

## **Fast and Slow Recovery Following Acute Ischemic Stroke**

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***DEDICATION:***

To all those who awake each day to lead momentous lives despite the illnesses they face. Their courage, passion, and strength fuel my commitment to the pursuit of knowledge.

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**ABSTRACT:**

**OBJECTIVE:** To investigate the variability in early recovery after hemiparetic stroke.

**BACKGROUND:** Prior work suggests that most hemiparetic patients recover approximately 70% of their initial impairment by 3-months, but the speed of the recovery is unknown.

**METHODS:** We assessed 30 patients with first-ever hemiparetic stroke using the Fugl-Meyer upper extremity score (max score=66) at 24-72 hours ( $FM_{init}$ ), 1-week ( $FM_{1wk}$ ), and 3-months ( $FM_{3mo}$ ). Patients who did not demonstrate proportional recovery ( $0.70 \times$  initial impairment) were excluded from analysis. The distribution of recovery at 7-days among the proportional recoverers was characterized and contrasted with recovery at 90-days using the Shapiro-Wilk test for normality and Sarle's binomial coefficient. Cluster analysis was then used to assess the distribution of recovery rates at 7-days. Tests of differences and association were performed to assess if the early recovery-rate groups differed significantly in clinical and demographic characteristics.

**RESULTS:** Twenty-six of the 30 initial patients were identified as proportional recoverers, the other 4 were non-recoverers at 90-days. Among the proportional recoverers, there was a bimodal distribution of recovery at 7-days. Cluster analysis identified patients who achieved virtually all of their total recovery at 7-days ( $n=13$ , percent recovery= $0.89 \pm 0.19$ ; 95%CI:0.79-1.00) and patients who achieved virtually none their total recovery at 7-days ( $n=13$ , percent recovery= $-0.23 \pm 0.77$ , 95%CI:-0.65-0.19), but went on to achieve the expected recovery at 90 days. Initial stroke severity was the only characteristic that showed a statistically significant correlation with early recovery group membership.

**SIGNIFICANCE:** Patients who demonstrate proportional recovery over the first 3-months fall into 2 distinct early recovery groups, either achieving approximately 90% of their total recovery by 1-week or making little or no recovery early, and only later achieving their total expected recovery. Implications for treatment planning are profound.

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**INTRODUCTION:**

Stroke is the fourth most common cause of death and the leading cause of serious, long-term disability among adults.<sup>1-3</sup> Though many stroke survivors regain functional independence, 15% to 30% are left permanently disabled, with hemiparesis being the most common disability. As a result, there has been an increasing effort to characterize motor recovery after stroke, including the ability to accurately predict the extent and time table of recovery, with the goals of more targeted rehabilitation interventions, and more efficient resource allocation. Observational studies of motor recovery suggest that the best predictor of prognosis is the initial severity of hemiparesis, as measured by impairment or disability scales.<sup>4-12</sup> Previous work done by this lab group has supported this finding, and introduced the concept of “proportional recovery,” in which most patient outcomes at 3-months after stroke can be predicted as a proportion (approximately 70%) of initial motor deficit.<sup>11</sup> There has been little information, however, about how fast the recovery occurs among those who are destined to recover. In this retrospective study, we sought to characterize the variability in early stroke recovery to help determine whether distinct recovery-rate groups could be identified.

## ***SUBJECTS AND METHODS:***

### *Performance and Recovery in Stroke (PARIS) Registry:*

As described in previous publications, the PARIS registry is a prospective, natural history examination of neurological deficits following first-time ischemic stroke. The PARIS database comprises patients who presented to Columbia University Medical Center between May 2002 and May 2008 with a new motor or language deficit and MRI diffusion-weighted image (DWI) positive for ischemia. Those with prior clinical stroke or other known neurological disease were excluded. This study was approved by the Columbia University Institutional Review Board.

