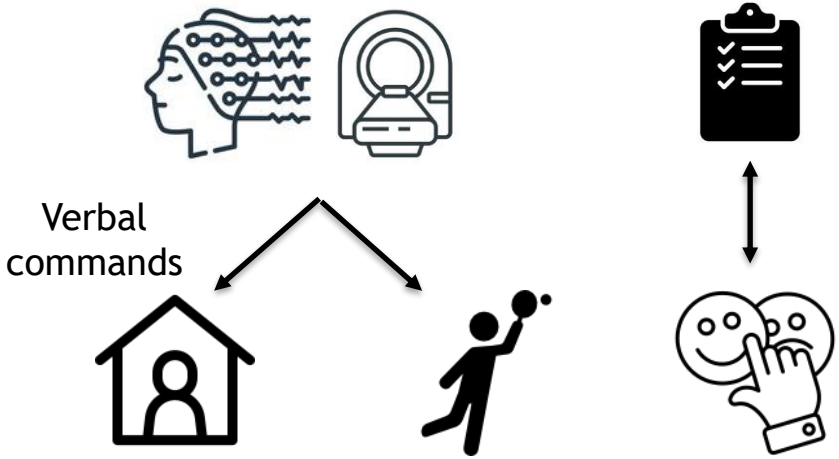
Passive tasks



Implicit language abilities

Reduced controllability
Lack of intention

Active tasks



Explicit language abilities

High controllability
Voluntary

Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Objectives

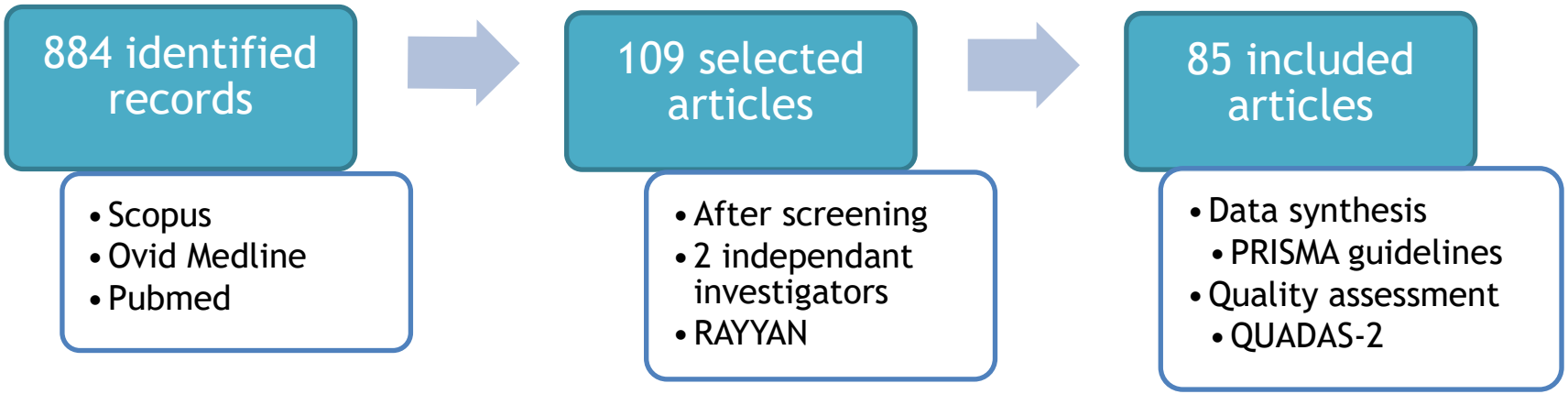
1) Identify the level and quality of language residual abilities as a function of DoC diagnosis
2) Examine *how*, *when* and *where* implicit and explicit language abilities reappear after severe brain injury associated with impaired consciousness

→ Review question:

Which residual language abilities were observed in patients with DoC following severe acquired brain injury using neuroimaging, electrophysiological and behavioral bedside assessment methods?

Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Systematic review process



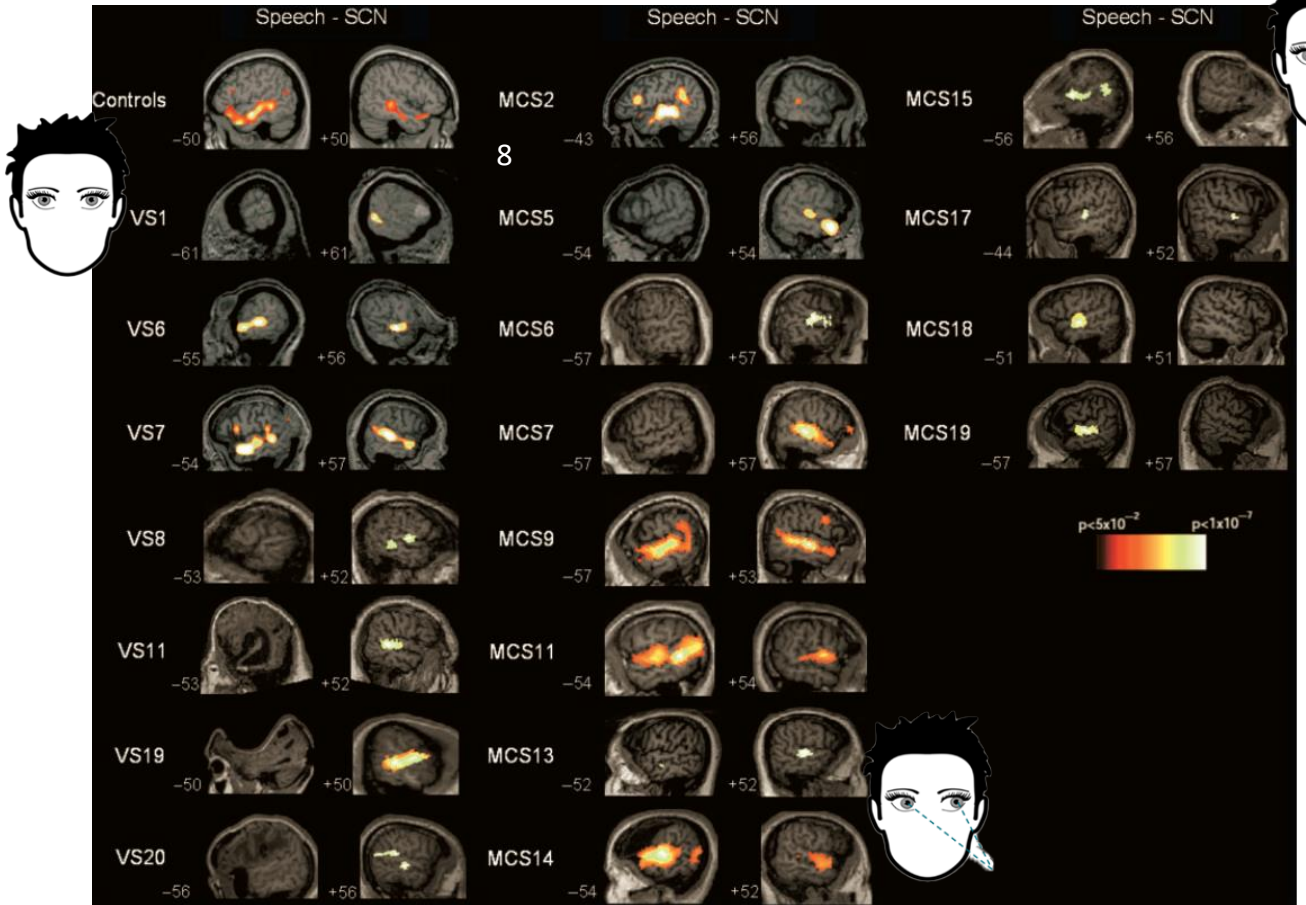
Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Which residual language abilities in the DoC entities?

