Title: How Do You Feel? Subjective Perception of Recovery as a Reliable Surrogate of Cognitive and Functional Outcome in Cardiac Arrest Survivors.

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TITLE PAGE

Title: How do you feel? Subjective perception of recovery as a reliable surrogate of cognitive and functional outcome in cardiac arrest survivors.

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ABSTRACT

Objective: To show that subjective estimate of patient's condition is related to objective cognitive and functional outcome in cardiac arrest survivors.

Design: Longitudinal cohort study.

Setting: Intensive Care Unit (ICU) and Neuropsychology Service, Lausanne University Hospital and Valais Hospital, Switzerland.

Patients: 50 survivors were included from a prospective cohort of 138 patients admitted at the ICU for cardio-pulmonary arrest.

Interventions: Comprehensive cognitive and functional evaluation at 6 months follow-up.

Measurements and Main Results: Subjectively, 70% of survivors reported that they returned to their pre-injury functioning and 29% reported no complaints. Objectively, 76% were classified as good neurological outcome (Cerebral Performance Category 1), 26% as having no symptoms (modified Rankin Scale 0) and 38% as upper good recovery (GOSE 1). Cognitive assessment detected substantial cognitive impairment in 26%, primarily concerning processing speed, language, long-term memory and executive functions. Subjective complaints severity correlated significantly with objective cognitive impairment (r_S=0.64, p<0.001). Finally, patients reporting unsatisfactory recovery displayed lower functional scores than those reporting satisfactory recovery (e.g. quality of life satisfaction: 64% vs. 79%; Z=2.18, p=0.03) and more cognitive impairment (3 (2-4.5) vs. 1 (0-3) cognitive domains impaired; Z = -3.21, p < 0.001), concerning in particular learning and long-term verbal and visual memory.

Conclusions: Long-term subjective and objective outcome appears good in the majority of CA survivors. Specific functional and cognitive impairments were found in patients reporting unsatisfactory recovery. Subjective recovery seems to was strongly correlate with objective

measures.

INTRODUCTION

Cardiac arrest (CA) represents the leading cause of death, with at most 11% of patients surviving hospital discharge (1). Among these, neurological recovery is usually good, with 85% classified as Cerebral Performance Category (CPC) (2) 1 or 2 (3). However, previous studies reported some degree of long-term cognitive dysfunction in about 50% of survivors (4–6), particularly in memory, attention, and executive functioning(6–10). Compared to control subjects with myocardial infarction, CA survivors are more frequently impaired in attention and mental speed, while memory and executive functions seem similar (6). Long-term functional impairment in CA survivors has also been described in several studies: up to 50% of patients report severe fatigue (11), 18% need help with everyday activities (12), and 24% report anxiety, though in similar proportion to controls (13). Altered quality of life has also been noted, particularly in survivors with CPC 2 or 3 (14).

Interestingly, patients' subjective perception of their recovery has rarely been addressed, though subjective perception of well-being is the ultimate aim of any clinical intervention. In addition, how subjective evaluation is related to objective measures is even less clear. Significant complaints have been found in 14% of survivors, but these were not associated with cognition (15). In contrast, complete subjective recovery has been reported in 62-66% of survivors (12) and correlated with anxiety and depression symptoms (13).

Here we present the results of an exhaustive cognitive and functional evaluation, including subjective measures, at six months follow-up. In addition to describing overall outcome, we hypothesized that subjective perception of recovery constitutes a reliable surrogate for detailed objective assessment of patients' cognitive and functional status. In particular, we postulated that

patients who report a satisfactory recovery would show better results in standard objective measures.

MATERIAL AND METHODS

Study design and population

We prospectively considered all adult comatose patients admitted after CA to the interdisciplinary ICU between July 2012 and May 2015 at the Lausanne University Hospital, and between June 2014 and May 2015 at the Valais Hospital. All patients were treated using a standardized protocol (16, 17). Decision to withdraw intensive care was based on early multimodal assessment performed during the first days of coma (see Suppl. Doc 1 for further description). This study received full approval from both local Ethics Commissions. Informed consent was obtained on admission, from a family member or a physician not involved in the study, and at follow-up, from the patient or a family member. Six months after CA, patients with no prior severe neurologic or psychiatric conditions were offered functional and cognitive assessment.

Subjective and objective functional outcome assessment

Functional outcome was evaluated 6 months after CA by EJ, through a semi-structured phone interview or in person, prior to the neuropsychological assessment (in order to limit the influence of the upcoming cognitive evaluation). Global outcome was assessed both subjectively and objectively. Subjective outcome measures included perception of recovery ("Do you feel that you are back to your baseline functioning, before the cardiac arrest?")—used to classify patients as "satisfactory recovery" for a "yes" answer, or "unsatisfactory recovery" for a "no" answer—and severity of patients' reported complaints, from 0 (no complaints, spontaneously or upon questioning) to 4 (severe complaints). Objective outcome measures included Cerebral

Performance Category (CPC), ranging from 1 (good) to 5 (death) (2), the Modified Rankin scale (mRS), ranging from 0 (no symptoms) to 6 (death) (18), and the French version of the Glasgow Outcome Scale Extended (GOSE), ranging from 1 (upper good recovery) to 8 (death) (19). Complementing these global rating scales, we also assessed specific functional aspects: complaints systematically prompted by questions for eight domains (language, gnosia, praxia, memory, attention, fatigue, behavior or emotional changes, slowing), the Quality of Life after Brain Injury scale (QOLIBRI) (20), anxiety and depression (Hospital Anxiety and Depression scale, HAD) (21, 22), independence in daily activities (Instrumental Activities of Daily Living scale, IADL) (23), professional activity and driving resumption.

