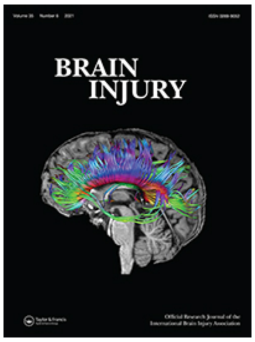

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ARTICLE

The Brief Evaluation of Receptive Aphasia test for the detection of language impairment in patients with severe brain injury

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ABSTRACT

Primary objective: The assessment of language in patients post-comatose patients is limited by their reduced behavioral repertoire. We developed the Brief Evaluation of Receptive Aphasia (BERA) tool for assessing phonological, semantic and morphosyntactic abilities in patients with severe brain injury based on visual fixation responses.

Research design: Prospective cross-sectional study and case reports.

Methods and procedure: The BERA and Language Screening Test were first administered to 52 conscious patients with aphasia on two consecutive days in order to determine the validity and reliability of the BERA. Four post-comatose patients were further examined with the BERA, the Coma Recovery Scale-Revised (CRS-R), positron emission tomography and structural magnetic resonance imaging.

Main outcome and results: The BERA showed satisfactory intra- and inter-rater reliability, as well as internal and concurrent validity in patients with aphasia. The BERA scores indicated selective receptive difficulties for phonological, semantic and particularly morphosyntactic abilities in post-comatose patients. These results were in line with the cortical distribution of brain lesions.

Conclusions: The BERA may complement the widely used CRS-R for assessing and diagnosing patients with disorders of consciousness by providing a systematic and detailed characterization of residual language abilities.

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Coma; aphasia; minimally conscious state; behavioral assessment; language

Introduction

Disorders of consciousness (DoC) are characterized by prolonged impaired awareness following severe brain damage (1). Patients in coma are neither awake nor aware, and they are considered as having an unresponsive wakefulness syndrome (i.e., vegetative state) as soon as eye-opening reappears without any signs of awareness (2,3). When patients recover minimal yet definite behavioral evidence of self or environmental awareness (e.g., visual pursuit or automatic oriented movements), they are in a minimally conscious state (MCS) (4). Multimodal assessments combining behavioral and neuroimaging examinations recently supported a sub-categorization of the MCS based on language-related signs of consciousness (i.e., command-following, intelligible verbalization and/or intentional communication). Patients not displaying language-related behaviors are classified as MCS minus (MCS-), while patients displaying these signs are classified as MCS plus (MCS+) (5–8). Patients finally emerge from the minimally conscious state (EMCS) once they regain the ability to functionally communicate (i.e., using a “yes”/”no” code) and/or use objects (4).

Previous literature highlighted the difficulty of obtaining accurate diagnoses in patients with DoC and the serious consequences of this situation regarding daily management (i.e., pain treatment or stimulation protocols), end-of-life decisions and prognosis (9–11). The presence of language deficits may further lead clinicians to misestimate the level of consciousness of post-comatose patients. Such deficits may indeed interfere with behavioral assessments of consciousness which are highly language-dependent (12,13). For instance, the Coma Recovery Scale-Revised (CRS-R) (14,15), one of the main behavioral instruments for assessing level of consciousness, includes at least 10/23 items requiring understanding of verbal instructions (i.e., receptive language abilities). Schnakers et al. (10) showed that when using this scale in stroke patients with aphasia, level of consciousness was underestimated in half of patients with global aphasia (54%), while based on other criteria (e.g., spontaneous vocalizations, visual pursuit) these patients had to be considered as being fully conscious (some of these patients had never been in a comatose state). Besides, it is also of high clinical importance to determine whether patients with severe brain injury can understand their relatives and caregivers. Still, a specific assessment of language abilities in patients with DoC is a critical issue, particularly due to their limited behavioral responses. If language-related signs of consciousness can be detected using the CRS-R (i.e., MCS+ patients), this scale has not been designed for providing a detailed characterization of language functions in patients with severe brain injury.

Consequently, several authors stressed the urgent need for new behavioral assessment tools in order to provide a better

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characterization of language functions – in particular receptive abilities – in post-comatose patients (e.g. (13,16),). Murphy (17) presented the Cognitive Assessment by Visual Election (CAVE), which is composed of 6 subscales evaluating recognition of objects, pictures, numbers, letters, written words and colors in patients with DoC, and consequently involves language comprehension. The CAVE showed high levels of inter-rater and test-retest reliability, and is particularly adapted for MCS or EMCS patients as it only requires looking at a target picture presented next to a distractor. This recent tool does however not evaluate specific language domains such as phonology, semantics or morphosyntax (17,18). It is crucial that these different language domains are targeted in a specific manner given that they frequently dissociate in aphasic patients requiring specific assessment and rehabilitation methods (19).

A targeted determination of the language domain(s) that is (are) impaired is thus crucial in post-comatose patients, in order to be able to optimize a patient's understanding of verbal commands and questions and also to enable implementation of targeted language rehabilitation. We therefore developed the "*Brief Evaluation of Receptive Aphasia*" (BERA), which examines in a specific manner phonological, semantic and morphosyntactic receptive abilities. In this pilot study, we first validated the BERA within a population of aphasic conscious (AC) patients in order to demonstrate its sensitivity to language impairment, and to determine its psychometric qualities (intra- and inter-rater reliability). We then examined the utility of BERA tool for assessing language profiles in four post-comatose patients with severe brain injury. Due to their extended brain lesions, an impact of associated cognitive deficits on BERA scores was expected, but we argued that this new tool might still help refine their receptive language profile. We hypothesized that patients in MCS+ and EMCS (i.e., patients with language-related signs of consciousness) should show higher scores than MCS- patients. Most importantly, we examined whether specific domains of language (phonology versus semantics versus morphosyntax) are more severely affected than others in these patients, and we compared language profiles with structural and functional neuroimaging data obtained in these patients.

Material and methods

Participants

In this study, we first recruited a convenience sample of 10 healthy control subjects (i.e., age range 21–79 years old, 4 women, 5 low [scored 10] and 5 high [scored 2] socio-economic statuses according to the European Socio-Economic Classification (19)).