Implicit:

Low level

→ Speech vs. noise



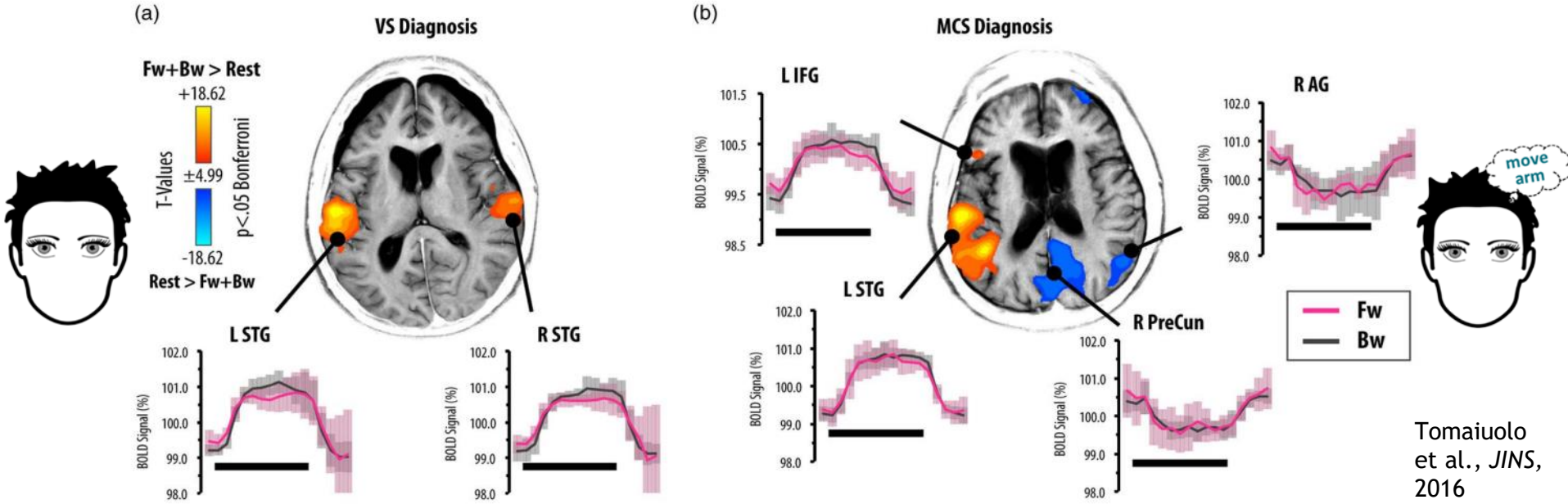
Coleman et al., *Brain*, 2009

Which residual language abilities in the DoC entities?

Implicit:

Low level

→ Forward vs. backward speech



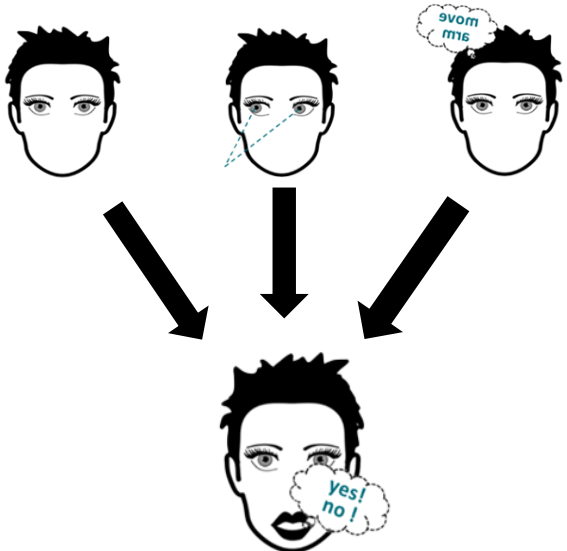
Tomaiuolo et al., *JINS*, 2016

Which residual language abilities in the DoC entities?

Implicit:

High level

→ Semantically congruent vs. incongruent sentences



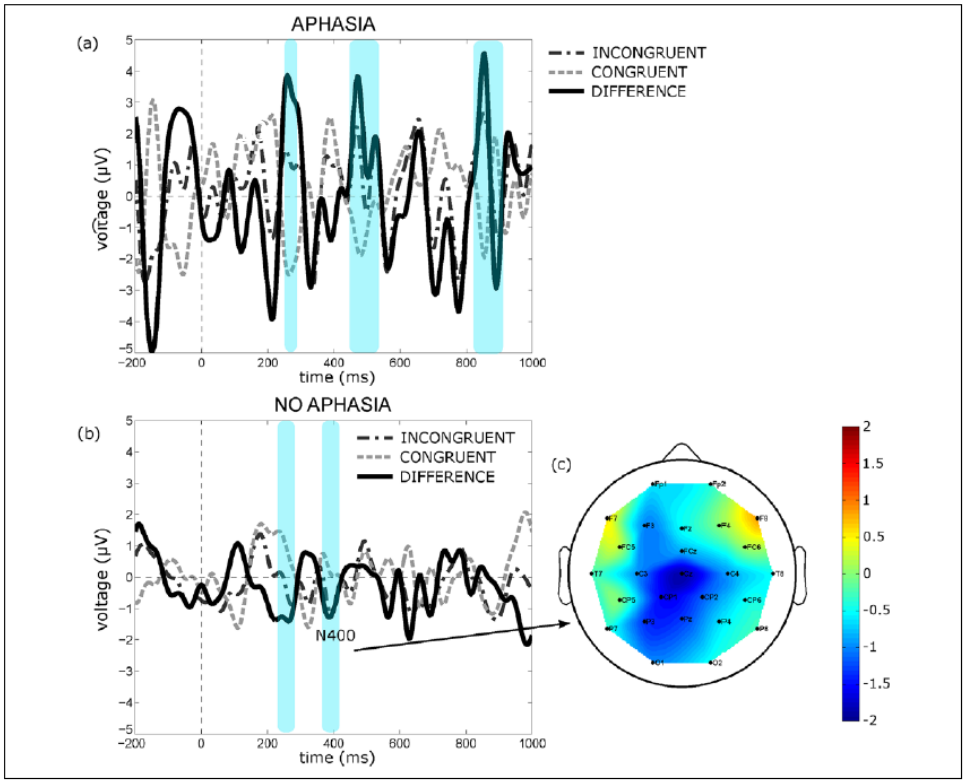


Figure 2. N400 in DoC patients. GA of the incongruent and congruent difference waves computed at Pz in DoC patients grouped according to the presence (panel A, Aphasia; n = 4) or not (panel B, No Aphasia; n = 4) of aphasia. Temporal windows in which we found a significant difference between incongruent and congruent conditions (nonparametric test, $P < .05$) are highlighted in light blue. Topographical map of averaged scalp potential at N400 latency in the No Aphasia patient group (panel C).