All patients for the current analysis were consented and enrolled within 72-hours after symptom onset. Demographic information, past medical history, medications and vascular risk factors were collected through patient interview and the electronic medical record. Baseline examination, performed between 24-72 hours after stroke onset, included a neurologic examination, assessment with the National Institute of Health Stroke Scale (NIHSS), manual motor testing (hand dynamometry and Nine-Hole Peg Test), and the Fugl-Meyer Upper Extremity Motor Exam (FM<sub>Init</sub>). All enrolled patients were expected to have follow-up exams at 1-week (FM<sub>1wk</sub>) and 3-months (FM<sub>3Mo</sub>) post-stroke, at which time the same neurological battery was administered. Radiographic data on infarct topography and volume were also obtained at initial screening. Lesion volume was calculated via a semi-automated cylindrical estimate using the NIH freeware Medical Imaging Processing Analysis and Visualization (MIPAV) program.<sup>13</sup> Lesion location was described as involving subcortical structures, cortical structures, or both. Based on the history and clinical evaluation by the attending neurologist, stroke etiology was assigned to one of four subtypes, as depicted by the TOAST criteria.<sup>14</sup>

### *Subjects:*

From the overall cohort of 118 PARIS-enrolled patients, 30 fulfilled the inclusion criteria for this study: (1) first-ever, unilateral hemiparetic stroke; (2) motor deficit within 24-72 hours of symptom onset (mean =2.3 days, SD =1.0) as measured by the Fugl-Meyer Upper Extremity Motor Exam (max score=66); and (3) had follow-up FM impairment assessments at

approximately 7 days (mean=7.1 days, SD=1.4) and 3 months (mean=68.7 days, SD =20.3) after onset. Proportional recoverers were defined as those who had regained approximately 70% of their initial motor deficit on the Fugl-Meyer upper extremity scale (maximum 66 points) at 3 months (i.e.:  $\text{Recovery}_{3\text{mo}} = \text{FM}_{3\text{mo}} - \text{FM}_{\text{init}} = (0.70) * (66 - \text{FM}_{\text{init}})$ ). Studentized deleted residuals were calculated for all study patients (N=30) using the above linear model. Those patients whose residual values had a two-tailed  $p$ -value of less than 0.05 (corresponding with  $|t(27)| > 2.05$ ) were identified as non-recoverers, and excluded from further analysis. To insure that the recovery of the remaining patients was consistent with proportional recovery model, the Pearson correlation coefficient of patients' actual vs. predicted 3-month recovery was measured. Each patient in this study received standard bedside physical (PT) and occupational therapy (OT) (approximately 30 minutes of each per day) while on the inpatient acute stroke service. Patients were then discharged to inpatient rehabilitation or home, with outpatient PT and OT as deemed clinically appropriate.

#### *Analysis:*

Among the cohort of proportional recoverers, the variability in recovery at 7-days was characterized and contrasted with the variability in recovery at 90 days. Recovery was defined as the proportion of initial impairment, measured by the FM exam, that was recovered at a given end point following stroke onset:  $\text{Recovery at X-Days} = (\text{FM}_{\text{X-days}} - \text{FM}_{\text{init}}) / (66 - \text{FM}_{\text{init}})$ . The following methods were used to characterize the variability and modality of the distribution in patient recovery at 7-days: (1) a histogram of patient recovery at 7-days was plotted and inspected; (2) the standard deviation and Sarle's bimodality coefficient of the recovery distribution at 7-days were evaluated, and compared to the corresponding statistics for the recovery distribution at 90-days<sup>15</sup>; (3) the Shapiro –Wilk test for normality was used to assess if recovery was normally distributed at 7- and 90-days.

Once visual inspection and the above statistical methods established that the distribution of patient recovery at 7-days was multimodal, hierarchical clustering, using Ward's minimum variance method with squared Euclidian distances, was applied to impute the optimal number of distinct, early recovery rate groups.<sup>16</sup> This hierarchical clustering was applied to

patients' "7-day recovery rate," a metric assessing the % of total recovery (i.e. at 90 days) achieved by patients at day 7. K-means clustering analysis was used to identify the modality of the distribution in percent recovery and assign patients to recovery groups.<sup>17</sup> This clustering algorithm was applied to patients' 7-day recovery rates after transforming these values to allow for minimum and maximum rates of 0% and 100% respectively. Subsequent analysis was performed to assess if these groups demonstrated statistically significant differences in clinical and demographic characteristics. T-tests were used to measure the significance of group differences in the means of continuous variables: Student's t-tests with pooled variances were used when F-tests of the non-equivalence of group variances were not statistically significant; Welch-Satterthwaite t-tests were used when the group variances were shown to be statistically significant.<sup>18</sup> Pearson and Yates' continuity-adjusted chi-squared and Fisher exact tests were used to test the significance of the association of categorical variables with the recovery groups. The Fisher's exact test was used when over 20% of the expected contingency table cell values were less than 5<sup>19</sup>.