Cognitive outcome assessment

This was assessed at 6 months by a standard neuropsychological evaluation lasting 2.5 h performed by the same certified neuropsychologist (EJ) in the outpatient consultation. Thirteen scores were extracted to characterize representative cognitive domains: the naming subtest of the Lexis battery (language) (24), the French version of the California Verbal Learning Test (learning and long-term verbal memory) (25), the Doors and People test (long-term visual memory) (26), WAIS-IV digit span forward subtest (short-term verbal memory) (27), MEM-III block tapping forward subtest (short-term visual memory) (28), the Five-points test (productivity) (29), WAIS-IV digit-symbol subtest (processing speed) (27), and the alert and divided attention subtests of the Test battery for Attentional Performance (resp. reaction times and divided attention) (TAP) (30). Initiation, Inhibition and Generation scores were calculated following a method proposed by Godefroy (31) using semantic and phonemic verbal fluency, Trail Making and Stroop tests from the GREFEX battery (18) (see Suppl. Doc2 for details). Raw

scores were corrected for age and socio-cultural level according to published norms, and transformed into standard z-scores. The cut-off for impaired performance was a z-score ≤ –1.65 SD of published norms. An individual global cognitive impairment index (GCI) was calculated as the number of tests impaired. Patients with three or more domains impaired (≥23% of the test battery) were considered to have substantial cognitive impairment.

Comparing subjective vs. objective recovery

Spearman's rank correlations tested associations between subjective and objective global functional outcome measures; performance of subjective measures to identify objectively good outcomes, defined as CPC 1, was addressed with a 2x2 table (using exact binomial confidence intervals).

To address whether subjective assessment is informative about detailed objective outcomes, we tested whether patients reporting "satisfactory recovery" differed from those with "unsatisfactory recovery" in several cognitive and functional domains, using two-sided non-parametric tests for continuous variables (Wilcoxon signed rank test) or Fisher exact tests for categorical variables. Finally, to determine whether subjective perception of cognitive status accurately reflects actual cognitive performance, we correlated complaints severity with GCI.

Descriptive statistics are given as median (range), unless otherwise specified. The significance level was set at 2-sided $\alpha = 0.05$. We did not correct for multiple comparisons, given the exploratory nature of this study. All analyses were run on MATLAB 2015b.

RESULTS

Population

Over the study period, 138 post-CA comatose patients were admitted (Lausanne: 121, Valais: 17). Among them, 67 were discharged (49% survival). Six months after CA (29 ± 3 weeks), 50 (Lausanne: 48, Valais: 2; see Table 1) received long-term assessment, and 42 also undergo neuropsychological testing (Fig.1).

Main reasons for non-inclusion were patient's refusal (n = 7), severe pre-existing neurologic or psychiatric comorbidities (n = 5), and patients living too far from the assessment center or being otherwise impossible to reach (n = 4). The 17 non-included survivors (59 (48–78) years old, 5 women (29%)) did not differ in demographics, but exhibited worse CPC at 3 months (2 (1-3) vs. 1 (1-2); $Z = 2.32$, $p = 0.02$).

Functional outcome

At 6 months follow-up, all but one patient had returned home . Subjective measures showed that 35 (70%) reported a satisfactory recovery, 14 (29%) with no complaint. Objective measures classified 38 (76%) as CPC 1, 13 (26%) as mRS 0, and 19 (38%) as GOSE 1 (see Fig. 2). Subjective and objective outcome measures were strongly and positively correlated (CPC and subjective recovery: $r_s = 0.56$, $p < 0.001$; mRS and complaints severity: $r_s = 0.53$, $p < 0.001$; see Fig. 2). Performances of subjective recovery in identifying patients with objective good outcomes (CPC 1) were: sensitivity 0.84 (95% CI: 0.73–0.96), specificity 0.75 (95% CI: 0.51–0.99), positive predictive value (PPV) 0.91 (95%CI: 0.82-1.00).

Fatigue was the most frequently reported complaint (35/49 patients (one patient was unable to respond); 71%), followed by change in behavior or emotion (25; 51%), slowing (24; 49%), attention (18; 37%), memory (17; 35%), language (12; 24%). Gnosia or praxia impairment were rare (1; 2%). The majority of patients were independent for daily activities (IADL > 6 points: 42/50; 84%); 16/26 (61%) were able to resume working and 29/40 (73%) could resume driving. Five patients (10%) showed signs of anxiety and 3 (6%) of depression (HAD). Overall quality of life satisfaction was 75 ± 17%.

Regarding subjective outcome, those reporting "unsatisfactory recovery" showed significantly worse results on all global objective and subjective outcome scales (Table 2). They also reported lower quality of life satisfaction (total QOLIBRI score, physical problem score, and to a lesser extent emotional and cognitive scores), more frequent complaints (memory, attention, slowing, fatigue), depression symptoms (HAD), and impairment of daily living activities (IADL); they were less likely to return working or resume driving.

Cognitive outcome

Forty-two patients (30 "satisfactory recovery", 12 "unsatisfactory recovery") underwent neuropsychological examination (seven refused to participate, one was too severely impaired; CPC at 6 months: 1.5 (1-2) vs. 1 (1-2) in the participating group; $Z = 1.98$, $p = 0.05$). Domains most frequently impaired were processing speed (9 patients impaired; 21%), language (9; 21%), long-term memory (8; 19%) and initiation (8; 19%). In contrast, domains most often preserved were short-term verbal memory (2 patients impaired; 5%), reaction times (2; 5%), generation (3; 7%) and productivity (3; 7%) (see Suppl. Doc 2). Overall, patients had 1 (0–3) impaired cognitive domains (GCI) and 11 (26%) were considered to have substantial impairment.

Patients with “unsatisfactory recovery” showed significantly worse performance in 7 out of the 13 (54%) cognitive dimensions considered: learning, verbal and visual long-term memory, short-term visual memory, initiation, processing speed, and divided attention (see Fig. 3, Suppl. Doc 2). GCI was also significantly higher in the group “unsatisfactory recovery” (3 (2–4.5) impaired domains) vs. “satisfactory recovery” (1 (0–3) impaired domains; $Z = –3.21$, $p < 0.001$) with respectively 7 patients (58%) and 4 (13%) having substantial cognitive impairment.