Formisano et al., *NNR*, 2019

Which residual language abilities in the DoC entities?

Implicit:

High level (even in some UWS patients)

→ Factually correct vs. incorrect sentences

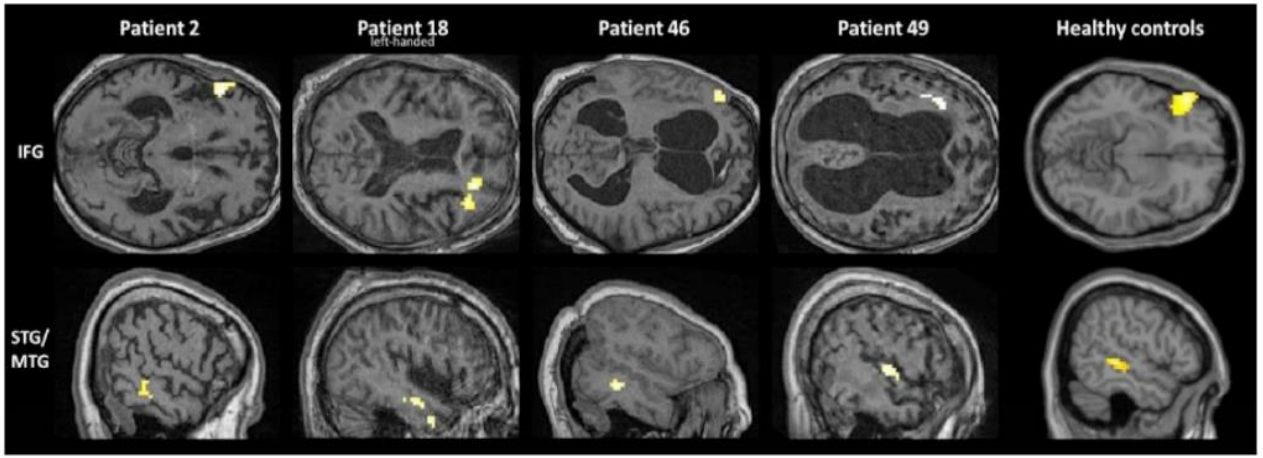
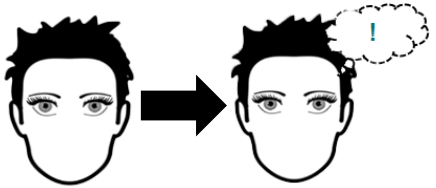


Fig. (1). Brain responses in the inferior frontal gyrus (IFG) and in the superior/middle temporal gyri (STG/MTG). These scans were obtained from a group of 21 age-matched healthy subjects and 4 patients who were regarded as "full responders". The statistical threshold employed was an uncorrected p value of 0.001 for illustrative purposes.

Kotchoubey et al., *Curr. Pharm. Des.*, 2013

Which residual language abilities in the DoC entities?

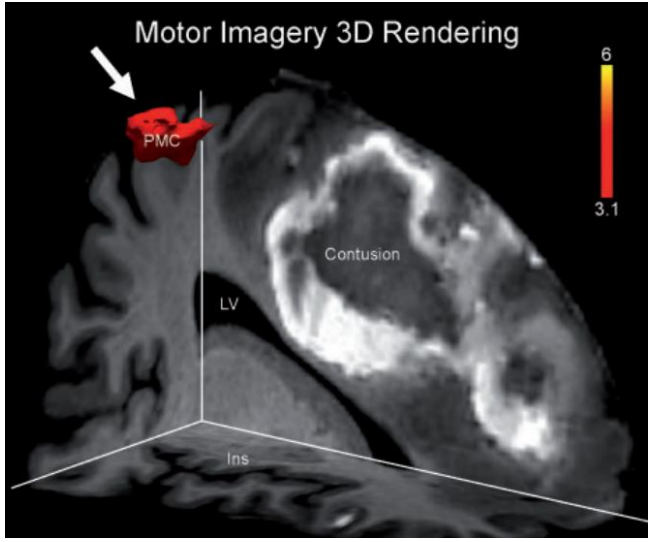


Explicit:

Command-following using brain-computer interfaces

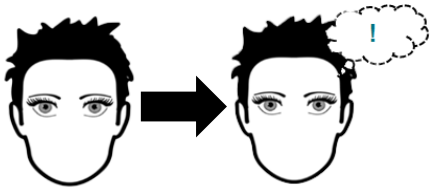
→ Detection of Cognitive-Motor Dissociation (CMD)

E.g.: Right hand squeeze imagery task → brain response in 3/3 UWS patients using fMRI, 0/3 UWS patients using EEG



Edlow et al., *Brain*, 2017

Which residual language abilities in the DoC entities?

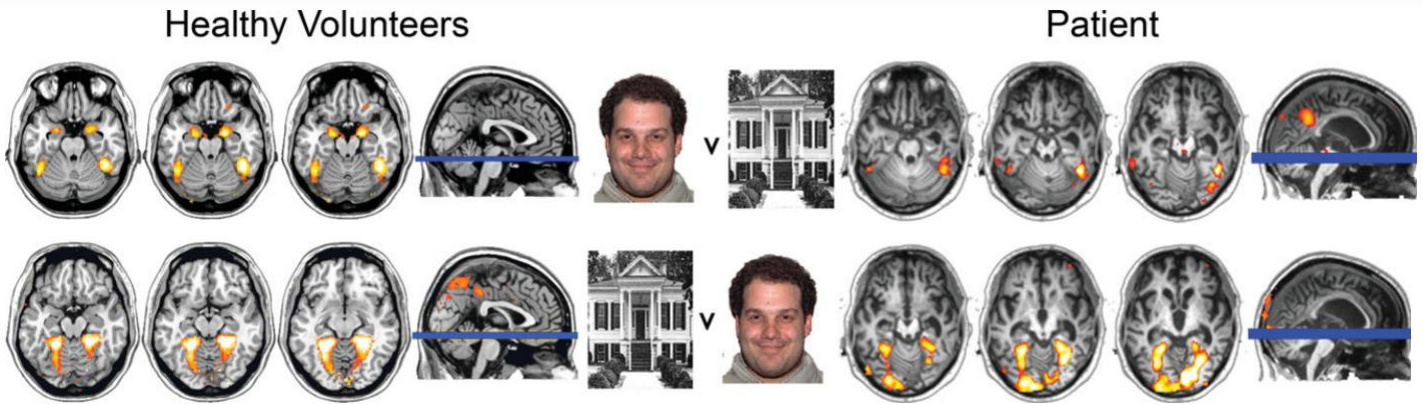


Explicit:

Command-following using brain-computer interfaces

→ Detection of Cognitive-Motor Dissociation (CMD)

