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1 **TITLE PAGE**

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

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5  
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**1 ABSTRACT**

2

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

5 *Design:* Longitudinal cohort study.

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

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

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

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

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

1 measures.

## 1 INTRODUCTION

2

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

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

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

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

3

4

## 1 MATERIAL AND METHODS

2

### 3 Study design and population

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

14

### 15 Subjective and objective functional outcome assessment

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

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

10

### 11 **Cognitive outcome assessment**

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



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

6

### 7 **Comparing subjective vs. objective recovery**

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

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

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

21

## 1 RESULTS

2

### 3 Population

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

8 Main reasons for non-inclusion were patient's refusal ( $n = 7$ ), severe pre-existing neurologic or  
9 psychiatric comorbidities ( $n = 5$ ), and patients living too far from the assessment center or being  
10 otherwise impossible to reach ( $n = 4$ ). The 17 non-included survivors (59 (48–78) years old, 5  
11 women (29%)) did not differ in demographics, but exhibited worse CPC at 3 months (2 (1-3) vs.  
12 1 (1-2);  $Z = 2.32, p = 0.02$ ).

13

### 14 Functional outcome

15 At 6 months follow-up, all but one patient had returned home . Subjective measures showed that  
16 35 (70%) reported a satisfactory recovery, 14 (29%) with no complaint. Objective measures  
17 classified 38 (76%) as CPC 1, 13 (26%) as mRS 0, and 19 (38%) as GOSE 1 (see Fig. 2).  
18 Subjective and objective outcome measures were strongly and positively correlated (CPC and  
19 subjective recovery:  $r_s = 0.56, p < 0.001$ ; mRS and complaints severity:  $r_s = 0.53, p < 0.001$ ; see  
20 Fig. 2). Performances of subjective recovery in identifying patients with objective good  
21 outcomes (CPC 1) were: sensitivity 0.84 (95% CI: 0.73–0.96), specificity 0.75 (95% CI: 0.51–  
22 0.99), positive predictive value (PPV) 0.91 (95%CI: 0.82-1.00).

1 Fatigue was the most frequently reported complaint (35/49 patients (one patient was unable to  
2 respond); 71%), followed by change in behavior or emotion (25; 51%), slowing (24; 49%),  
3 attention (18; 37%), memory (17; 35%), language (12; 24%). Gnosia or praxia impairment were  
4 rare (1; 2%). The majority of patients were independent for daily activities (IADL > 6 points:  
5 42/50; 84%); 16/26 (61%) were able to resume working and 29/40 (73%) could resume driving.  
6 Five patients (10%) showed signs of anxiety and 3 (6%) of depression (HAD). Overall quality of  
7 life satisfaction was  $75 \pm 17\%$ .

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

14

### 15 **Cognitive outcome**

16 Forty-two patients (30 “satisfactory recovery”, 12 “unsatisfactory recovery”) underwent  
17 neuropsychological examination (seven refused to participate, one was too severely impaired;  
18 CPC at 6 months: 1.5 (1-2) vs. 1 (1-2) in the participating group;  $Z = 1.98$ ,  $p = 0.05$ ). Domains  
19 most frequently impaired were processing speed (9 patients impaired; 21%), language (9; 21%),  
20 long-term memory (8; 19%) and initiation (8; 19%). In contrast, domains most often preserved  
21 were short-term verbal memory (2 patients impaired; 5%), reaction times (2; 5%), generation (3;  
22 7%) and productivity (3; 7%) (see Suppl. Doc 2). Overall, patients had 1 (0–3) impaired  
23 cognitive domains (GCI) and 11 (26%) were considered to have substantial impairment.