Finally, objective measures of cognitive performance correlated strongly and positively with subjectively perceived cognitive status (GCI and complaint severity: $r_S = 0.64$, $p < 0.001$).

DISCUSSION

This study shows that subjective evaluation appears to be a reliable indicator of cognitive and functional long-term outcome in CA survivors. In fact, 70% of patients deemed they had returned to pre-injury functioning level, while objective evaluation identified 76% as CPC 1. Subjective assessment had high sensitivity and PPV in identifying CPC 1. Subjective measures correlated strongly with all objective global outcome scales and objective evaluation of cognitive impairment. Grouping patients by subjective outcome assessment, we showed that survivors reporting satisfactory recovery exhibit consistently better results than those with unsatisfactory recovery on specific functional dimensions, including quality of life, domains of complaints, independence, depression, ability to return to work and resume driving. They also displayed better cognitive performance in most of the cognitive domains tested, particularly learning, long-term memory, and selected dimensions of attention and executive functions.

As a whole, our sample of CA survivors experienced good overall long-term outcomes, consistent with previous literature reporting CPC 1 in 84% (8) and complete subjective mental recovery in 62 to 66% (12). However, as highlighted in previous reports (4), detailed evaluation tempers these proportions: our patients had frequent complaints, especially concerning fatigue (71%) and being unable to go back to work (39%). In contrast, quality of life satisfaction was high (75%, similar to 76% previously reported at a more distant follow-up time (32)) and anxiety and depressive symptoms were rare (10% and 6% respectively, similar to the findings of 11% and 7% in (13)). Detailed neuropsychological evaluation detected substantial cognitive impairment in 26% of survivors, higher than the 13% at 3 months or 11% at one year reported in

(15) (potentially explained by the higher number of tests considered in our study, 13 vs. 6), but lower than the 50% of patients showing mild cognitive impairment reported in (6). In particular, we revealed that impairment in processing speed (21%) and language (21%) were as frequent as the classical impairments in long-term verbal memory (19%) or executive functions (19% for initiation, 17% for inhibition) (6, 15).

Long-term memory complaints have been previously associated with general physical and mental health (33), while the only study directly testing the association between subjective and objective measures reported null results (15), using a complex questionnaire (34) to assess subjective outcome, rendering comparison with our binary measure difficult. Our subjective recovery measure seems more similar to item 2 of the Two Simple Questions (35): "Do you feel that you have made a complete mental recovery after your heart arrest?", leading to a similar proportion of patients reporting complete recovery (12), and an association with anxiety and depression symptoms (13).

Our results appear consistent with previous studies with larger sample sizes, both on global functional scales and specific functional and cognitive dimensions (6, 8, 12, 13, 15, 32), suggesting that these may be generalizable. Furthermore, we report a rigorous cognitive evaluation, unveiling the importance of processing speed and language impairment in CA survivors, in addition to the classically demonstrated impairments in memory and executive functions. Finally, the novel combination of such a detailed evaluation with simple subjective assessment measures showed a strong association between subjective and objective recovery in CA survivors.

This study has some limitations. First, excluded survivors had worse CPC scores at 3 months, which might indicate a selection bias. However, many excluded survivors had pre-existing psychiatric or neurologic conditions, which might explain their mitigate outcomes. Therefore, especially our cognitive results, are applicable only to healthy patients prior to CA and are able to undergo a prolonged neuropsychological evaluation. Second, grouping patients by subjective reports may have shortcomings: self-evaluation is modulated by the ability to assess one's own condition, *i.e.* nosognosia, which is also influenced by mood disorders (36). It is therefore possible that some patients reporting satisfactory recovery minimized their impairment, while some in the "unsatisfactory recovery" group were influenced by depression (37). However, since subjective reports correlated strongly with several objective measures, this seems unlikely. Third, considering that some of the "objective" data are nevertheless based on patient's responses, subjective and objective measures are likely not fully independent. This seems a common issue, and obtaining consistent results in this context reinforces internal validity (32). Fourth, the same neuropsychologist conducted assessments of subjective and objective measures; we do not believe that this introduced an information bias, since the CPC at 3 months collected by a blinded research nurse showed consistent results with other functional data, functional outcome was obtained before cognitive testing, and most functional measures did not include neuropsychologist's involvment (i.e. self-administered questionnaires). Fifth, including a control group in the study would have allowed estimating the specific impact of CA. However, the tests' published norms provide a reliable appreciation of performances. Finally, we lack information on pre-morbid functional conditions, as in other major studies on this topic (6, 12, 15); however, subjective assessment provides an indirect evaluation of patient's premorbid status as it refers to baseline functioning.

CONCLUSIONS

To the best of our knowledge, this work constitutes the first attempt to investigate the association between patients' subjective perception of recovery and detailed quantitative assessment, providing a simple measure of patients' evaluation taking into account premorbid level of functioning. In addition, subjective measures correlate significantly with objective cognitive and functional assessments. Therefore, if confirmed in other settings, this approach could yield new insight regarding functional follow-up and appropriate calibration of rehabilitation efforts.

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FIGURES LEGENDS

Fig.1: Flow of post-anoxic comatose survivors included in the study. The last four boxes represent the included population: 50 patients were included in the functional assessment (35 "complete recovery" and 15 "incomplete recovery") and 42 also participated to the neuropsychological assessment (30 "complete recovery" and 12 "incomplete recovery").

Fig.2: Results of subjective (S) and objective (O) global outcome scales. Best scores (e.g. complete subjective recovery, CPC1, mRS 0) are in white on the left side of the graph, while worst scores are in dark on the right side, with number of patients for each category in corresponding bins. Thirty-five survivors (70%) reported complete subjective recovery (in white) and 15 (30%) incomplete recovery (in grey). Scores ranged from 0 to 4 for Complaints severity (n=49), 1 to 3 for CPC, 0 to 4 for mRS and 1 to 6 for GOSE. Stars show significant correlations between Subjective recovery and CPC ($r_s = 0.56$, $p < 0.001$) and between Complaints severity and mRS ($r_s = 0.53$, $p < 0.001$) (see Suppl. Figure 2 for full correlation table).