Fifty-two AC patients were then recruited in several rehabilitation centers with the following inclusion criteria: 1) French-speaking adults (older than 18 years old); 2) brain injury resulting from a stroke, traumatic brain injury (TBI), anoxia, cortical edema or hypoglycemia without any documented period of coma; 3) language impairment as assessed by an experienced speech and language therapist (based on both clinical observation and specific testing); and 4) time since onset exceeding three weeks (i.e., avoiding the presence of confusion). Exclusion criteria were: 1) blindness or any other peripheral visual deficit without correction; 2) deafness or any other auditory deficit without correction; 3) impairment of vigilance or confusion according to the medical staff.

Third, we recruited four MCS or EMCS patients who were hospitalized in the University Hospital of Liege during one week for diagnostic and prognostic purposes, according to the following criteria: 1) French-speaking adults (older than 18 years); 2) a diagnosis of chronic (> 1 month) MCS or EMCS as based on repeated CRS-R assessments (20); 3) severe brain injury and period of coma (all TBI); 4) preserved visual fixation and pursuit as assessed with the CRS-R and preserved visual evoked potentials (as confirmed by an experienced ophthalmologist). The exclusion criteria were similar to those for AC patients but we additionally excluded patients medically unstable (e.g., respiratory congestion).

Table 1 reports individual demographic data of all participants. In order to validate the BERA, it was necessary to include a patient population with deficits pertaining to the different domains of language processing (phonological, semantic and morphosyntactic levels) assessed by the BERA. Therefore we favored the inclusion of a heterogeneous sample of patients with aphasia, so that there was a high likelihood that deficits in all language domains could be examined and identified across the aphasic patient sample. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege and written informed consent, including for publication of data, was obtained from the patients or their legal representatives as well as from the healthy control subjects.

Material.

Brief Evaluation of Receptive Aphasia (BERA)

The BERA involves the visual selection of one image out of two possible choices. This mode of presentation and response was chosen since reproducible visual fixation and pursuit have been shown to be the most robust behaviors in a group of 282 MCS patients (21). The two images for each item were presented at about 40 centimeters of the patient's face with a between-picture horizontal distance of 30 centimeters. In case of suspected spatial neglect (as reported by the medical staff), the images were presented in a vertical arrangement. The examiner first asked the patient to look at both images, and then pronounced a word or a sentence and encouraged the patient to fixate only the target-image. The material of the BERA was developed for use in French-speaking patients.

[INSERT Figure 1 AROUND HERE]

A total of 120 items was divided into four parallel versions of the BERA, each containing 30 items assessing phonological (i.e., 10 items), semantic (i.e., 10 items) and morphosyntactic (i.e., 10 items) language domains (Figure 1). For each language domain, half of the items (i.e., 5 items) were considered as "simple" since the distractor is unrelated to the target (e.g., *mont* [mount] versus *gant* [glove], *trompette* [trumpet] versus *botte* [boot] or *Elle marche* [She walks] versus *Elle chante* [She sings]), while the other half of the items was labeled as "complex" as they shared phonemes, semantic category or

Table 1. Individual demographical data and BERA scores .

Patient	Age	Gender	Etiology	Days post-onset	Brain lesion	Aphasia type	BERA phonology	BERA semantics	BERA morphosyntax	BERA total score	Duration (minutes)
AC1	45	Male	Stroke	26	Left perisylvian area*	Non-fluent	10	10	10	30	6
AC2	61	Female	Cortical edema	77	Left parieto-temporal cortex*	Fluent	10	10	10	30	6
AC3	48	Male	Stroke	37	Left perisylvian area*	Fluent	6	7	8	21	5
AC4	46	Female	Stroke	126	Extended bilateral cortex*	Global	9	8	8	25	10
AC5	64	Female	Stroke	44	Left fronto-temporal cortex	Non-fluent	8	7	6	21	12
AC6	68	Male	Stroke	41	Left fronto-parietal cortex	Non-fluent	10	10	8	28	5
AC7	17	Female	Anoxia	137	Bilateral perivylsvian areas*	Non-fluent	7	10	10	27	10
AC8	54	Female	Stroke	128	Left fronto-temporo-parietal cortex*	Global	8	10	8	26	8
AC9	78	Female	Stroke	22	Left perisylvian area*	Non-fluent	10	10	9	29	4
AC10	85	Female	Stroke	52	Left capsular area*	Global	9	9	8	26	13
AC11	48	Male	TBI	179	Right subdural area	Fluent	9	9	5	23	8
AC12	63	Male	Stroke	81	Left parietal cortex*	Conduction	10	10	10	30	5
AC13	75	Male	Stroke	78	Left perisylvian area*	Non-fluent	5	6	6	17	6
AC14	68	Male	Stroke	44	Left perisylvian area*	Conduction	10	8	9	27	6
AC15	30	Female	Stroke	163	Left fronto-temporo-insular cortex	Mixed	10	10	10	30	4
AC16	79	Female	TBI	61	Right temporo-parieto-occipital cortex	Non-fluent	7	9	9	25	6
AC17	66	Male	TBI	123	Left temporal cortex	Mixed	9	10	7	26	10
AC18	78	Male	Stroke	69	Left perisylvian area*	Mixed	7	8	7	22	7
AC19	80	Female	Stroke	37	Left temporal cortex	Fluent	7	8	8	23	5
AC20	65	Male	Stroke	80	Left perisylvian area*	Global	8	10	6	24	7
AC21	83	Male	Stroke	58	Left hemisphere	Non-fluent	9	9	10	28	10
AC22	68	Female	Stroke	125	Left perisylvian area*	Fluent	7	6	2	15	9
AC23	67	Male	Stroke	101	Left perisylvian area*	Non-fluent	8	8	9	25	6
AC24	52	Male	Stroke	547	Left perisylvian area*	Mixed	9	10	9	28	3
AC25	68	Female	Stroke	91	Left hemisphere	Mixed	10	10	9	29	6
AC26	29	Male	Stroke	543	Left perisylvian area*	Non-fluent	9	10	9	28	4
AC27	57	Male	Stroke	93	Left capsulo-lenticular cortex	Fluent	7	9	10	26	10
AC28	87	Female	Stroke	49	Left fronto-parietal cortex	Non-fluent	9	10	9	28	5
AC29	50	Female	Stroke	152	Left perisylvian area*	Non-fluent	9	8	8	25	5
AC30	56	Male	Stroke	85	Left hemisphere	Non-fluent	9	10	9	28	6
AC31	56	Male	Stroke	105	Left perisylvian area*	Fluent	10	10	10	30	3
AC32	80	Female	Stroke	130	Left perisylvian area*	Non-fluent	7	8	7	22	9
AC33	64	Female	Stroke	86	Left occipito-temporal cortex*	Fluent	10	9	9	28	5
AC34	54	Female	Hypoglycemia/ ethilysm	64	Left hemisphere	Transcortical motor	6	8	5	19	4
AC35	89	Female	Stroke	120	Left perisylvian area*	Non-fluent	8	6	6	20	9
AC36	67	Male	Stroke	50	Bilateral perivylsvian areas*	Non-fluent	10	10	9	29	4
AC37	82	Female	Stroke	59	Left perisylvian area*	Non-fluent	9	10	9	28	5
AC38	45	Female	Stroke	350	Right perisylvian area	Non-fluent	8	10	7	25	3
AC39	44	Male	Stroke	174	Right perisylvian area	Non-fluent	10	10	10	30	4
AC40	69	Male	Stroke	57	Left perisylvian area*	Non-fluent	9	9	10	28	4
AC41	59	Male	TBI	120	Left temporal cortex	Fluent	10	10	7	27	5
AC42	78	Male	Stroke	45	Left parieto-occipital cortex*	Non-fluent	8	10	9	27	5
AC43	87	Male	Stroke	58	Left hemisphere	Non-fluent	10	10	10	30	5
AC44	42	Male	TBI	207	Left parieto-temporal cortex*	Non-fluent	10	10	10	30	4