E.g.: Visual recognition of faces vs. houses



Monti et al., *Brain*, 2017

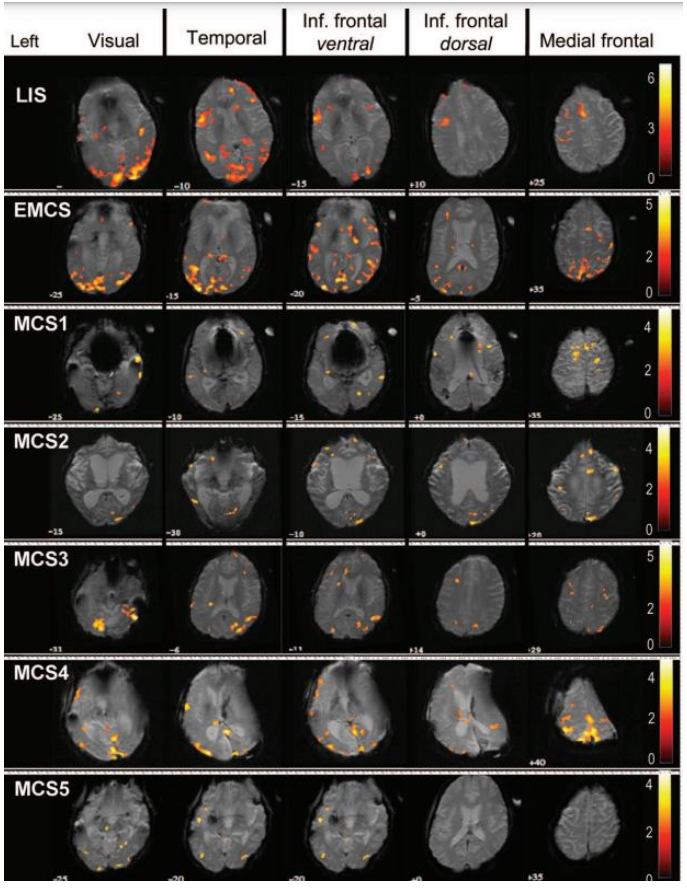
Which residual language abilities in the DoC entities?

Explicit:

Command-following using brain-computer interfaces

→ Detection of Cognitive-Motor Dissociation (CMD)

E.g.: silent picture-naming task



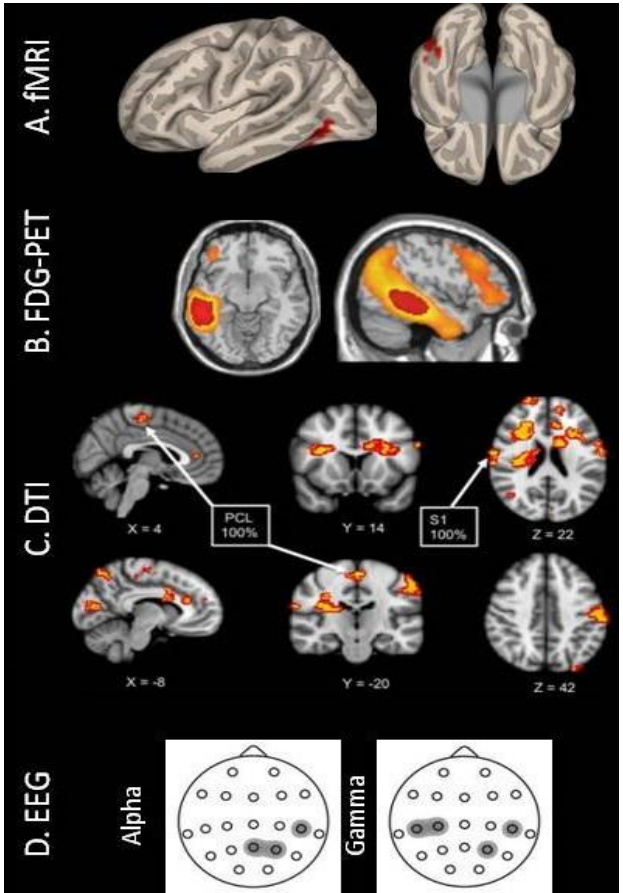
Rodriguez-Moreno et al., *Neurology*, 2010

Which residual language abilities in the DoC entities?

Explicit:

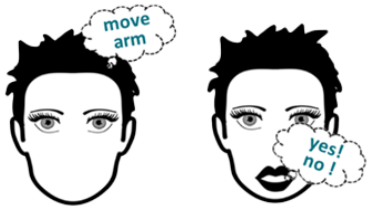
Behavioral command-following

→ MCS- < MCS+



Aubinet et al., *HBM*, 2018
Aubinet et al., *NNR*, 2020
Zheng et al., *HBM*, 2017
Claassen et al., *Annals Neurol.*, 2016

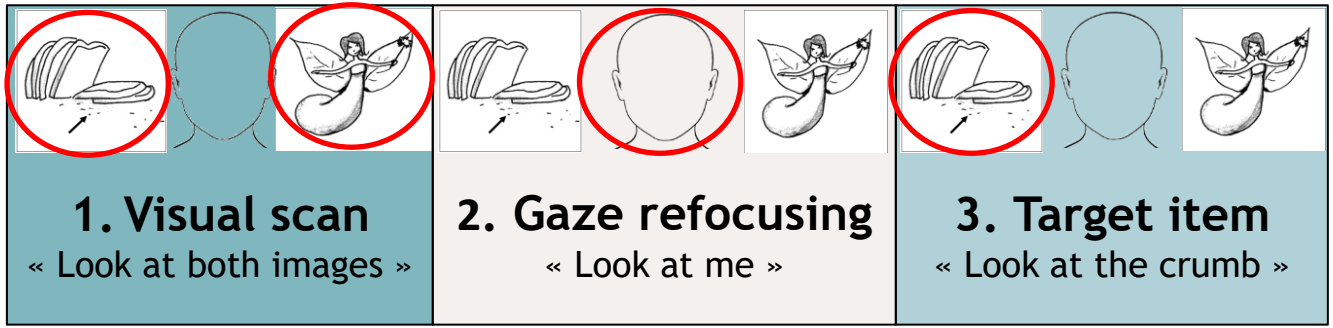
Which residual language abilities in the DoC entities?