Fig.3: Cognitive performance (mean and SD of standard z scores) for 13 cognitive domains by subjective recovery group ("returned to pre-injury functioning in grey, "not returned to pre-injury functioning" in black). The mean of the reference population (as obtained from published norms) is a z-score of 0; positive values indicate a score above the norms, i.e. better performance than the reference population, while negative values indicate a score below, i.e. worse performance. Significant differences between the two subjective recovery groups are reported in

parenthesis (* $p < 0.05$; ** $p < 0.01$). See supplementary Table 1 for an exhaustive description of raw scores, z scores and statistical results.

SUPPLEMENTARY DATA

Doc 1: Description of all cognitive tests used in the neuropsychological assessment.

Table 1: Results of all neuropsychological tests.

Table 2: Results to the early clinical variables by recovery group.

Table 1. Results of clinical tests performed during coma of patients stratified according to their subjective recovery at 6 months.

Clinical tests	**Survivors reporting satisfactory recovery (n = 35)**	**Survivors reporting unsatisfactory recovery (n = 15)**	***p* value (*Z* value)**	**All patients (n=50)**
Socio-demographics				
Age, median (IQR), years	61 (53-72)	56 (46-72)	0.6 (0.57)	60 (49-72)
Female gender, n (%)	7 (20)	6 (40)	0.2	13 (26)
Cardiac arrest variables				
Cardiac etiology, n (%)	30 (86)	13 (87)	1	43 (86)
Out-of-hospital CA, n (%)	32 (91)	15 (100)	0.5	47 (94)
First rhythm shockable, n (%)	30 (86)	10 (67)	0.1	40 (80)
Time to ROSC, median (IQR), min	15 (10-21)	15 (10-31)	0.4 (0.9)	15 (10-22)
Hypothermic treatment	35 (100)	13 (87)	0.09	48 (96)

Continuous variables are presented as median and interquartile and statistically tested with Wilcoxon signed rank test. Categorical variables are presented as number (and percentage) and analyzed with Fisher exact test (no Z value). Shockable rhythms include ventricular fibrillation and ventricular tachycardia and exclude asystolia and pulseless electrical activity. *IQR* interquartile range; *ROSC* return of spontaneous circulation.

Table 1. Long-term functional outcome results by subjective recovery group.

Functional measure	Survivors reporting satisfactory recovery (n = 35)	Survivors reporting unsatisfactory recovery (n = 15)	*p* value (*Z* value)	All survivors (n=50)
Global scales, median (IQR)				
CPC (6 months)	1 (1-2)	2 (1-3)	<0.001 (-3.88) **	1 (1-2)
CPC (3 months)	1 (1-2)	2 (1-3)	<0.001 (3.97) **	1 (1-2)
mRS	1 (0-2)	2 (1-3)	<0.001 (-4.21) **	1 (0-2)
GOSE	1 (1-2)	4 (3-6)	<0.001 (-4.78) **	2 (1-4)
Complaints severity §	1 (0-2)	3 (1.5-4)	<0.001 (-4.64) **	0 (1-2)
Quality of life, median (IQR)				
QOLIBRI total §	81 (72-86)	64 (45-86)	0.03 (2.18) *	79 (63-86)
QOLIBRI cognition §	86 (75-96)	59 (32-93)	0.06 (1.88)	82 (64-96)
QOLIBRI self §	79 (64-89)	63 (53-86)	0.09 (1.71)	75 (61-86)
QOLIBRI daily life & autonomy §	86 (64-96)	61 (50-93)	0.09 (1.68)	79 (61-95)
QOLIBRI social relationships §	79 (73-92)	73 (58-88)	0.10 (1.53)	79 (71-90)
QOLIBRI emotions §	90 (60-95)	68 (55-80)	0.05 (1.96)	85 (60-95)
QOLIBRI physical problems §	85 (70-95)	68 (55-80)	0.008 (2.66) **	85 (65-95)
Domain of complaints, n (%)				
Memory §	7 (20)	10 (71)	0.002 **	17 (35)
Language §	6 (17)	6 (43)	0.08	12 (25)
Gnosia §	0 (0)	1 (7)	0.29	1 (2)
Praxia §	0 (0)	0 (0)	1.00	0 (0)
Attention §	8 (23)	10 (71)	0.003 **	18 (37)
Slowing §	13 (37)	11 (79)	0.01 *	24 (49)
Fatigue §	21 (60)	14 (100)	0.004 **	35 (71)
Behavioral/emotional change §	17 (48)	8 (57)	0.75	25 (49)
Mood disorders, median (IQR)				
HAD anxiety, n impaired §	4 (3-8), 2	8 (4-11), 3	0.07 (-1.84)	6 (3-9), 5
HAD depression, n impaired §	2 (1-4), 0	5.5 (3-9), 3	0.004 (-2.87) **	3 (1-5), 3
Daily living				
IADL, median (IQR), n impaired	8 (6.5-8), 3	8 (4.5-8), 5	0.05 (-1.99) *	8 (5-8), 8
Working resumption, n (%)	14/17 (82)	2/9 (22)	0.009 **	16/26 (61)
Driving resumption, n (%)	24/29 (83)	5/11 (45)	0.04 *	29/40 (73)

All measures were obtained at 6 months follow-up by the same certified neuropsychologist, except CPC at 3 months, which was obtained through a phone interview by one research nurse. *CPC* Cerebral Performance Category; *GOSE* Glasgow Outcome Scale Extended; *mRS* modified Rankin scale; *QOLIBRI* Quality Of Life after Brain Injury (high percentage means high satisfaction); *HAD* Hospital Anxiety and Depression scale (a score > 11 points indicates the probable presence of the disorder); *IADL* Instrumental Activities of Daily Living (8 points: maximal independence). * $p < 0.05$; ** $p < 0.01$.

§ 49 patients (14/15 patients in the “not returned to pre-injury functioning” group: one patient was unable to answer further questions due to severe cognitive impairment).