(*Continued*)

Table 1. (Continued).

AC45	62	Female	TBI	90	Left temporal cortex	Non-fluent	10	10	9	29	4
AC46	67	Male	Stroke	49	Left hemisphere	Mixed	6	10	8	24	7
AC47	72	Female	Stroke	43	Left perisylvian area*	Non-fluent	7	8	10	25	7
AC48	84	Female	Stroke	37	Left perisylvian area*	Global	8	9	9	26	3
AC49	79	Male	Stroke	14	Left parietal cortex*	Non-fluent	10	9	10	29	4
AC50	84	Female	Stroke	58	Left perisylvian area*	Non-fluent	7	8	9	24	9
AC51	77	Female	Stroke	19	Left temporo-occipital cortex*	Transcortical motor	10	9	9	28	5
AC52	84	Female	Stroke	34	Left capsulo-lenticular cortex	Conduction	10	10	10	30	5
Mean							8.615	9.077	8.423	26.115	6.154
Standard-deviation							1.189	0.958	1.287	2.76	1.938
Minimum							5	6	2	14	3
Maximum							10	10	10	30	13
DoC1	40	Male	TBI	750			8	8	**5**	21	17
DoC2	30	Male	TBI	2340			7	8	7	22	5
DoC3	63	Male	TBI	150			8	**6**	**2**	**16**	20
DoC4	34	Male	TBI	150			7	**6**	**3**	**16**	15

*Posterior lesions of the left hemisphere. The BERA scores of patients with disorders of consciousness (DoC) which are presented in bold type are significantly lower than the group of aphasic conscious (AC) patients. MCS: minimally conscious state; EMCS: emergence from the minimally conscious state.

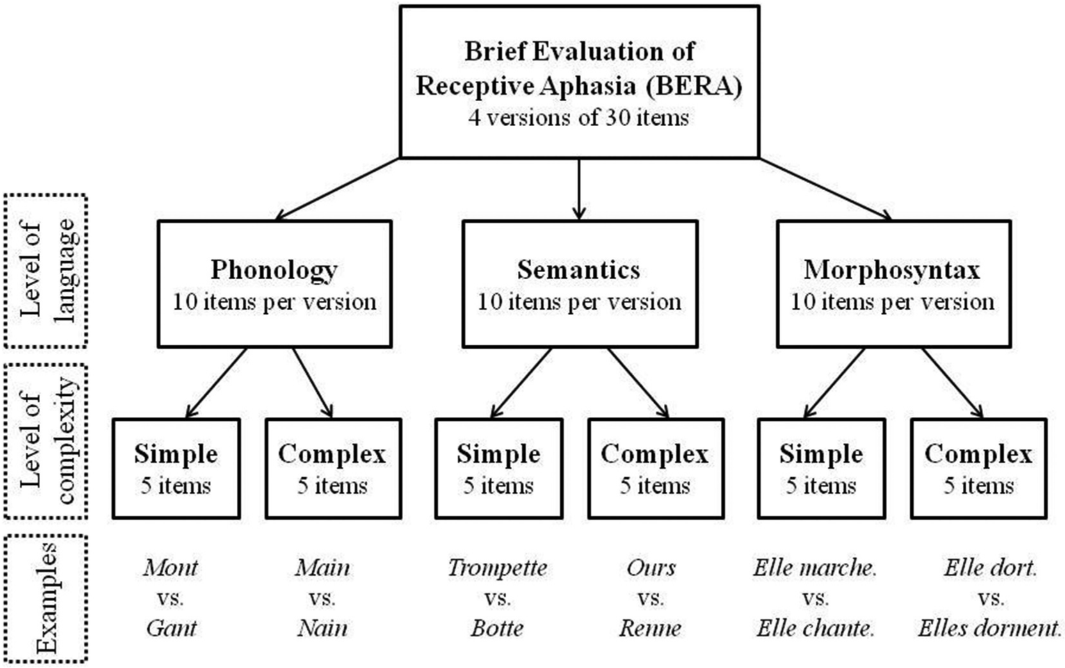

Figure 1. Repartition of items within the BERA.