1 Patients with “unsatisfactory recovery” showed significantly worse performance in 7 out of the  
2 13 (54%) cognitive dimensions considered: learning, verbal and visual long-term memory, short-  
3 term visual memory, initiation, processing speed, and divided attention (see Fig. 3, Suppl. Doc  
4 2). GCI was also significantly higher in the group “unsatisfactory recovery” (3 (2–4.5) impaired  
5 domains) vs. “satisfactory recovery” (1 (0–3) impaired domains;  $Z = -3.21$ ,  $p < 0.001$ ) with  
6 respectively 7 patients (58%) and 4 (13%) having substantial cognitive impairment.  
7 Finally, objective measures of cognitive performance correlated strongly and positively with  
8 subjectively perceived cognitive status (GCI and complaint severity:  $r_S = 0.64$ ,  $p < 0.001$ ).

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11

## 1 DISCUSSION

2

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

14

15 As a whole, our sample of CA survivors experienced good overall long-term outcomes,  
16 consistent with previous literature reporting CPC 1 in 84% (8) and complete subjective mental  
17 recovery in 62 to 66% (12). However, as highlighted in previous reports (4), detailed evaluation  
18 tempers these proportions: our patients had frequent complaints, especially concerning fatigue  
19 (71%) and being unable to go back to work (39%). In contrast, quality of life satisfaction was  
20 high (75%, similar to 76% previously reported at a more distant follow-up time (32)) and anxiety  
21 and depressive symptoms were rare (10% and 6% respectively, similar to the findings of 11%  
22 and 7% in (13)). Detailed neuropsychological evaluation detected substantial cognitive  
23 impairment in 26% of survivors, higher than the 13% at 3 months or 11% at one year reported in

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

6  
7 Long-term memory complaints have been previously associated with general physical and  
8 mental health (33), while the only study directly testing the association between subjective and  
9 objective measures reported null results (15), using a complex questionnaire (34) to assess  
10 subjective outcome, rendering comparison with our binary measure difficult. Our subjective  
11 recovery measure seems more similar to item 2 of the Two Simple Questions (35): “Do you feel  
12 that you have made a complete mental recovery after your heart arrest?”, leading to a similar  
13 proportion of patients reporting complete recovery (12), and an association with anxiety and  
14 depression symptoms (13).

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

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

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**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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2

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2

1 **FIGURES LEGENDS**

2

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

7

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

16

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

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

3

4

1 **SUPPLEMENTARY DATA**

2

3

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

5

6 **Table 1:** Results of all neuropsychological tests.

7

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

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11



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

<b>Clinical tests</b>	<b>Survivors reporting satisfactory recovery (n = 35)</b>	<b>Survivors reporting unsatisfactory recovery (n = 15)</b>	<b>p value (Z value)</b>	<b>All patients (n=50)</b>
<b>Socio-demographics</b>				
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)
<b>Cardiac arrest variables</b>				
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.

<b>Functional measure</b>	<b>Survivors reporting satisfactory recovery (n = 35)</b>	<b>Survivors reporting unsatisfactory recovery (n = 15)</b>	<b>p value (Z value)</b>	<b>All survivors (n=50)</b>
<b>Global scales, median (IQR)</b>				
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)
<b>Quality of life, median (IQR)</b>				
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)
<b>Domain of complaints, n (%)</b>				
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)
<b>Mood disorders, median (IQR)</b>				
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
<b>Daily living</b>				
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). \*  $p < 0.05$ ; \*\*  $p < 0.01$ .  
<sup>§</sup>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).