Figure 1

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AT HOSPITAL ADMISSION

138
Post-anoxic comatose
patients admitted

AT HOSPITAL DISCHARGE

67
Patients discharged
alive

AT 6 MONTHS FOLLOW UP

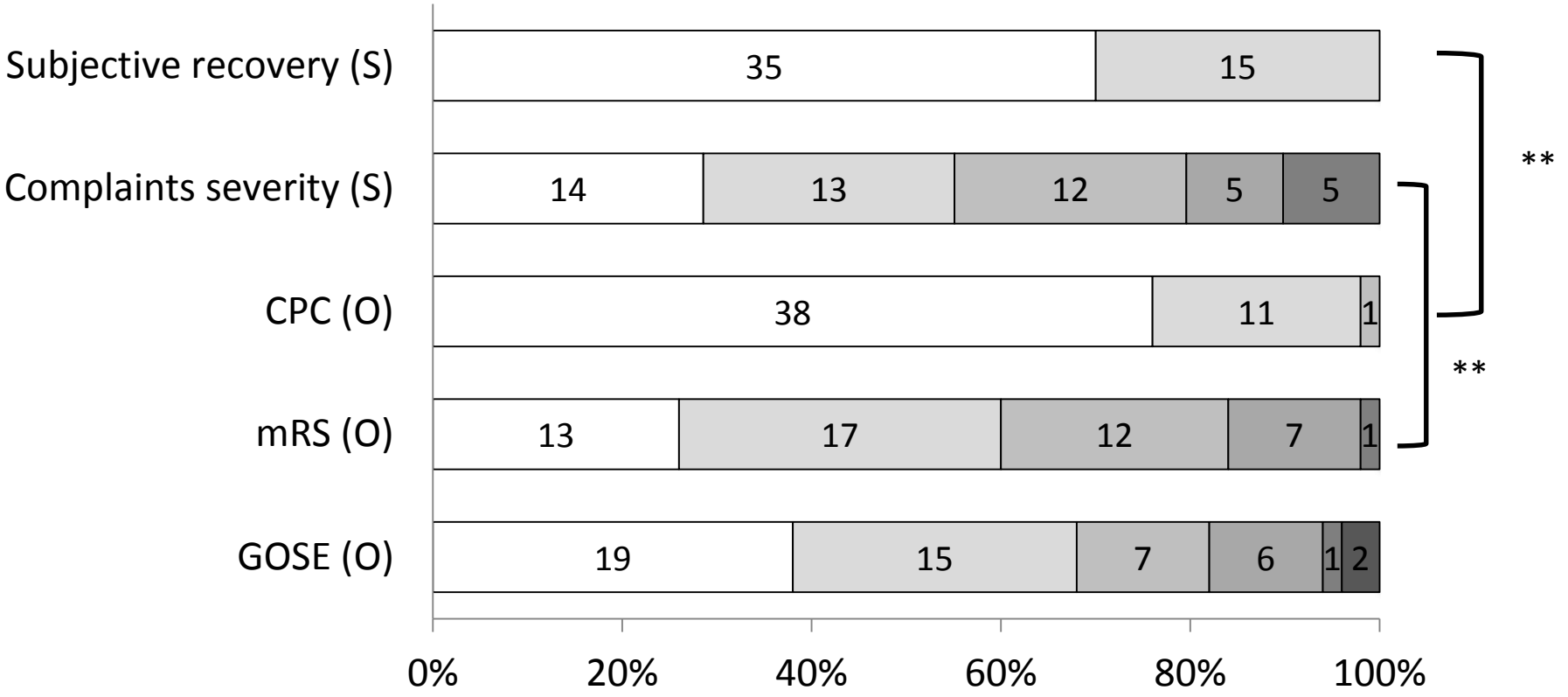
50
Patients participating to the
functional assessment

35
Patients reporting
satisfactory recovery

30
Also participating to the
neuropsychological
assessment

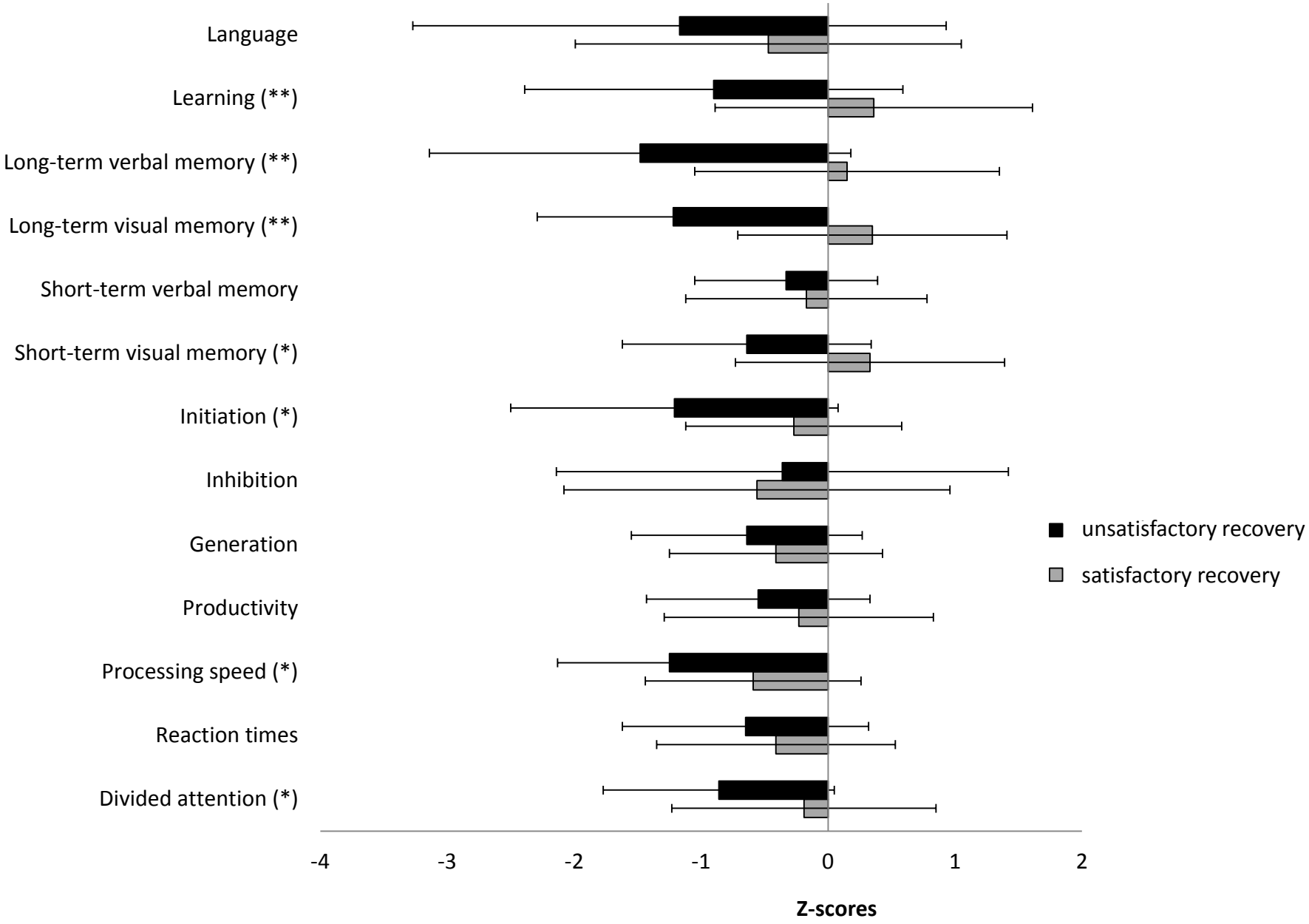
15
Patients reporting
unsatisfactory recovery