morphosyntactic elements with the target (e.g., *main* [hand] versus *nain* [dwarf], *ours* [bear] versus *renne* [reindeer] or *Elle dort* [She sleeps] versus *Elles dorment* [They sleep]). The items of all four versions are presented in the Supplemental Material section, as well as examples of the drawings. Specifically, the phonological items were composed of pairs of monosyllabic words, which either shared a single phoneme (i.e., minimal pairs) or not. This allows detection of the presence of an effect of phonological similarity (i.e., reduced performance for phonologically similar versus dissimilar words), as frequently observed in patients with aphasia (22). The semantic items had been adapted from “Lexis” (23) test battery and were composed of pairs of frequent words that were either from different semantic categories or from the same semantic category. This allows detection of the presence of a semantic similarity effect (i.e., reduced performance for comparing words from the same semantic category as frequently observed in patients with aphasia) (24). The morphosyntactic items were short sentences in order to minimize the recruitment of attention and short term memory resources and were based on the Montréal-Toulouse protocol (25). They varied either with regard to their meaning (i.e., same grammatical construction for the two sentences), or with regard to grammatical aspects (i.e., change of active versus passive voice, use of reversible phrases, use of irregular verbs, change of prepositions and determinants). The presented pairs of sentences (target and distractor) had a similar number of words.

Each BERA version proposed an equal number of left and right target presentations and a randomized order of phonological, semantic and morphosyntactic items (avoiding confounding factors such as fatigue). The presence of associated cognitive deficits was taken into account during the administration of our tool by accepting responses with time latency (slow processing speed), emphasizing the transitions between items (avoiding perseverations in case of inhibition impairment), and repeating verbal instructions (memory deficits). The first fixation was taken into account and the examiner scored 1 point if the patient fixated the target-image, 0 in case of error or absence of fixation. Several scores were calculated: total score (/30), score for left- or right-sided items (/15), phonological/semantic/morphosyntactic scores (/10) and simple or complex phonological/semantic/morphosyntactic scores (/5).

Language Screening Test (LAST)

The LAST (26) was administered to AC patients only and was used, for the purpose of our study, as a gold standard against which the validity of the BERA could be assessed. This test had been designed to detect language impairment in acute stroke patients and is composed of two parallel versions of 5 subtests (naming, repetition, automatic speech, picture recognition and verbal instructions) and a total of 15 items (i.e., 8 language production items and 7 comprehension items) for each version. The LAST was selected due to its short administration duration (avoiding fatigue effects) and good psychometric properties: good internal (Cronbach α = 0,88) and external validity (sensitivity = 0,98; specificity = 1), as well as near perfect inter-rater agreement (intra-class correlation coefficient = 0,998).

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)

FDG-PET data were acquired with a Gemini TF CT scanner (Philips Medical Systems) (8). All data were preprocessed as described elsewhere (27), smoothed with an isotropic 14 mm full-width at half-maximum (FWHM) Gaussian kernel and analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK). To partially overcome the issue of brain lesions, normalization was performed using a customized FDG template as described in a previous study (28). Global normalization was performed by proportional scaling.

Structural magnetic resonance imaging (MRI)

Structural MRI data were obtained with a T1-weighted 3D gradient echo sequence on a 3 T MRI scanner (Siemens Magnetom Vida). A T1 voxel-based morphometry (VBM) analysis (29) was carried out with the CAT12 toolbox, with non-linear warping and modulation of the gray matter to ensure the preservation of the volumes after the normalization step, and a DARTEL (30) template as previously described (31). Normalized modulated gray matter data were smoothed with an isotropic Gaussian kernel of 12 mm FWHM.

General procedure

As a first step, we assessed the ability of a socio-economic representative sample of French-speaking healthy subjects to achieve the maximal score using the BERA tool. As all these healthy subjects perfectly performed the task, we ensured that the images provided an accurate representation of the word/sentence to which they were associated, thus avoiding any influence of the material on the results in the AC and post-comatose patients.

In a second step, all AC patients were assessed by three different speech therapists using either the BERA (three evaluations) or the LAST (one evaluation). Each examiner remained blind regarding the scores obtained by the two other examiners. The evaluations were performed on two consecutive days as illustrated in Figure 2. The order of administration and the examiner (1, 2 or 3) were randomized across the sample of patients with aphasia. In order to avoid fatigue effects in AC patients, two out of the four versions of the BERA were randomly chosen to be administered to each of them, as well as one of the two versions of the LAST. For example, in patient 1 the LAST (e.g., version A) was administered together with the BERA (e.g., versions 1 and 2) on Day 1, and the BERA (e.g., again versions 1 and 2) was performed twice on Day 2 (Figure 2). As the same BERA versions were repeatedly administered, no feedback was given to the patients in order to prevent any learning effect. Each assessment was separated by a break of 40 to 100 minutes, again to avoid fatigue effects.

In a third step, four post-comatose patients were behaviorally assessed using repeated CRS-R (i.e., at least 5 evaluations as recently recommended (20), two of them prior to the neuroimaging assessments) during a one-week hospitalization. Only one version of the BERA was administered (two days after the MRI scan and one day prior to the FDG-PET scan) simultaneously by two examiners in order to score the response based on both opinions. This consensus allowed to objectify the visual selection of images as accurately as possible. Indeed, the scoring of visual responses in post-comatose patients is complicated by the common presence of motor and visual difficulties, whereas the AC patients were clearer in responding to the “look at” commands.