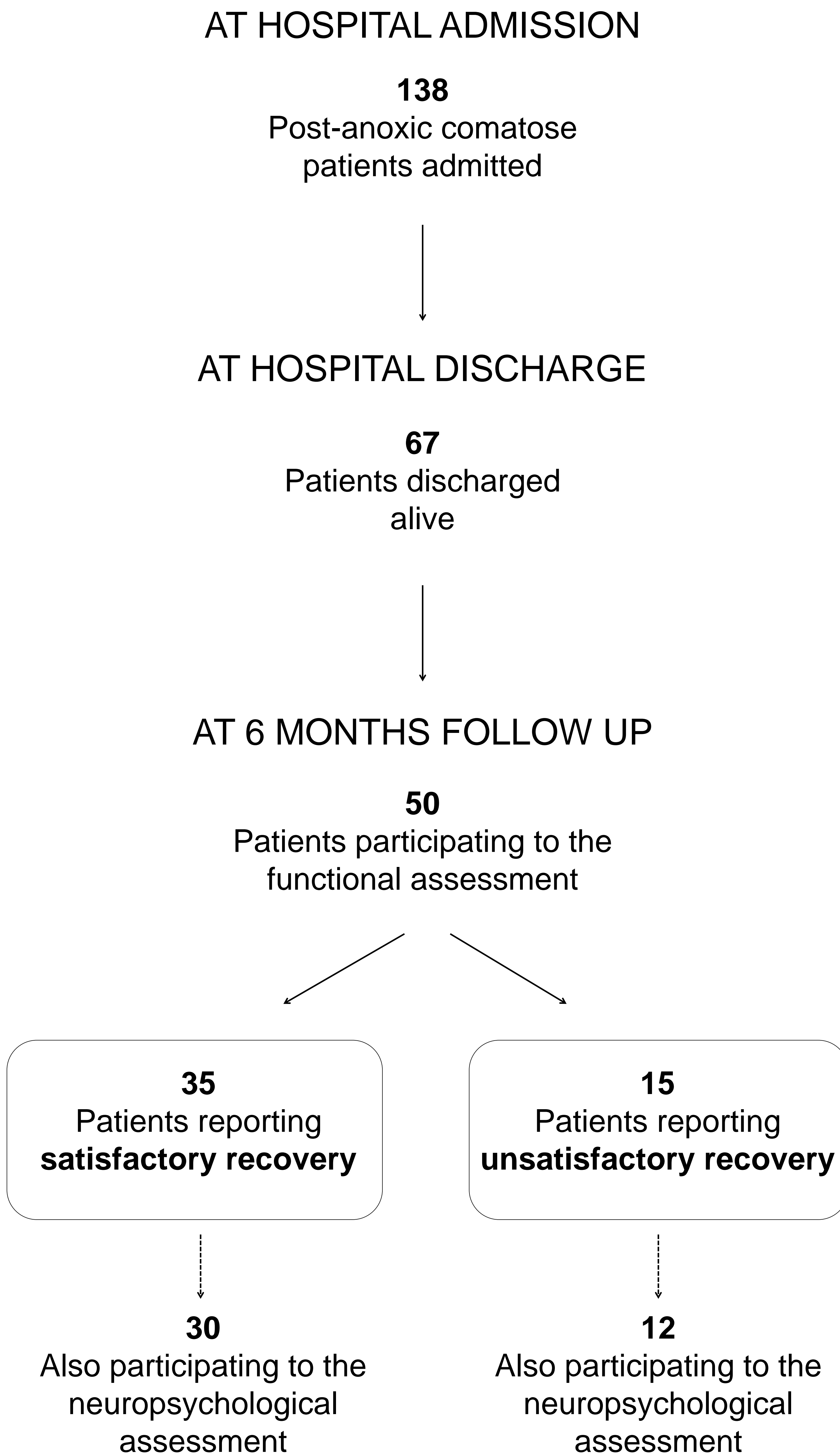