## **RESULTS:**

Among the 30 patients who satisfied the inclusion criteria, four patients demonstrated impairment changes that were not consistent with proportional recovery. As shown in Figure 1, the Studentized residual values for these four patients exceeded the critical value of  $|t(27)|=2.05$  and, thus, had associated  $p$ -values of less than 0.05. These patients, identified as non-recoverers, were excluded from subsequent analysis. As shown in Figure 2, these non-recoverers had severe deficits at onset and made little to no recovery by 3 months. Of note, there were other patients with severe deficits at onset whose impairments *did* follow proportional recovery. The patient demographics and clinical characteristics of the resulting, final cohort (N=26) are described in Table 1.

With the non-recoverers removed, a large positive Pearson correlation coefficient ( $R=0.96$ ;  $R^2=0.93$ ) was found between observed 3-month recovery and the 3-month recovery predicted by the proportional recovery model, indicating that this subset of the overall patient cohort followed the proportional recovery rule for 3-month recovery. Inspection of the recovery distribution at 7-days (Figure 3), strongly suggested that early recovery, unlike recovery at 90 days, is bimodally distributed among proportional recoverers. A substantial number of patients showed nearly all of their total recovery at 7 days, and another large number showed almost no recovery at 7 days, despite their eventual recovery to the expected 70% at 90 days. The non-normality of this recovery distribution was statistically validated by the Shapiro-Wilk test for non-normality ( $P<.001$ ). Furthermore, the large value of Sarle's bimodality coefficient for this distribution ( $\beta=0.565$ ) suggested that the distribution is multi-modal. By contrast, the distribution of recovery at 90 days appears normally distributed (Shapiro-Wilk test,  $P=.089$ ; bimodality coefficient,  $\beta=0.364$ ) with much smaller variability ( $\sigma_{90 \text{ day}}=0.16$  vs.  $\sigma_{7 \text{ day}}=0.72$ ). Hierarchical clustering of patients' "7-day recovery rate" using Ward's minimum variance method revealed that there were 2 distinct early recovery rate groups. K-means cluster analysis empirically assigned patients to one of these two distinct groups, with markedly different 7-day mean recoveries: those who achieved  $\geq 50\%$  of their impairment at one week (termed "fast recoverers,"  $n=13$ ), and those who achieved  $<50\%$  of their impairment (termed "slow recoverers,"  $n=13$ ). It should be emphasized that all patients in this cohort were

Figure 1. Studentized residual values for proportional recoverers and non-recoverers