Statistical analyses

Several psychometric variables of the BERA were examined in the AC sample. Internal consistency was assessed via Spearman correlations between the scores of the four different versions of the BERA. As only two versions of the BERA could be administered per patient, only a few assessments could be compared (e.g., only 9 patients performed both versions 1 and 2). Wilcoxon tests were used to assess the difference between left versus right presentation of items, or between simple versus complex items. Moreover, concurrent validity (i.e., comparison between LAST and BERA scores) and intra-rater reliability (i.e., comparison between the two BERA assessments performed by the same examiner) were analyzed using Spearman correlations, whereas inter-rater reliability was

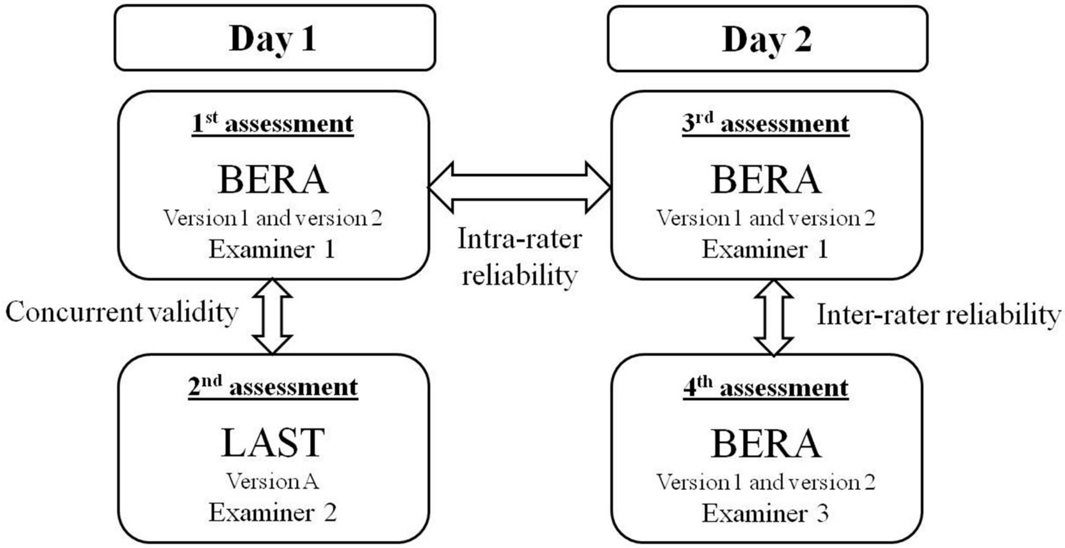

Figure 2. Example of assessment procedure using one LAST and multiple BERA evaluations for AC patients.

examined using intra-class correlations (Cronbach's alpha). Chi-squared tests were used to assess the difference in the proportion of patients with aphasia presenting phonological, semantic or morphosyntactic deficits (i.e., at least one error to the items related to one domain).

The BERA scores and sub-scores obtained in MCS and EMCS patients were compared to the mean scores obtained by the AC patients using Crawford and Howell's modified t-tests (32). Results that were similar to (or lower than) those obtained in patients with aphasia would suggest the presence of language comprehension difficulties, due to aphasia and/or other associated cognitive deficits. Differences between left versus right presentation of items (i.e., allowing the detection of spatial neglect) and simple versus complex items (i.e., highlighting complexity effects) were analyzed at the individual level using Chi-squared tests.

For assessing brain metabolism, the standardized uptake value (SUV) was visually inspected for each patient and compared to healthy control subjects (n = 34, age range 19–70 years, 15 women). The VBM analysis also compared each patient to healthy control subjects (n = 10, age range 23–46 years, 6 women). Statistical Parametric Mapping (i.e., SPM 12) analyses were used to identify brain regions showing decreased or relatively preserved metabolism or reduced gray matter volume in each patient compared to the corresponding control group. For both analyses (i.e., FDG-PET and VBM), two-sample t-tests were performed to compare each patient to the control group, and the results were considered significant at $p < .05$ corrected for false discovery rate (FDR).

Results.

Psychometric characteristics of the BERA assessment tool in conscious patients with aphasia

Table 1 reports the BERA scores (i.e., at the first administration regardless of the version) for AC patients.

Internal consistency and validity

We observed moderate to strong correlations (33) between the four versions of the BERA administered to the AC group: version 1 and 2 (r = 0,858; p = 0,003; Df = 7), version 1 and 3 (r= 0,945; p < 0,001; Df = 6), version 1 and 4 (r= 0,677; p = 0,045; Df = 6), version 2 and 3 (r = 0,833; p = 0,020; Df = 5), version 2 and 4 (r = 0,935; p < 0,001; Df = 8) and version 3 and 4 (r = 0,670; p = 0,049; Df = 8).

As expected, Wilcoxon tests showed a difference between complex and simple items (W = 835; p < 0,001; Df = 96,957), suggesting increased task difficulty for complex items. There was also no significant difference between left and right presentation of items (W = 1223; p = 0,392; Df = 94,04).

Concurrent validity

The concurrent validity analysis showed moderate to strong correlations between the LAST total score and the score of the first BERA (r = 0,667; p < 0,001; Df = 50), the LAST total score and the second BERA (r = 0,658; p < 0,001; Df = 50), the LAST comprehension sub-score and the first BERA (r = 0,586; p < 0,001; Df = 50), as well as the LAST comprehension sub-score and the second BERA (r = 0,729; p < 0,001; Df = 50).

Intra- and inter-rater reliability

The comparison of BERA scores that were obtained by the same examiner on the two consecutive days led to a strong correlation (r = 0,826; p < 0,001; Df = 50). The intra-class correlation coefficient between both BERA assessments of the same day (i.e., administered by two different examiners) showed a very good inter-rater reliability (α = 0,919; Df = 50).

Examination of individual performance profiles in conscious patients with aphasia

Given that healthy control subjects presented 100% accurate performance on all subscales, we considered the presence of a deficit in a specific domain when at least one item was incorrect. By doing this, we observed that 9/52 patients had no deficit, 33/52 patients presented phonological impairment, 25/52 semantic impairment and 37/52 morphosyntactic impairment. This proportion of patients with morphosyntactic impairment was significantly higher than the proportion of patients with semantic impairment ($\chi2$ = 5,751; Df = 1; p = 0,016). Moreover, 1/52 patients showed either phonological or semantic deficit exclusively, while an exclusive morphosyntactic deficit was observed in 6/52 patients. Finally, 4/52 patients presented both phonological and semantic impairments, 10/52 both phonological and morphosyntactic impairments, 4/52 both semantic and morphosyntactic impairments, and 17/52 showed impairments in the three domains of language (Table 1).