12
Also participating to the
neuropsychological
assessment



	Subjective recovery (S)	Complaints severity (S)
CPC (O)	< 0.001 (0.56) **	0.003 (0.42) **
mRS (O)	< 0.001 (0.6) **	< 0.001 (0.53) **
GOSE (O)	< 0.001 (0.68) **	< 0.001 (0.66) **

Figure 3


Language
Learning (**)
Long-term verbal memory (**)
Long-term visual memory (**)
Short-term verbal memory
Short-term visual memory (*)
Initiation (*)
Inhibition
Generation
Productivity
Processing speed (*)
Reaction times
Divided attention (*)
unsatisfactory recovery
satisfactory recovery
-4
-3
-2
-1
0
1
2
Z-scores

Clinical examination during coma

Methods

Early clinical variables were prospectively collected in the first days following admission, while patients were comatose. Neurological examination testing brainstem reflexes (1), motor response and early myoclonus were performed repetitively after rewarming and up to 72h after CA. Serum NSE was sampled at 24h and/or 48h after CA and analyzed with an automated immunofluorescent assay (BRAHMS Kryptor, Immunodiagnostic Systems, Hennigsdorf, Germany); the highest value was selected for this study. Cortical response to median-nerve somatosensory evoked potentials (SSEP) was tested once after rewarming, 24h to 72h after CA (2). Two video-EEGs recordings (21 electrodes, Viasys Neurocare, Madison, WI, USA) were performed, 2-36 hours and 24-72h after CA onset and visually qualified by EEG-certified neurologists (3). Here we report only background reactivity to stimuli, since it has been robustly related to survival in previous studies (4). Using the same EEG clinical montage, most patients were also tested with an auditory discrimination paradigm predicting survival (5) and good early cognitive outcome (6). CPC was assessed at 3 months through a routine phone interview with patients or caregivers (7).

Results

All patients but two were treated with mild therapeutic hypothermia to 33-34°C for 24h (8). Two patients (4%) had a non-reactive EEG background on Day 1 and none on Day 2; one (2%) presented an early myoclonus; six (12%) had at least one brainstem reflex absent at 72 hours; 13 (26%) had absent motor response and none had bilaterally absent SSEP. Serum NSE peak was available in 46 patients (mean: 24 ± 15 µg/ml) with one outlier above 75 µg/ml (3). Evolution of auditory discrimination was available for a subset of 42 patients and

showed progression in 18 (43%). On average, patients spent 6 ± 4 days in coma and a total of 19 ± 16 days in the hospital. Twelve patients (24%) were referred to a specialized neurorehabilitation center at discharge.

In order to assess whether subjective recovery can be predicted from early clinical examination, we compared patients reporting complete vs. incomplete recovery on these variables. No difference was found on clinical tests, progression of auditory discrimination, or coma and hospital duration (see Table 1 below). However, the two groups differed early after hospital discharge, since more of the "incomplete recovery" survivors were addressed to neurorehabilitation centers.

Discussion

Early multimodal prognostication during coma did not discriminate survivors with complete vs. incomplete recovery, making detailed long-term recovery difficult to predict. Finding association between multimodal examination during coma and long-term outcome is particularly challenging since acute examination is specific to mortality prediction (4), therefore providing very limited information for good outcome. Much fewer tests are associated with survival and even less have been shown to delineate the quality of recovery. S-100B protein and long-latency SSEP (N70) have been related with memory performances and executive functions(9, 10), while recently our group showed that progression of auditory discrimination predicted early cognitive and functional outcome (6). As opposed to early assessment where outcome variability is large, at 6 months follow-up most recovery has happened and the range of neurological impairment is reduced, therefore making it difficult to find any predictors.

Table 1. Results of the clinical tests performed during coma split by subjective recovery groups.