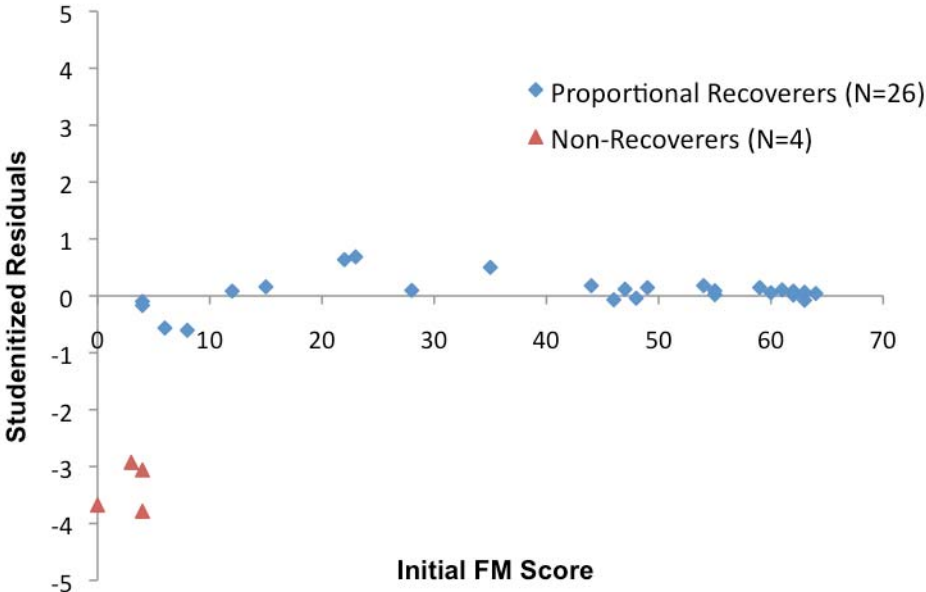


Figure 2. Observed vs. Predicted Recovery at 3-months

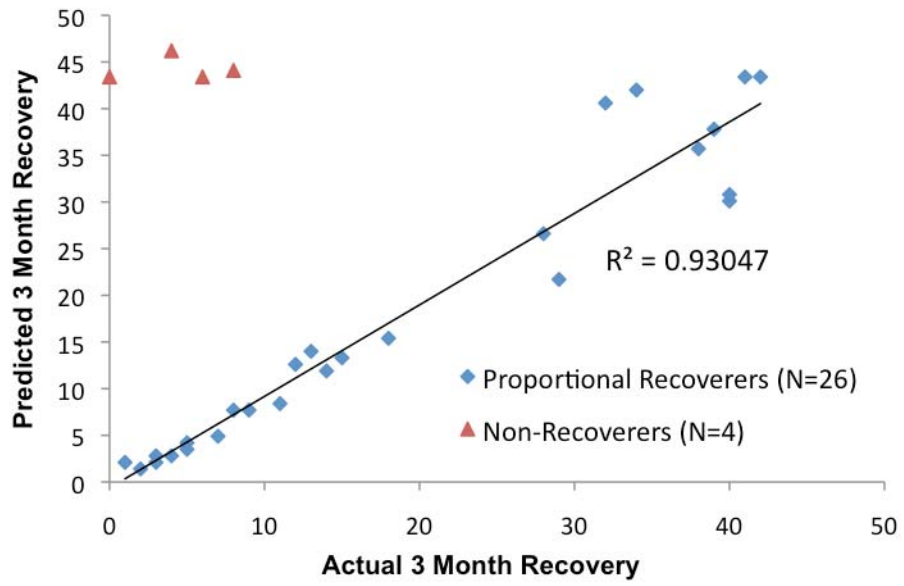


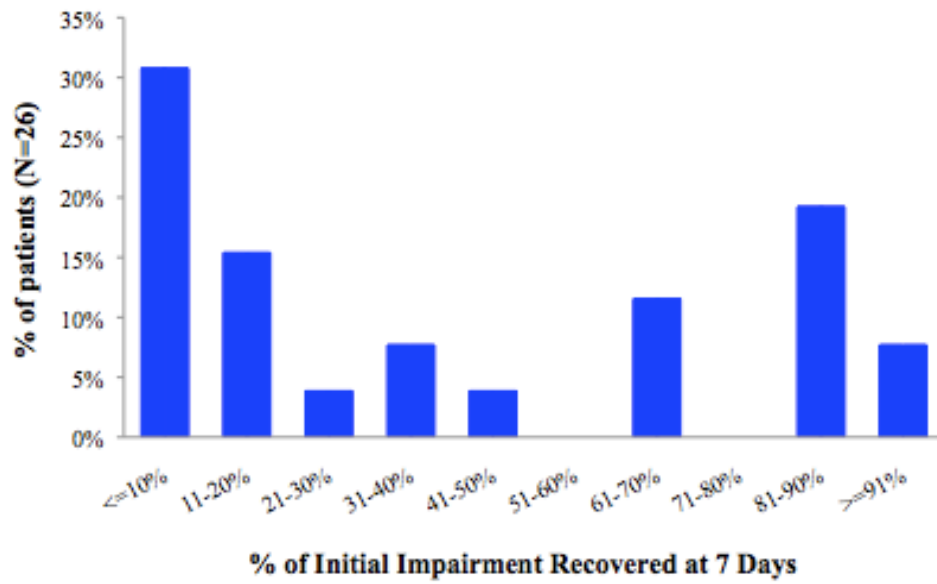
Table 1. Demographics and clinical characteristics