Use of the BERA assessment tool in patients with severe brain injury

One EMCS patient, two MCS+ patients and one MCS- patient were diagnosed by repeated CRS-R and assessed using the BERA, FDG-PET and VBM. Table 2 reports the results from all evaluations and neuroimaging data are also illustrated in Figure 3. The presence of an auditory startle reflex in all patients during the administration of the CRS-R allows to exclude deafness.

Patient 1

This patient showed reproducible command-following capacity during the CRS-R assessments and was consequently diagnosed as MCS+. The BERA total score (i.e., 21/30; t= −1,836; p= 0,036) was significantly lower than the mean of the AC patients. Regarding the BERA sub-scores, morphosyntactic performance (i.e., 5/10; t= −2,634; p= 0,006) was significantly impaired as compared to the patients with aphasia. On the other hand, the phonological (i.e., 8/10; t= −0,512; p= 0,305) and semantic (i.e., 8/10; t= −1,112; p= 0,136) sub-scores were similar to those of the AC patients. A significant difference was detected between the left and right presentation of items ($\chi2$ = 3,968; Df = 1; p= 0,046), suggesting the presence of spatial neglect, but not between simple and complex items ($\chi2$ = 0,159;

Table 2. Demographical data, scores using the CRS-R and the BERA, brain metabolism results and main hypothesis regarding the patients with DoC.

		DoC 1	DoC 2	DoC 3	DoC 4
Best CRS-R	**Total score**	11/23	23/23	15/23	9/23
	Auditory function	3	4	4	1
	Visual function	3	5	3	3
	Motor function	2	6	5	1
	Oromotor/ verbal function	1	3	2	2
	Communication	0	2	1	0
	Arousal	2	3	N/A	2
	Diagnosis	MCS *plus*	EMCS	MCS *plus*	MCS *minus*
BERA	**Total score**	21/30	22/30	16/30*	16/30*
	Phonology	8/10	7/10	8/10	7/10
	Semantic	8/10	8/10	6/10*	6/10*
	Morphosyntax	5/10*	7/10	2/10*	3/10*
Brain areas showing significant hypometabolism		Frontal lobules (median superior and left inferior [pars opercularis] frontal gyrus and right frontal pole), paracingulate and posterior cingulate gyri, bilateral caudate, left thalamus	Left frontal pole and frontal orbital cortex, right inferior temporal, supramarginal gyri	N/A	Left hemisphere, including the left temporal lobule and the Heschl's gyrus
Brain areas showing relatively preserved metabolism		Occipital areas and cerebellum	Left premotor cortex, temporo-parietal and temporo-occipital regions, right occipital fusiform and precentral gyri	N/A	Right parahippocampus and hippocampus, left insular cortex and precentral gyrus
Grey matter atrophy		Left temporo-occipital fusiform gyrus, right frontal orbital cortex, right caudate, left thalamus	Bilateral posterior temporal gyri, left supramarginal gyrus, parietal operculum cortex and frontal lobule, precuneus and thalamus	Right amygdala, left temporal lobule, left insular cortex, right precentral and paracingulate gyri, right insular cortex, planum polare and angular gyrus	Right Heschl's gyrus, temporal pole, supplementary motor cortex, temporo-occipital fusiform cortex and lingual gyrus, and left amygdala, posterior superior temporal gyrus, angular gyrus, thalamus

DoC: disorders of consciousness; MCS: minimally conscious state; EMCS: emergence from the minimally conscious state; * scores which are significantly lower than the group of aphasic conscious (AC) patients; N/A: not applicable.