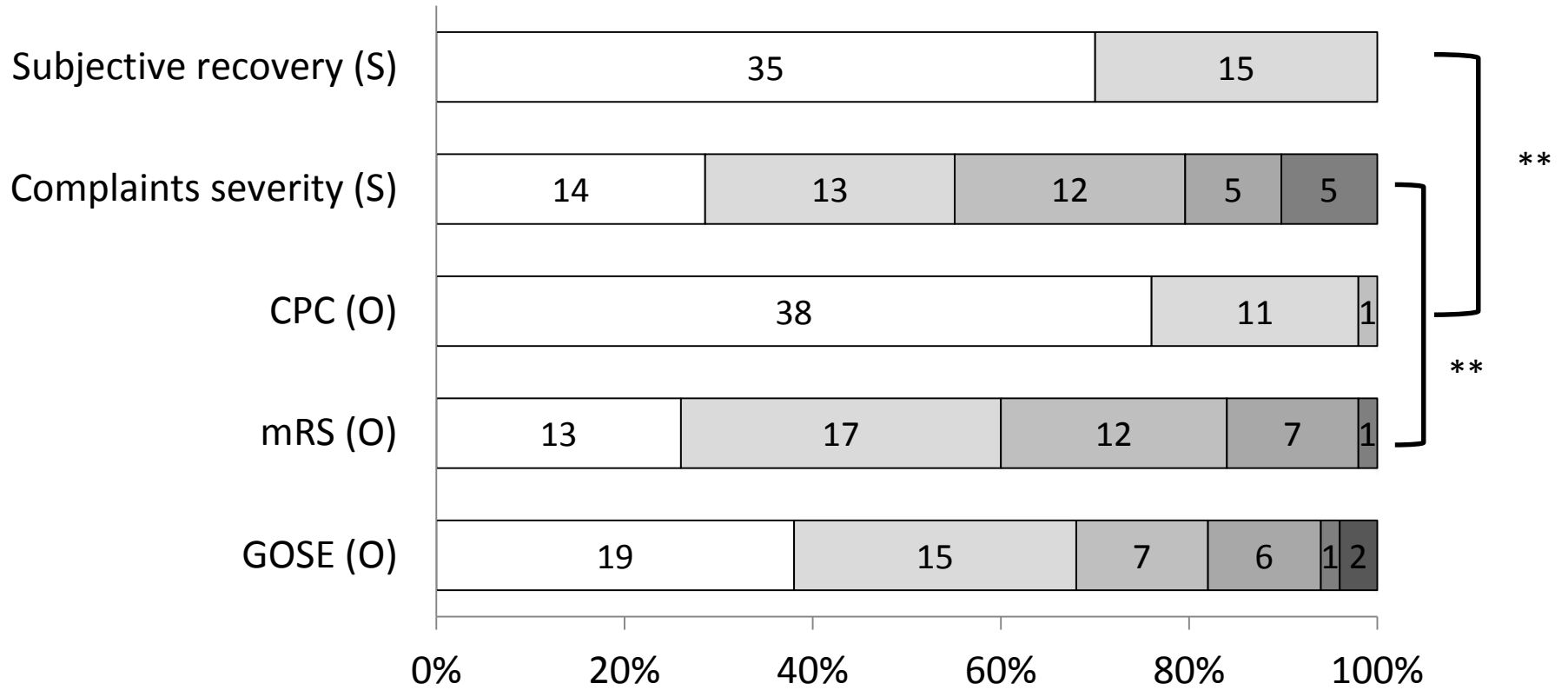