(N=26)		
Age, y	Mean (SD)	63.0 (10.9)
	Median	64.5
Male, n (%)		22 (84.6)
Race, n (%)		
	White	3 (11.5)
	Black	9 (34.6)
	Hispanic	10 (38.5)
	Asian	1 (3.8)
	Other	3 (11.5)
Hypertension, n (%)		20 (76.9)
Diabetes, n (%)		9 (34.6)
Dyslipidemia, n (%)		10 (38.5)
Atrial Fibrillation, n (%)		4 (15.4)
Smoking, n (%)		7 (26.9)
Thrombolytic treatment, n (%)		1 (3.8)
Stroke subtype, n (%)		
	Small vessel	16 (61.5)
	Large vessel	1 (3.8)
	Cardioembolic	8 (30.8)
	Cryptogenic	1 (3.8)
Infarct Location, n (%)		
	Small (<2cm <sup>3</sup> ) deep subcortical only	19 (73.1)
	Large (>2cm <sup>3</sup> ) subcortical ± Cortical	1 (3.8)
	Cortical only	6 (23.1)
DWI volume (cm <sup>3</sup> )	Mean (SD)	3.2 (8.5)
	Median	0.9
Baseline NIHSS Score	Mean (SD)	5.4 (2.6)
	Median	5
Baseline FM	Mean (SD)	40.3 (21.6)
	Median	47.5
1-Week FM	Mean (SD)	46.9 (21.4)
	Median	59
3-Month FM		

	Mean (SD)	59.3 (8.2)
	Median	63
Hospital stay (days)		
	Mean (SD)	5.7 (2.5)
	Median	5
Admitted		
Acute/Outpatient		
Rehabilitation, n (%)		10 (38.5)

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Figure 3. Histogram of Patient Recovery at 7 Days



proportional recoverers by 3 months, regardless of the amount of recovery they achieved in the early period.

The 7-day recovery rates of Fast vs. Slow Recoverers had means and standard deviations of  $0.89 \pm 0.19$  (95% CI: 0.78-1.01) vs.  $-0.23 \pm 0.77$  (95% CI: -0.69-0.23) respectively. A comparison of clinical characteristics for fast and slow recoverers is shown in Table 2. At baseline, only stroke severity distinguished the two groups, both by FM-UE and NIHSS.

Table 2. Comparison of clinical characteristics among fast and slow recoverers

		Fast Recoverers (N=13)	Slow Recoverers (N=13)	2-Tailed P-value
Age, y	Mean (SD)	64.0 (12.5)	62.1 (9.4)	0.662 <sup>a</sup>
	Median	67.0	64.0	
DWI volume (cm <sup>3</sup> )	Mean (SD)	1.4 (1.2)	4.9 (11.9)	0.309 <sup>b</sup>
	Median	0.9	0.9	
Baseline NIHSS Score	Mean (SD)	4.2 (1.8)	6.7 (2.8)	<b>0.016<sup>a</sup></b>
	Median	4.0	6.0	
Baseline FM	Mean (SD)	49.7 (13.1)	31 (24.7)	<b>0.027<sup>b</sup></b>
	Median	54.0	23.0	
1-Week FM	Mean (SD)	61.1 (4.9)	32.7 (22.3)	<b>&lt;0.001<sup>b</sup></b>
	Median	64	27	
3-Month FM	Mean (SD)	62.8 (3.4)	55.8 (10.1)	<b>0.031<sup>b</sup></b>
	Median	64.0	59.0	
Hospital stay (days)	Mean (SD)	4.8 (1.8)	6.5 (2.9)	0.076 <sup>a</sup>
	Median	5.0	5.0	
Male, n (%)		11 (84.6)	11 (84.6)	1.000 <sup>c</sup>
Race, n (%)				0.461 <sup>c</sup>
	White	1 (7.7)	2 (15.4)	
	Black	3 (23.1)	6 (46.2)	
	Hispanic	7 (53.8)	3 (23.1)	
	Asian	1 (7.7)	0 (0)	
	Other	1 (7.7)	2 (15.4)	
Hypertension, n (%)		10 (77.0)	10 (77.0)	1.000 <sup>c</sup>
Diabetes, n (%)		4 (30.8)	5 (38.5)	1.000 <sup>c</sup>
Dyslipidemia, n (%)		7 (53.8)	3 (23.1)	0.227 <sup>d</sup>
Atrial Fibrillation, n (%)		1 (7.7)	3 (23.1)	0.593 <sup>c</sup>
Smoking, n (%)		5 (38.5)	2 (15.4)	0.378 <sup>c</sup>
Thrombolytic treatment, n (%)		0 (0)	1 (7.7)	1.000 <sup>c</sup>
Stroke subtype, n (%)				1.000 <sup>c</sup>
	Small vessel	8 (61.5)	8 (61.5)	
	Large vessel	1 (7.7)	0 (0)	
	Cardioembolic	4 (30.8)	4 (30.8)	
	Cryptogenic	0 (0)	1 (7.7)	