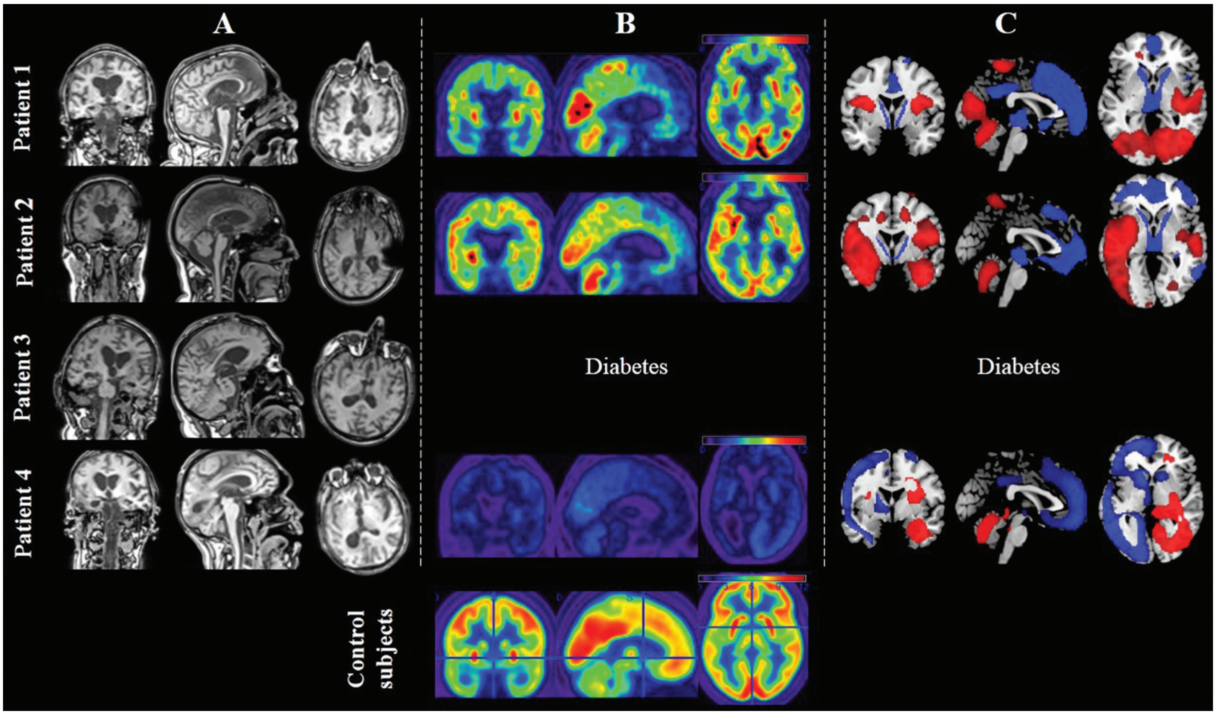

Figure 3. Brain structure and glucose metabolism in MCS/EMCS patients as assessed with structural MRI and FDG-PET, respectively. (A) T1 images of the four patients. (B) Standardized uptake value (SUV) in patient 1, 2 and 4, as well as mean SUV in 34 healthy control subjects. (C) Comparison of global brain metabolism between each patient and the group of healthy control subjects: significant hypometabolism (in blue) and relatively preserved metabolism (in red) at $p < 0{,}05$ corrected for false discovery rate. The presence of diabetes in Patient 3 prevented to obtain reliable FDG-PET data.

Df = 1; *p*= 0,919). The FDG-PET mainly showed an extended bilateral frontal hypometabolism and gray matter volume was reduced in areas such as the left temporo-occipital fusiform gyrus and thalamus.

Patient 2

Patient 2 was diagnosed as EMCS since he was able to functionally use some objects and communicate with a yes/no code. No significant differences were highlighted between the BERA scores of this patient and those of the AC patients (total score: 22/30; *t*= −1,477; *p*= 0,073; phonology: *t*= −1,345; *p*= 0,092; semantic: *t*= −1,114; *p*= 0,135; morphosyntax: *t*= −1,095; *p*= 0,139), suggesting deficits of similar severity for all language aspects. Moreover, no left-right ($\chi 2$ = 0,682; *Df* = 1; *p*= 0,409) nor simple-complex ($\chi 2$ = 0,682; *Df* = 1; *p*= 0,409) dissociations were detected. A relative preservation of brain glucose metabolism was observed in left-sided language-related cortical areas but gray matter atrophy was observed in diverse regions such as the bilateral posterior temporal gyri and thalamus.

Patient 3

The third patient had a palpebral ptosis which prevented the evaluation of arousal. Nevertheless, he showed systematic responses to command and intentional communication, leading to the diagnosis of MCS+. Regarding the administration of the CRS-R visual subscale and the BERA tool, the patient required some help from the examiner in order to keep his eyes opened. In comparison with the AC patients, his BERA total score was significantly lower (i.e., 16/30; *t*= – 3,630; *p*< .001), with particularly poor scores on the semantic (i.e., 6/10; *t*= −3,178; *p*< 0,001) and morphosyntactic (i.e., 2/10; *t*= −4,943 avec *p*< 0,001) items. However, phonological items (i.e., 8/10; *t*= −0,512 avec *p*= 0,305) did not show significant difference with those of the AC patients. These results could suggest relatively mild impairment for phonological items, and severe impairment for semantic and morphosyntactic items. No difference was found between left and right presentation of items ($\chi 2$ = 0; *Df* = 1; *p*= 1), but there was a difference between complex (i.e., 5/15) and simple items (i.e., 11/15; $\chi 2$ = 4,821; *Df* = 1; *p*= .028). The presence of diabetes prevented to obtain reliable FDG-PET data and gray matter atrophy was shown in various cortical regions such as the left temporal lobule (Table 2).

Patient 4

This patient showed visual pursuit and was therefore diagnosed as MCS-. His BERA total score (i.e., 16/30; *t*= −3,630; *p*< 0,001) as well as semantic (i.e., 6/10; *t*= −3,178; *p*< 0,001) and morphosyntactic (i.e., 3/10; *t* = −4,174; *p*< 0,001) sub-scores were significantly lower than those of the AC patients. Nevertheless, the phonological sub-score (i.e., 7/10; *t*= −1,344; *p*= 0,092) was in the same range as observed in AC patients. Like patients 1 and 3, this patient showed particularly severe language impairment for the morphosyntactic items. The scores did not differ in terms of level of complexity ($\chi 2$ = 0,536; *Df* = 1; *p*= 0,464) and there was no difference between left and right item presentation of items ($\chi 2$ = 0; *Df* = 1; *p*= 1). With regard to neuroimaging data, this patient presented an extended left-sided hypometabolism and gray matter atrophy in numerous regions (Table 2) including the left posterior superior temporal gyrus (34,35).

Discussion

This study aimed to fill a gap in the assessment of language comprehension in post-comatose patients with severe brain injury (13,16) through the development of a new assessment tool for characterizing receptive language impairment in these patients.

We obtained promising results in terms of psychometric properties, based on the AC patient data. A good internal consistency was observed, particularly for the first three parallel versions. As expected, an effect of item complexity was also reported. Moreover, our tool showed good concurrent validity with the LAST language assessment tool. Finally, the BERA showed satisfactory intra- and inter-rater reliability.

As regards the post-comatose patients, the language difficulties that were identified were in line with their CRS-R diagnosis and with a decrease of gray matter volume and/or brain glucose metabolism in several language processing areas. In line with our hypotheses, a lower BERA performance was observed in Patient 4 (i.e., MCS-) compared to Patient 1 (i.e., MCS+) and 2 (i.e., EMCS). Patient 4's total score was however similar to Patient 3 (i.e., MCS+), whose results should be cautiously interpreted given his palpebral ptosis.

The comparison of the phonological, semantic and morphosyntactic sub-scores of the BERA is of particular interest. In the AC patients, the semantic subscale led to the highest scores, followed by the phonological subscale, and the morphosyntactic subscale was the most often failed (i.e., at least one error). The most frequent co-occurrence of deficits concerned phonological and morphosyntactic impairments. According to these results, the gradient of impairment in patients with aphasia tends to range from morphosyntax to phonology, and then semantics. In contrast, post-comatose patients rather tend to show a gradient of impairment from semantics to phonology. The phonological subscale was indeed the one presenting the best performance in patients 3 and 4 (who were the most impaired patients), and all phonological sub-scores of the post-comatose patients were not significantly lower than the mean of AC patients. On the contrary, semantic (in two patients) and morphosyntactic abilities (in three patients) were significantly impaired as compared to the AC group. In these patients with severe brain injury, difficulties accessing to higher levels of language processing (i.e., semantics and sentence processing compared to phonology) which are also those acquired later during language development (36) could be suggested.