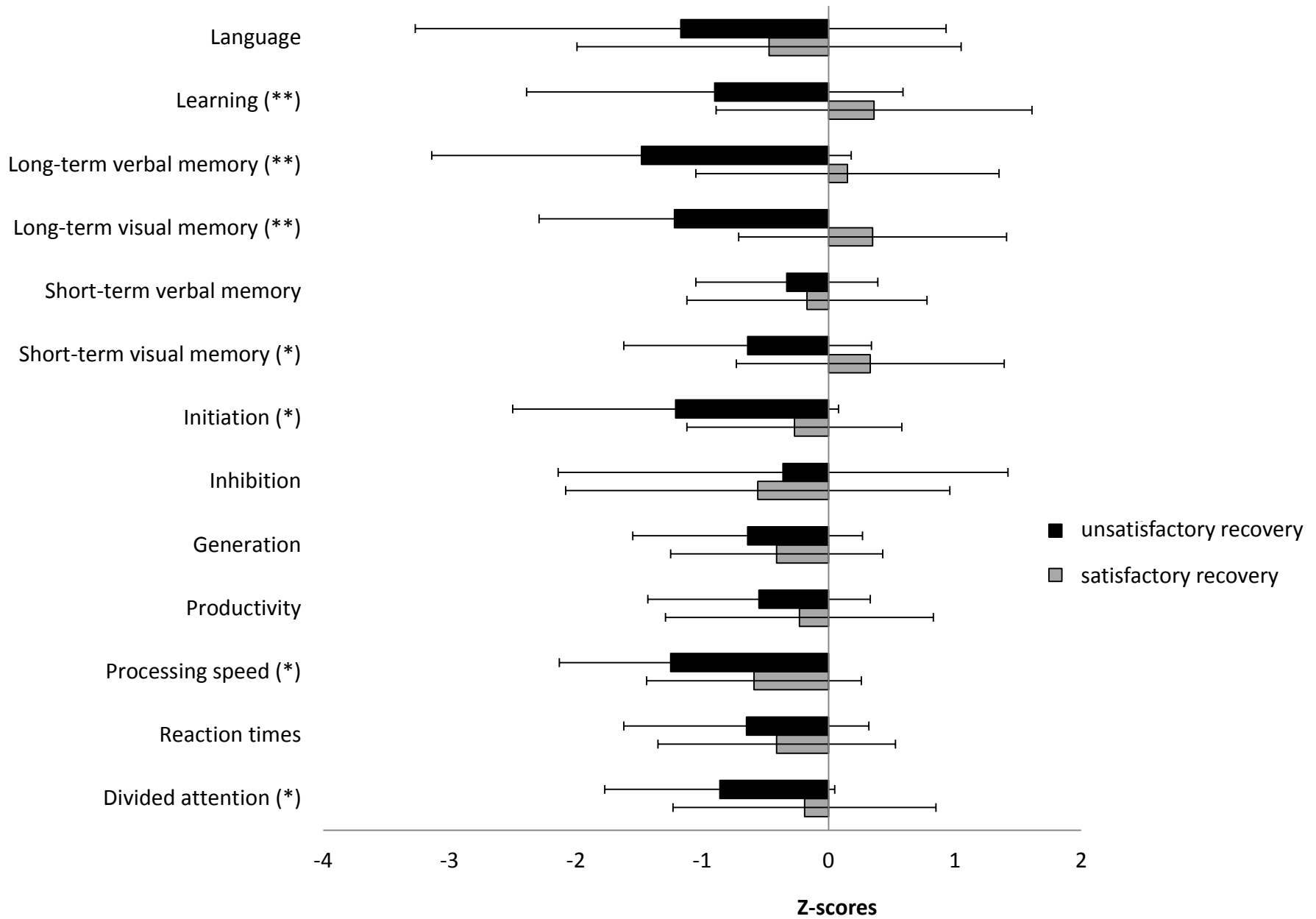