## **DISCUSSION:**

In this retrospective analysis we demonstrated that the early time period in the evolution toward proportional recovery was highly variable. Among patients with initial motor deficits ranging from mild to severe and who later showed proportional recovery at 3-months, observed changes at 1-week fell into two categories: Those who achieved an average 90% of their total recovery after 7 days and another group who demonstrated little of their 3-month recovery at the same time point, termed fast and slow recoverers, respectively. By holding constant the final level of performance (all were proportional recoverers) and measuring performances at an early time point, we were able to demonstrate this dichotomy not predictable on the basis of final motor scores. Perhaps most striking was the fact that at 7-days one could not distinguish the slow recoverers from non-recoverers— those who would not realize any gain by the 3-month endpoint. This has important implications for rehabilitation interventions.

Previous studies of motor recovery after stroke have utilized clinical variables such as age, demographics, clinical features, lesion volume and location, initial severity, and stroke subtype to predict of recovery; however, these models have only had modest value in predicting patient outcomes, and none have investigated early versus late recovery.<sup>6-10</sup> Among our cohort, the only significant variables that correlated with the dichotomous recovery patterns were those that conveyed the stroke severity at the time of presentation. Only the National Institute of Health Stroke Scale (NIHSS) and the initial Fugl-Meyer Upper Extremity Motor Exam scores were found to be significantly different between the two groups at the time of presentation. All other commonly-cited predictors of outcome did not differentiate fast from slow recoverers.

It is important to note that all patients received routine bedside physical and occupational therapy during their hospitalization as part of standard of care. Thirty-one percent of the fast recoverers and 46% of the slow recoverers were then discharged to acute rehabilitation, although any difference in therapy after 1-week did not have bearing on the early recovery period. Though the consistency of early rehabilitation care across all patients suggests that, early

“standard-of-care” therapy had little effect on early stroke recovery, this finding requires further investigation. Advances targeting acute-phase patient therapies may yield both faster and more substantial recoveries than those identified by our current model.

The large variability of recovery in the acute period raises the question of whether proportional recovery is governed by two different rate dynamics or by a single, unifying set of variables. In the original proportional recovery study, motor recovery capacity at 90 days was found to be relatively invariate, at least among those with mild-to-moderate initial deficits. It was therefore suggested that a common recovery mechanism might govern proportional recovery. If, however, recovery rates of fast versus slow recoverers were found to obey different rate dynamics, this would challenge the notion of a common recovery mechanism, and raise the possibility that different rehabilitation strategies should be pursued for different patients depending on whether they were likely to recover their deficits early, late, or not at all.

#### *Study Limitations*

There were several limitations to this study. These include the small sample size and the use of just two points to assess recovery. Future study of recovery rate dynamics should include additional serial evaluation points across the first weeks of recovery. In addition, because we deliberately eliminated patients who were deemed non-recoverers at 90-days, the generalizability of our findings to the entire acute stroke population may be limited.

**CONCLUSION:**

We have shown that patients who experience proportional motor recovery in the first 3-months after stroke can be categorized into 2 groups— those who achieve approximately 90% of their total expected recovery by 1-week vs. those who make little recovery early on, and only later achieve their total expected recovery. The ability to accurately predict early recovery could potentially improve post-stroke care by enabling tailored rehabilitation interventions for individuals, and providing realistic goal setting and efficient resource allocation. In addition, from a clinical research prospective, the development of a model that can predict both a patient's recovery rate and ultimate recovery capacity could provide a benchmark against which the effectiveness of new interventions could be measured.

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