Explicit:

Behavioral command-following

→ *Brief Evaluation of Receptive Aphasia (BERA)*

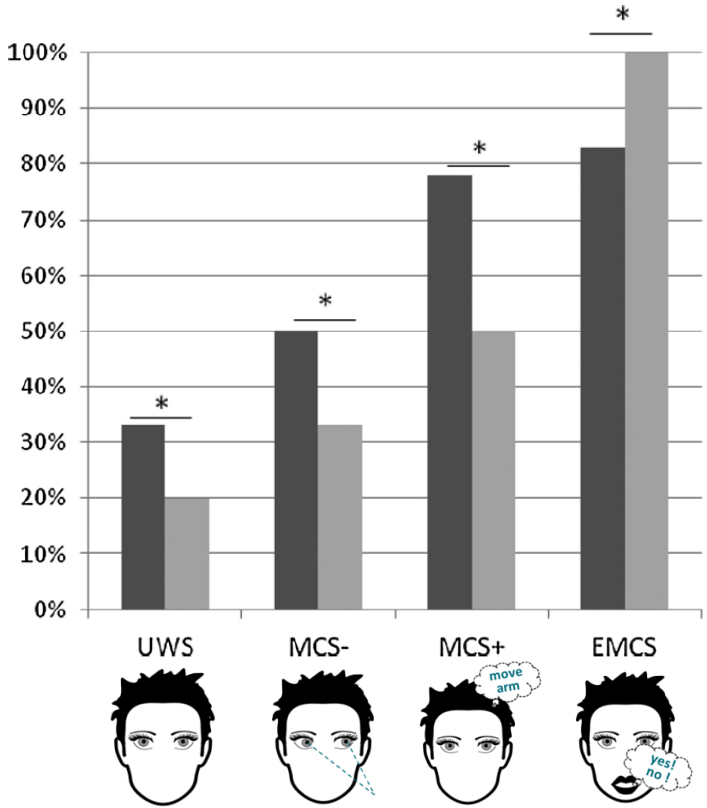


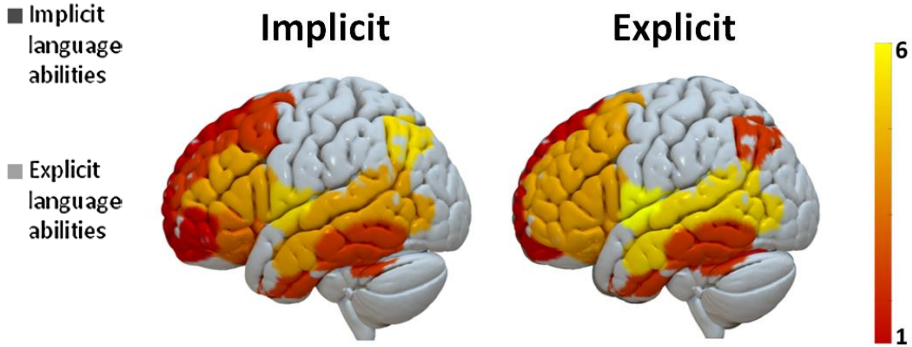
→ ≠ language domains (word phonological/semantic contrasts, sentences contrasting various morphosyntactic elements

Good psychometric properties in aphasic conscious patients, feasible in post-comatose patients

Aubinet et al., *Brain Inj.*, 2021

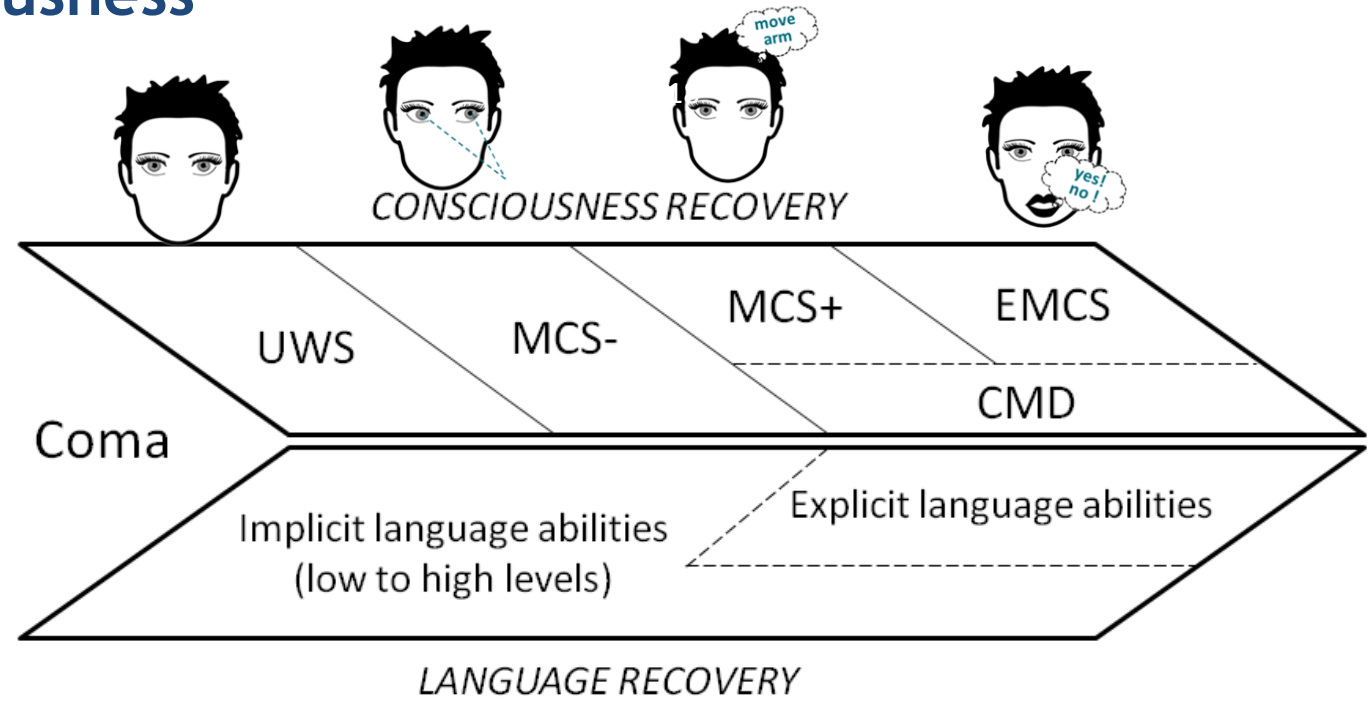
Residual language abilities in the DoC entities





Aubinet et al., *Neurosci. Biobeh. Rev.*, 2022

Recovery trajectory of both language functions and consciousness



Aubinet et al., *Neurosci. Biobeh. Rev.*, 2022

Implicit vs. explicit language assessment

Explicit language assessment

→ Detect CMD and reduce DoC misdiagnosis

Implicit language assessment

- Not considered in the current DoC taxonomy!
- Patients with the lowest level of consciousness can show residual brain activity reflecting complex semantic processing

→ *Is the presence of complex language processing in the absence of "consciousness" possible?*

- First-order theories (activity in sensory areas → Consciousness) vs. higher-order theories (higher-order activity focusing on sensory activity → Consciousness) of consciousness
- Cognitive-motor dissociation?

Melloni et al., *Science*, 2021
Edlow et al., *Brain*, 2017

Conclusion

- Residual language abilities in DoC patients < neuroimaging, electrophysiological and behavioral assessments
- Implicit language abilities in 33% UWS, 50% MCS-, 78% MCS+ and 83% EMCS patients
  - → language recognition, detection of intelligibility, lexical and semantic processing of words and sentences
  - → theoretical and clinical issues
- Explicit language processing in 20% UWS and 33% MCS- (CMD), 50% MCS+ and 100% EMCS patients
- Need for standardized and sensitive language assessment protocols targeting both behavioral and neural responses to language stimuli

Questions?

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Aubinet C, Chatelle C, Gosseries O, Carrière M, Laureys S, Majerus S. Residual implicit and explicit language abilities in patients with disorders of consciousness: A systematic review. *Neurosci Biobehav Rev.* 2022 Jan;132:391-409.