Figure 2



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

Figure 3



## **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:  $24 \pm 15$   $\mu\text{g/ml}$ ) with one outlier above 75  $\mu\text{g/ml}$  (3). Evolution of auditory discrimination was available for a subset of 42 patients and

showed progression in 18 (43%). On average, patients spent  $6 \pm 4$  days in coma and a total of  $19 \pm 16$  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.

<b>Clinical tests</b>	<b>Survivors reporting satisfactory recovery (n = 35)</b>	<b>Survivors reporting unsatisfactory recovery (n = 15)</b>	<b>p value (Z value)</b>
<b>Investigations during coma, n (%)</b>			
Early myoclonus present	1 (3)	0 (0)	1
Brainstem reflexes absent <sup>a</sup>	4 (11)	2 (13)	1
GCS motor response [1-2] <sup>b</sup>	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 <sup>c</sup>	1/31 (3)	1/13 (8)	0.5
Non reactive EEG on Day 2 <sup>c</sup>	0 (0)	0 (0)	1
Progression of auditory discrimination	13/29 (45)	5/13 (38)	0.7
<b>Hospital outcome, median (IQR)</b>			
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.

<sup>a</sup> pupillary, oculocephalic, corneal; all present vs. one or more absent

<sup>b</sup> flexion posturing or better vs. extension or no response

<sup>c</sup> 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)		
	<b>Language</b>					
Naming <sup>a</sup>	N/A	-0.47 ± 1.52 (7)	N/A	-1.17 ± 2.1 (2)	0.3 (1.03)	9 (21)
Metaphor interpretation <sup>§</sup>	35 ± 3	-0.37 ± 1 (5)	34 ± 2.5	-0.72 ± 1.66 (2)	0.7 (-0.42)	7/25 (28)
<b>Gnosia</b>						
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)
<b>Praxia</b>						
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)
<b>Short-term / working verbal memory</b>						
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)
<b>Short-term / working visual memory</b>						
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)
<b>Long-term verbal memory</b>						
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)
<b>Long-term visual memory</b>						
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)
<b>Executive functions</b>						
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)
<i>Inhibition</i>	<i>76 ± 45</i>	<i>-0.56 ± 1.52 (5)</i>	<i>69 ± 47</i>	<i>-0.36 ± 1.78 (2)</i>	<i>0.6 (-0.49)</i>	<i>7 (17)</i>
<i>Initiation</i>	<i>N/A</i>	<i>-0.27 ± 0.85 (2)</i>	<i>N/A</i>	<i>-1.21 ± 1.29 (6)</i>	<i>0.03 (2.19) *</i>	<i>8 (19)</i>
<i>Productivity (n)</i>	<i>27 ± 11</i>	<i>-0.23 ± 1.06 (2)</i>	<i>24 ± 8</i>	<i>-0.55 ± 0.88 (1)</i>	<i>0.5 (0.63)</i>	<i>3 (7)</i>
FAB total	16 ± 2 (5)	N/A	16 ± 2 (2)	N/A	0.6 (0.59)	7 (17)
<b>Attention</b>						
<i>Symbol-digit subtest, n</i>	<i>49 ± 16</i>	<i>-0.59 ± 0.85 (5)</i>	<i>42 ± 14</i>	<i>-1.25 ± 0.88 (4)</i>	<i>0.03 (2.14) *</i>	<i>9 (21)</i>
<i>TAP reactivity: no signal, ms §</i>	<i>263 ± 51</i>	<i>-0.41 ± 0.94 (1)</i>	<i>290 ± 95</i>	<i>-0.65 ± 0.97 (1)</i>	<i>0.6 (-0.53)</i>	<i>2 (5)</i>
<i>TAP reactivity: signal, ms §</i>	<i>260 ± 43</i>	<i>-0.62 ± 0.75 (2)</i>	<i>279 ± 91</i>	<i>-0.66 ± 0.95 (1)</i>	<i>0.8 (-0.21)</i>	<i>3(7)</i>
<i>TAP div. attention: auditive, ms §</i>	<i>649 ± 113</i>	<i>-0.92 ± 1.01 (6)</i>	<i>653 ± 162</i>	<i>-0.88 ± 1.06 (3)</i>	<i>0.9 (0.09)</i>	<i>9 (21)</i>
<i>TAP div. attention: visual, ms §</i>	<i>881 ± 168</i>	<i>-0.19 ± 1.04 (2)</i>	<i>993 ± 224</i>	<i>-0.86 ± 0.91 (2)</i>	<i>0.05 (-1.96) *</i>	<i>4 (10)</i>
<i>TAP div. attention: omissions, n §</i>	<i>3.6 ± 3.7</i>	<i>-0.64 ± 0.99 (5)</i>	<i>5.9 ± 3.8</i>	<i>-1.38 ± 1 (7)</i>	<i>0.02 (-2.25) *</i>	<i>12 (29)</i>
<i>GCI index, n</i>	<i>1.2 ± 1.8 (4)</i>	<i>N/A</i>	<i>2.8 ± 1.5 (7)</i>	<i>N/A</i>	<i>0.001 (-3.21) **</i>	<i>11 (26)</i>

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.

<sup>§</sup> 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).

<sup>a</sup> 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'Évaluation de la Communication (MEC) [2].

### **Gnosia**

- Figure recognition subtest, Batterie d'Évaluation 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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