In these patients with extended brain lesions, additional attention, executive and consciousness impairment might further explain why the BERA scores tended to be lower in the AC patients as compared to the AC patients. For instance, Patient 4 did not present any language-related sign of consciousness and he performed close to chance at the BERA assessment. It is therefore particularly difficult to determine whether this patient showed the most severe aphasic symptoms, or whether he had concurrent cognitive deficits preventing any functional communication, independently of language status. Given the severity of his lesions, it is likely that both language and cognitive deficits were involved. Besides, the comprehension of sentences compared to words obviously requires a higher cognitive load, not only involving both phonological and semantic abilities, but also more cognitive functions such as executive functions or verbal short term memory (37–39). The morphosyntactic processing in Patient 1 could have been impacted by executive dysfunctions, which are suggested by the frontal hypometabolism (40,41). Still, this patient presents receptive language difficulties and a partially impaired consciousness, which might correspond to the impairment of gray matter in the left temporo-occipital fusiform gyrus (35) and thalamus (31,42).

The two other patients showed more similarities regarding the AC patients. Indeed, Patient 2 presented the best CRS-R diagnosis since he was able to functionally communicate, and he also showed the best BERA total score (i.e., 22/30), in line with the relatively preserved left-sided metabolism (35,43). The comprehension impairments in the three domains of language were similar to those of the AC patients (including the gradient of impairment from phonology to semantics), which could be associated with gray matter atrophy in the posterior temporal gyri (35). Furthermore, an effect of item complexity (as classically observed in aphasic patients) was shown in Patient 3, and particularly concerning the semantic subscale (i.e., 5/5 for simple items versus 1/5 for complex items). Given this effect of semantic category, one could hypothesize the presence of specific semantic deficits in this patient, which is in line with gray matter impairment in the left temporal lobule (posterior superior and middle temporal gyri) (34). Yet, the presence of diffuse structural lesions was observed in both patients and other conscious and cognitive processes are certainly impaired.

Besides the distinction between the three language domains, the BERA might also help to detect command-following in post-comatose patients, which is a critical and challenging aspect of DoC assessment (e.g. (44–46),), as our tool proposes items that are similar to the CRS-R "object-related response to command" (14) (based on eye fixation). Using the BERA, the "look at" commands are repeatedly pronounced, which could help patients with slow cognitive processing to get involved and produce eye responses. This new assessment could also complement the CRS-R to better follow the progression of patients.

Our results should however be considered accounting for the limitations. First, the cognitive profiles of post-comatose patients still remain difficult to understand. Specifically, the BERA scores could reflect the presence of aphasia or rather a language system which has not yet been fully 'reactivated', and for which only the earliest aspects (i.e., phonological processing) are moderately functional. Moreover, this study only included four post-comatose patients. In a next step, more patients with DoC should be assessed using the BERA, the CRS-R and neuroimaging techniques, allowing for group-level analyses. In these patients both level of responsiveness and visual fixation and pursuit might fluctuate within hours and days (47–49), and the presence of fatigue or visual difficulties (such as the palpebral ptosis of Patient 3) could impact the evaluation of comprehension. As it was demonstrated using the CRS-R (20), the BERA assessments could further be repeated in post-comatose patients to obtain more reliable information. It should also be noted that a majority of stroke patients with focal lesions were recruited for this study, whereas the post-comatose patients had more diffuse and extended lesions due to TBI. The use of this type of aphasic patient sample as a comparison group with post-comatose patients might therefore appear questionable. It could indeed be argued that the language difficulties observed in the post-comatose patients are rather due to their more general cognitive impairment at the level of attention, executive control or self-consciousness. However, it is important to underline here that the purpose of our study was not to determine the origin of language impairment, but to formally demonstrate functional deficits in the use of language and to assess their similarity with the type of language symptoms presented by clearly diagnosed aphasic patients. Moreover, although there is more widespread hypometabolism in the post-comatose patients, hypometabolism is also observed in the language processing areas that are lesioned in aphasic patients, clearly raising the possibility of additional aphasic impairment in post-comatose patients. Furthermore, the BERA tool presented here has been developed for French-speaking patients. The adaptation of this tool into other languages will need language-specific validation studies given that each language has its own phonological and morphosyntactic characteristics. The use of an eye-tracking setting should finally be tested to obtain objective measures of eye fixation in this challenging population.

Still, recovery of cognitive functioning in post-comatose patients with DoC remains poorly documented, and the BERA could be a useful tool for establishing language recovery trajectories in this population. It might also help avoiding an underestimation of consciousness levels in patients patients with severe brain injury, and contribute to better informed end-of-life decisions in these patients.

Conclusions

We present a new assessment tool for receptive language abilities in post-comatose patients with severe brain injury. The BERA appears as a good tool to complement the CRS-R and other neurological examinations aiming at diagnosing the DoC. The comparison of phonological, semantic and morphosyntactic subscales also brings a strategic cue for language therapists in order to orientate their care and choose the best therapeutic strategies. Nonetheless, the interpretation of all combined data of a patient post-coma is necessary in order to better apprehend the overall profile. This research presents obvious clinical implications and opens numerous prospects for the future.

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Declaration of interest

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Author contribution

C.A., S.M. and S.L. conceived and planned the presented research. C.A., S. G., N.H. and M.T. assessed the aphasic conscious patients using the BERA. C.A., N.H., M.T., C.C., N.L. and H.C. contributed to clinical and neuroimaging data acquirement and analyses in post-comatose patients. C.A., S. M., S.L., S.G., N.H. and M.T. worked on data interpretation. C.A. drafted the manuscript under S.M.'s supervision and all authors provided critical feedback and helped shape the manuscript.

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