Methods

Preregistration on PROSPERO (CRD42020139361) database

Inclusion criteria :

1) *Patients > 16 years old with DoC following severe acquired brain injury*
2) *Reporting of language-related neuroimaging, electrophysiological or behavioral measurements*
3) *Study targets the detection of residual language abilities (speech comprehension and/or production)*
4) *Empirical studies published in international peer-reviewed journals, in English*
5) *Use of the 2002 consensus-based criteria for diagnosing MCS*

Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Methods

QUADAS 2:

i) "Patient selection": at high risk of bias if the study included a single case or convenience sample of patients;

ii) "Index test" (i.e., the language assessment technique): "unclear" risk of bias if the investigators performing the language-related analyses were not specified to be blinded of patients' diagnosis of DoC + "high" risk of bias as soon as non-blinding was reported;

iii) "Reference standard" (i.e., behavioral diagnostic tool used for diagnosis of DoC): "high" risk of bias when the resulting DoC diagnosis did not comply with established consensus-based diagnostic criteria for UWS and MCS (Giacino et al., 2002; Multi-Society Task Force on P.V.S, 1994) + when the behavioral assessor was not blinded to the results of language assessment;

iv) "Flow and timing" (i.e., patient flow and study timing): "high" risk of bias when the patient flow could have introduced bias (e.g., no appropriate interval between index test and reference standard or patients assessed by different reference standard).

https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/
Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Methodological issues

i) Studies particularly heterogeneous regarding language measures, even within the implicit or explicit language domains;

ii) Large variability of dependent variables (e.g., behavioral detection of command-following, neural responses to speech or visual recognition capacity), techniques (i.e., neuroimaging, electrophysiological or behavioral measures), as well as verbal stimuli (e.g., subject's own name, songs, words, narratives);

iii) QUADAS-2 criteria: lack of blinding procedures and clarity regarding the timing of data acquisition in numerous studies + high risk of bias regarding the population (convenience samples or single cases) → These criteria are however difficult to apply to DoC patients due to their lower frequency and large heterogeneity.

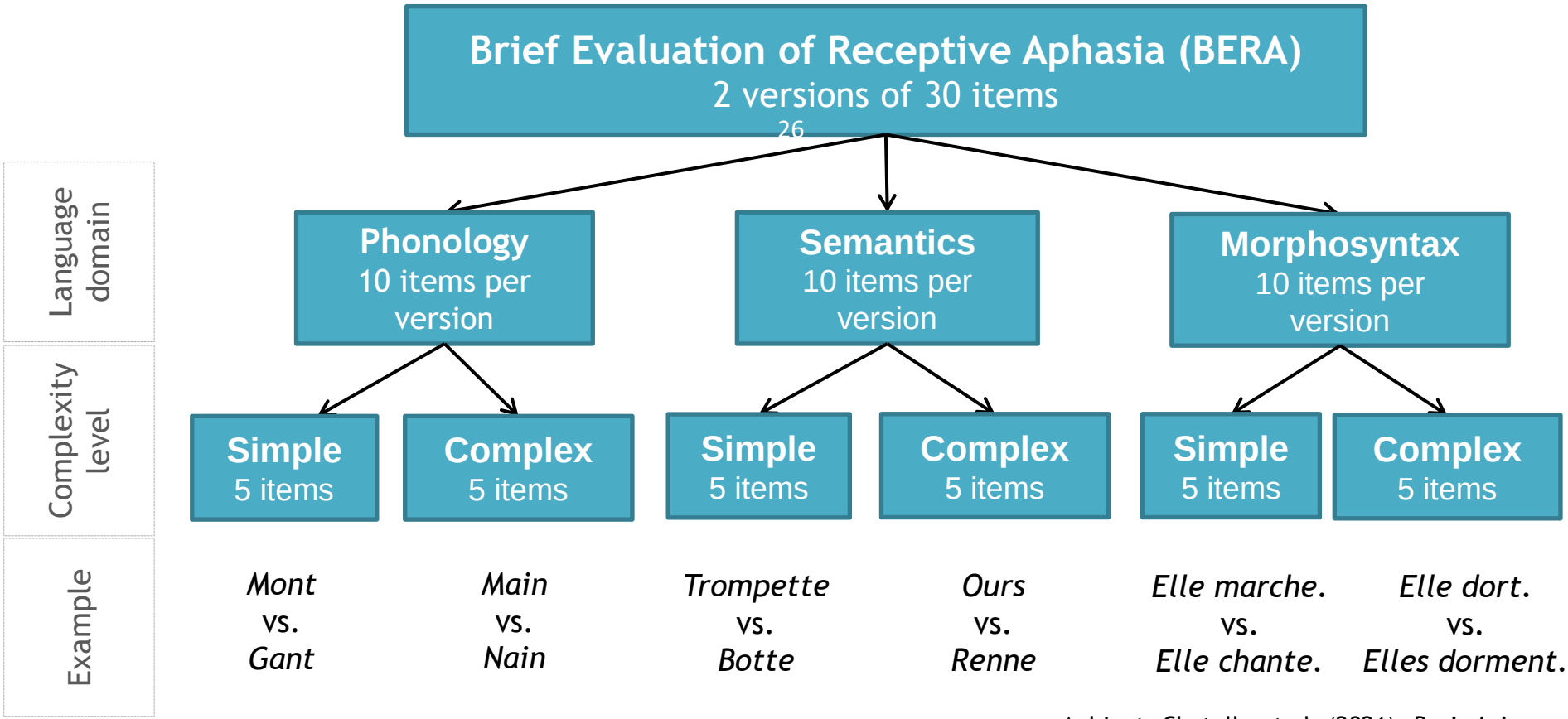
Aubinet et al., *Neurosci. Biobehav. Rev.*, 2022

Perspectives

- Longitudinal studies to assess the timing of recovery of both implicit and explicit language functions in a more systematic manner
- Neuroimaging studies to quantitatively assess the neural correlates of residual implicit language processing
- New taxonomy of DoC based on a multidimensional framework → residual language abilities should be included
- Multimodal assessment protocols to provide to clinicians: behavioral evaluations + neuroimaging and electrophysiology
- Behavioral level: BERA validation + other scales to develop (e.g., non-sighted patients)

Majerus et al., *PBR*, 2009
Bayne et al., *Ann. Neurol.*, 2017

Elaboration of the BERA language-specific tool

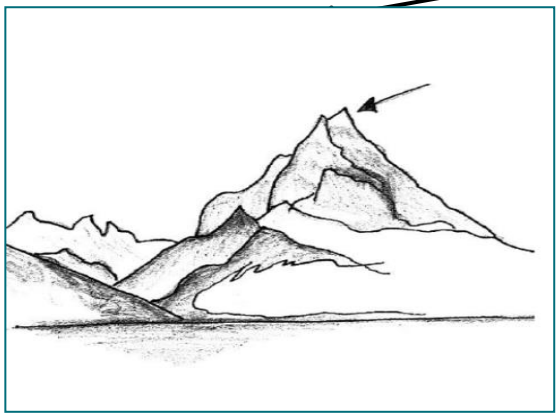


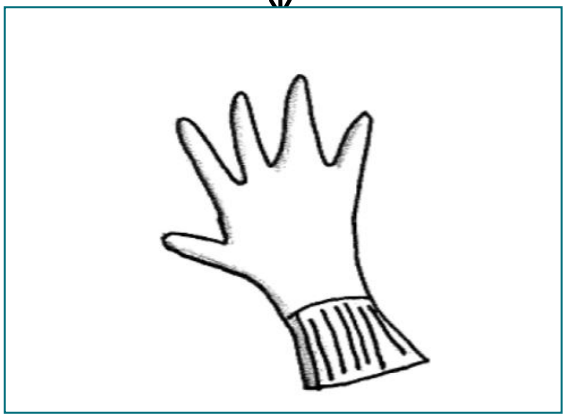
Aubinet, Chatelle et al. (2021), *Brain Injury*