Clinical tests	**Survivors reporting satisfactory recovery (n = 35)**	**Survivors reporting unsatisfactory recovery (n = 15)**	***p* value (*Z* value)**
Investigations during coma, n (%)			
Early myoclonus present	1 (3)	0 (0)	1
Brainstem reflexes absent [a]	4 (11)	2 (13)	1
GCS motor response [1-2] [b]	9 (26)	4 (27)	1
Cortical SSEP bilaterally absent	0/31 (0)	0/14 (0)	1
NSE peak, median (IQR), µg/ml	20 (15-29) (n=32)	19 (14-29) (n=14)	0.9 (0.13)
Non reactive EEG on Day 1 [c]	1/31 (3)	1/13 (8)	0.5
Non reactive EEG on Day 2 [c]	0 (0)	0 (0)	1
Progression of auditory discrimination	13/29 (45)	5/13 (38)	0.7
Hospital outcome, median (IQR)			
Coma duration, days	4 (3-7)	5 (3-7)	0.6 (-0.46)
Hospital stay duration, days	13 (9-21)	19 (15-25)	0.2 (-1.39)
Neurorehabilitation treatment, n (%)	5 (14)	7 (47)	0.03 *

Fisher exact test was used for categorical variables (*p* value reported) and Wilcoxon signed rank test for continuous variables (*p* value and *Z* value reported). *EEG* electroencephalography, *GCS* Glasgow Coma Scale, *IQR* interquartile range, *MRI* magnetic resonance imaging, *NSE* neuron-specific enolase, *ROSC* return of spontaneous circulation, *SSEP* somatosensory evoked potential. * $p < 0.05$.

[a] pupillary, oculocephalic, corneal; all present vs. one or more absent

[b] flexion posturing or better vs. extension or no response

[c] EEG reactivity to repetitive auditory and painful stimulations (categorized as present if clear and reproducible change in amplitude or frequency vs. absent)

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Table 2. Long-term cognitive results by subjective recovery group.

Cognitive test	**Survivors reporting satisfactory recovery (n = 30)**		**Survivors reporting unsatisfactory recovery (n = 12)**		***p* value (Z value)**	**Total impaired, n (%)**
	Raw scores (n impaired)	**Z scores (n impaired)**	**Raw scores (n impaired)**	**Z scores (n impaired)**		
Language						
Naming [a]	*N/A*	*-0.47 ± 1.52 (7)*	*N/A*	*-1.17 ± 2.1 (2)*	*0.3 (1.03)*	*9 (21)*
Metaphor interpretation [§]	35 ± 3	-0.37 ± 1 (5)	34 ± 2.5	-0.72 ± 1.66 (2)	0.7 (-0.42)	7/25 (28)
Gnosia						
Figures recognition	15 ± 0.4 (2)	N/A	15 ± 0 (0)	N/A	0.4 (0.87)	2 (5)
Celebrities identification	7.8 ± 0.5 (1)	N/A	7.7 ± 0.7 (1)	N/A	0.4 (-0.9)	2 (5)
Praxia						
Constructive praxia	10.7 ± 0.6	0.49 ± 0.63 (0)	10.5 ± 0.7	0.47 ± 0.47 (0)	0.5 (0.64)	0 (0)
Gestual praxia	12 ± 0.4 (0)	N/A	12 ± 0.3 (0)	N/A	0.4 (0.88)	0 (0)
Short-term / working verbal memory						
Digit span forward (nb)	*8 ± 2*	*-0.17 ± 0.95 (1)*	*8 ± 2*	*-0.33 ± 0.72 (1)*	*0.8 (0.24)*	*2 (5)*
Digit span backward (nb)	8 ± 2	-0.03 ± 0.81 (0)	7 ± 2	-0.30 ± 0.75 (1)	0.4 (0.8)	1 (2)
Digit span reorganization (nb)	8 ± 2	0.13 ± 0.92 (0)	7 ± 2	-0.33 ± 0.91 (1)	0.3 (0.98)	1 (2)
Short-term / working visual memory						
Visual span forward (nb)	*9 ± 2*	*0.33 ± 1.06 (1)*	*7 ± 2*	*-0.64 ± 0.98 (3)*	*0.02 (2.41) **	*4 (10)*
Visual span backward (nb)	7 ± 2	0.15 ± 0.75 (1)	6 ± 2	-0.28 ± 0.93 (0)	0.09 (1.66)	1 (2)
Long-term verbal memory						
CVLT learning	*55 ± 13*	*0.36 ± 1.25 (4)*	*47 ± 14*	*-0.9 ± 1.49 (2)*	*0.009 (2.6) ***	*6 (14)*
CVLT long-term free recall	*12 ± 4*	*0.15 ± 1.2 (2)*	*8 ± 4*	*-1.48 ± 1.66 (6)*	*0.003 (2.92) ***	*8 (19)*
Long-term visual memory						
Doors A (n correct)	*11 ± 1*	*0.35 ± 1.06 (1)*	*9 ± 2*	*-1.22 ± 1.07 (6)*	*<0.001 (3.5) ***	*7 (17)*
Doors B (n correct)	8 ± 3	0.31 ± 1.19 (2)	7 ± 2	-0.6 ± 0.83 (1)	0.02 (2.27) *	3 (7)
Executive functions						
Phonemic verbal fluency (n)	18 ± 7	-0.33 ± 1.06 (3)	17 ± 6	-0.45 ± 1.18 (3)	0.7 (0.39)	6 (14)
Semantic verbal fluency (n)	25 ± 7	-0.48 ± 0.82 (4)	24 ± 6	-0.82 ± 0.95 (2)	0.4 (0.84)	6 (14)
Generation	*N/A*	*-0.41 ± 0.84 (1)*	*N/A*	*-0.64 ± 0.91 (2)*	*0.48 (0.71)*	*3 (7)*
Trail Making test A (s)	43 ± 22	0.3 ± 0.58 (0)	46 ± 10	-0.07 ± 0.59 (0)	0.07 (1.82)	0 (0)
Trail Making test B (s)	116 ± 71	0.12 ± 0.81 (1)	121 ± 52	-0.38 ± 1.01 (2)	0.2 (1.36)	3 (7)
Trail Making test B-A (s)	73 ± 53	-0.04 ± 0.84 (1)	75 ± 54	-0.45 ± 1.15 (3)	0.4 (0.93)	4 (10)
Stroop naming (s)	75 ± 20	-0.59 ± 1.18 (4)	94 ± 40	-1.91 ± 2.3 (6)	0.05 (1.92)	10 (24)