Elaboration of the BERA language-specific tool

Brief Evaluation of Receptive Aphasia (BERA)
2 versions of 30 items
27

Language domain				**Morphosyntax** 10 items per version	
Complexity level				**Simple** 5 items	**Complex** 5 items
Example	*Mont* vs. *Gant*	*Main* vs. *Nain*	*Trompette* vs. *Botte*	*Ours* vs. *Renne*	*Elle marche.* vs. *Elle chante.*	*Elle dort.* vs. *Elles dorment.*





Aubinet, Chatelle et al. (2021), *Brain Injury*

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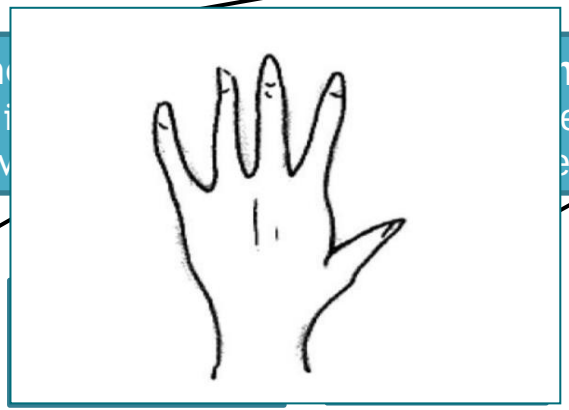
Complexity level	**Simple** 5 items				**Complex** 5 items
Example	*Mont* vs. *Gant*	*Main* vs. *Nain*	*Trompette* vs. *Botte*	*Ours* vs. *Renne*	*Elle marche.* vs. *Elle chante.*	*Elle dort.* vs. *Elles dorment.*



Aubinet, Chatelle et al. (2021), *Brain Injury*

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2 versions of 30 items
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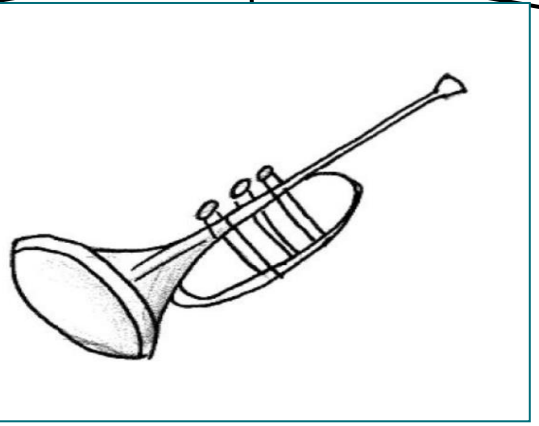
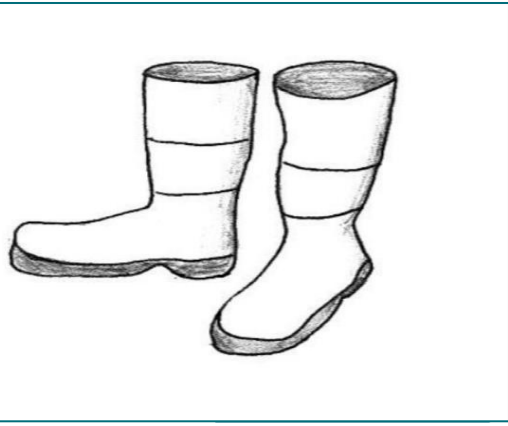
Phonology
10 items per version

Simple
5 items

Complex
5 items





Language domain					
Complexity level					
Example	*Mont* vs. *Gant*	*Main* vs. *Nain*	*Trompette* vs. *Botte*	*Ours* vs. *Renne*	*Elle marche.* vs. *Elle chante.*	*Elle dort.* vs. *Elles dorment.*

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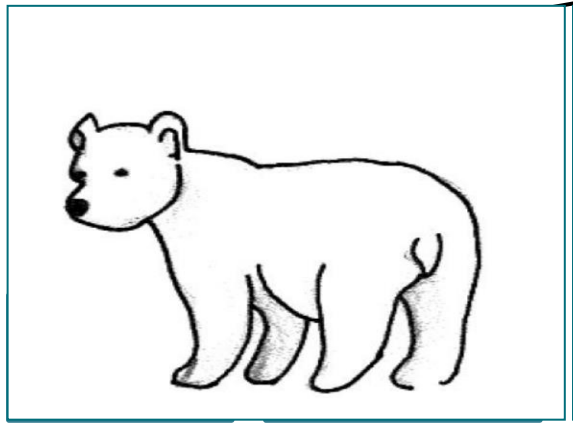

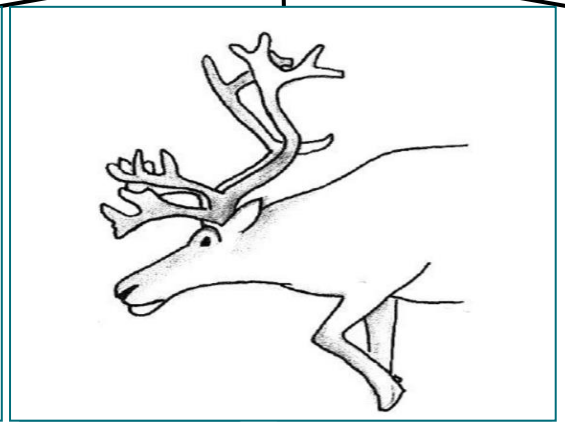

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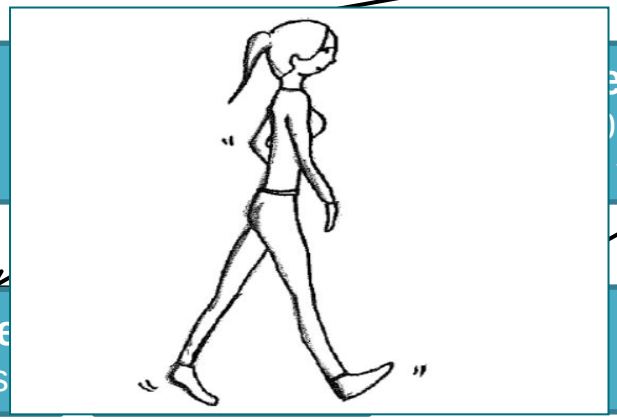
Elaboration of the BERA language-specific tool

Brief Evaluation of Receptive Aphasia (BERA)
2 versions of 30 items

31



Simple
5 items

Complex
5 items

Language domain			**…osyntax** per version		
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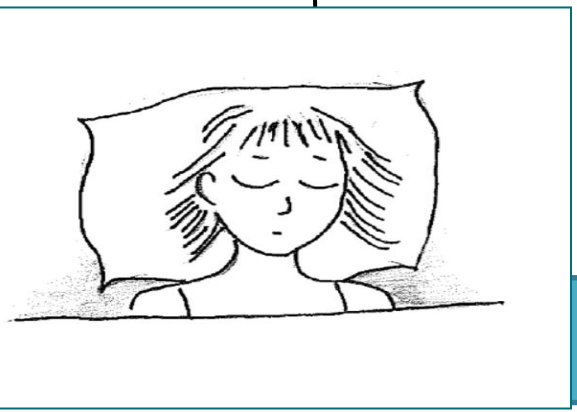
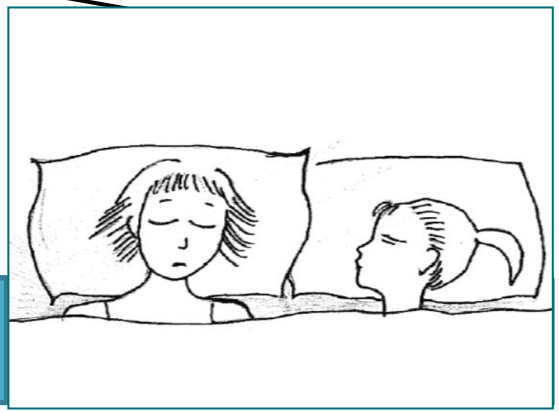
Elaboration of the BERA language-specific tool

Brief Evaluation of Receptive Aphasia (BERA)
2 versions of 30 items
32

Language domain: **Phonology** 10 items per version

Complexity level: **Simple** 5 items | **Complex** 5 items



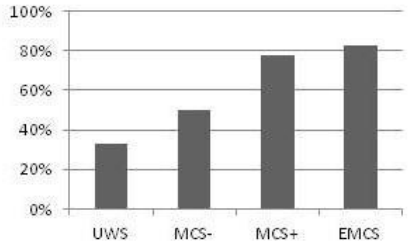
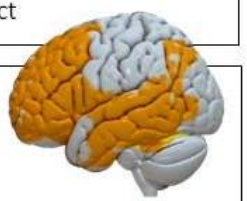
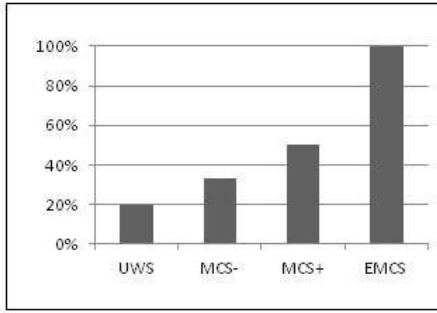


Example:

Mont vs. *Gant*	*Main* vs. *Nain*	*Trompette* vs. *Botte*	*Ours* vs. *Renne*	*Elle marche.* vs. *Elle chante.*	*Elle dort.* vs. *Elles dorment.*

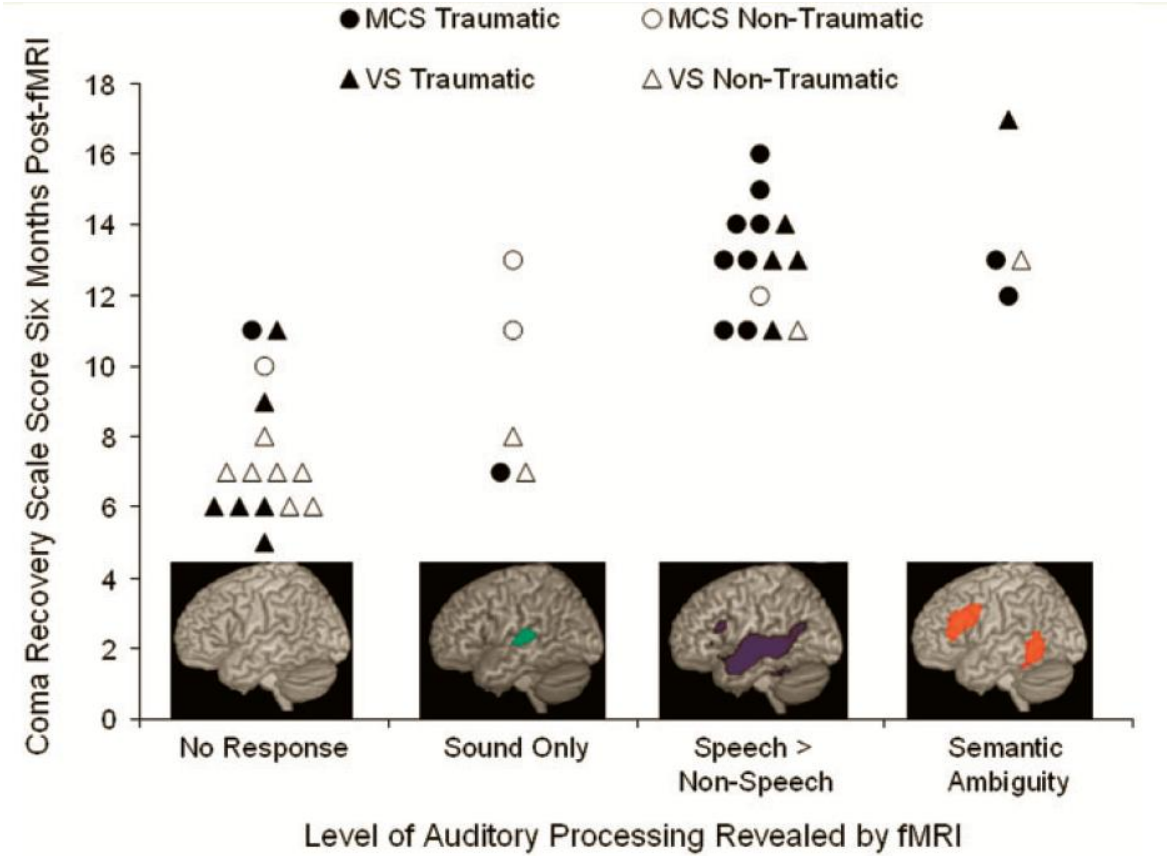
Aubinet, Chatelle et al. (2021), *Brain Injury*

Language assessment based on neuroimaging and electrophysiology

	Tasks and stimuli	Neural correlates	Residual language processing according to consciousness levels
Passive paradigms	Passive listening of language contrasts: - Speech versus noise - Words (semantically related/unrelated, words/pseudowords,...) - Sentences (factually correct/uncorrect sentences, low/high ambiguity,...) - Narratives	L and R temporal lobe, L and R angular gyrus, L and R inferior frontal gyrus, Broca area, L prefrontal gyrus, L superior frontal gyrus, R medial frontal gyrus N400 effect	
Active paradigms	Command-following Verbalization Communication Visual recognition of images	 L temporal lobe, L angular gyrus, L fusiform gyrus, L frontal gyrus	

Which residual language abilities in the DoC entities?

Implicit:



Coleman et al., *Brain*, 2009