Stroop reading (s)	49 ± 9	-0.52 ± 1.14 (6)	59 ± 14	-1.64 ± 1.65 (6)	0.04 (2.06) *	12 (29)
Stroop interference (s)	151 ± 59	-0.65 ± 1.58 (4)	164 ± 54	-1.27 ± 1.8 (4)	0.2 (1.21)	8 (19)
Inhibition	*76 ± 45*	*-0.56 ± 1.52 (5)*	*69 ± 47*	*-0.36 ± 1.78 (2)*	*0.6 (-0.49)*	*7 (17)*
Initiation	*N/A*	*-0.27 ± 0.85 (2)*	*N/A*	*-1.21 ± 1.29 (6)*	*0.03 (2.19) **	*8 (19)*
Productivity (n)	*27 ± 11*	*-0.23 ± 1.06 (2)*	*24 ± 8*	*-0.55 ± 0.88 (1)*	*0.5 (0.63)*	*3 (7)*
FAB total	16 ± 2 (5)	N/A	16 ± 2 (2)	N/A	0.6 (0.59)	7 (17)
Attention						
Symbol-digit subtest, n	*49 ± 16*	*-0.59 ± 0.85 (5)*	*42 ± 14*	*-1.25 ± 0.88 (4)*	*0.03 (2.14) **	*9 (21)*
TAP reactivity: no signal, ms §	*263 ± 51*	*-0.41 ± 0.94 (1)*	*290 ± 95*	*-0.65 ± 0.97 (1)*	*0.6 (-0.53)*	*2 (5)*
TAP reactivity: signal, ms §	260 ± 43	-0.62 ± 0.75 (2)	279 ± 91	-0.66 ± 0.95 (1)	0.8 (-0.21)	3(7)
TAP div. attention: auditive, ms §	649 ± 113	-0.92 ± 1.01 (6)	653 ± 162	-0.88 ± 1.06 (3)	0.9 (0.09)	9 (21)
TAP div. attention: visual, ms §	*881 ± 168*	*-0.19 ± 1.04 (2)*	*993 ± 224*	*-0.86 ± 0.91 (2)*	*0.05 (-1.96) **	*4 (10)*
TAP div. attention: omissions, n §	3.6 ± 3.7	-0.64 ± 0.99 (5)	5.9 ± 3.8	-1.38 ± 1 (7)	0.02 (-2.25) *	12 (29)
GCI index, n	*1.2 ± 1.8 (4)*	*N/A*	*2.8 ± 1.5 (7)*	*N/A*	*0.001 (-3.21) **	*11 (26)*

Raw scores (mean ± std), z scores (mean ± std) and number of patients impaired (n), p value (Z value) of Wilcoxon signed rank test. A given test was considered as impaired when z score <= -1.65 std, or according to each test's provided cut-off when no z score was available (i.e. FAB < 15/18; Figures recognition < 15/15; Celebrities identification < 7/8; Gestual praxia < 9/12). Statistics were performed on normalized z scores or on raw scores when z scores not available. *CVLT* California Verbal Learning Task, *FAB* Frontal Assessment Battery, *GCI* global cognitive impairment (number of cognitive domains impaired from the reduced battery, max = 13), *TAP* Test of Attentional Performance. * $p < 0.05$; ** $p < 0.01$. Scores in italic are displayed in Fig. 2.

§ Not all patients performed these tests: 'Metaphor recognition': 25/30 patients in the "complete recovery" group, 8/12 in the "incomplete recovery" group (test was included late to the protocol); 'TAP reactivity': 29/30 patients in the "complete recovery" group (one patient was tested at home with no TAP available); 'TAP divided attention': 28/30 patients in the "complete recovery" group (one patient was tested at home with no TAP available and one was unable to perform the test even after several training trials).

[a] Raw scores not presented because two versions were used depending on patient's age (< 60 years: standard version with 80 items; > 60 years: reduced version with 64 items).

Scores description

Language

- Naming subtest, Lexis battery [1].
- Metaphor interpretation subtest, Protocole Montréal d'Evaluation de la Communication (MEC) [2].

Gnosia

- Figure recognition subtest, Batterie d'Evaluation de la Négligence unilatérale (BEN) [3].
- Celebrities identification (home test consisting in identification and denomination of eight famous national and international personalities).

Praxia

- Constructive praxia, Praxis subtest, CERAD battery [4].
- Gestual praxia, Apraxia Screen of TULIA (AST) [5].

Short-term and working verbal memory

- Digit span forward, French version of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) [6].
- Digit span backward, French version of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) [6].
- Digit span ascending, French version of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) [6].

Short-term and working visual memory

- Block tapping forward, French version of the Wechsler Memory Scale, third edition (MEM III) [7].
- Block tapping backward, French version of the Wechsler Memory Scale, third edition (MEM III) [7].

Long-term verbal memory

- Learning score, French version of the California Verbal Learning Test (CVLT) [8].
- Long-term free recall score, French version of the California Verbal Learning Test (CVLT) [8].

Long-term visual memory

- Doors A subtest, Doors and People test [9].
- Doors B subtest, Doors and People test [9].

Executive functions

- Semantic verbal fluency (GREFEX battery) [10].
- Phonemic verbal fluency (GREFEX battery) [10].
    - Generation: average z scores of semantic and phonemic verbal fluency
- Trail Making Test (GREFEX battery) [10].
- Stroop test (GREFEX battery) [10].
    - Initiation: average z scores of Trail Making Test part A, Stroop reading and Stroop naming
    - Inhibition: subtraction of Stroop interference from Stroop naming times
- Productivity score, Five-points test [11].
- Frontal Assessment Battery (FAB) [12].

Attention

- Digit-symbol subtest, French version of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) [6].
- Alert subtest, Test battery for Attentional Performance (TAP) [13].
- Divided Attention subtest, Test battery for Attentional Performance (TAP) [13].

Global cognitive impairment index

- Individual number of tests impaired for each patient on the 13 cognitive domains (tests in italics).

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