Supplementary Information

First intravitreal mitochondrial transplantation for bilateral vision loss

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Unless stated otherwise, study day 0 is the day of the intracerebral hemorrhage, the right eye was treated on study day 95 and the left on study day 96, and a normal light reaction is defined as a Neurological Pupil index (NPi) of at least 3.0.

Supplementary Table 1 | Determinants of the Neurological Pupil index in this patient.

a. Model comparison

Model	Predictors	R^2	Leave-one-out R^2
Ordinary least squares, two-term	Size, CH	0.927 (adjusted 0.922)	0.910
Ordinary least squares, full	all six displayed parameters	0.945	0.906
Ridge regression	Size, CH	not applicable	0.910
Random forest	all six displayed parameters	not applicable	0.866

Fitted to the 36 of 40 device captures with a complete component vector. Ridge alpha selected by leave-one-out cross-validation over 50 values; random forest with 2,000 trees and a fixed random seed. In the full model only Size and CH reached significance.

b. Parameter contributions

Parameter	Coefficient	p value	Standardized β	Random forest importance
Resting size (mm)	-0.775	2.4×10^{-14}	-0.687	0.873
Constriction CH (%)	+0.103	4.5×10^{-9}	+0.422	0.088
Maximum constriction velocity (mm/s)	+0.222	0.59	not applicable	0.013
Average constriction velocity (mm/s)	-0.555	0.22	not applicable	0.010
Dilation velocity (mm/s)	-0.793	0.14	not applicable	0.009
Latency (s)	+0.941	0.20	not applicable	0.007

Coefficients and p values for Size and CH are from the two-term model and for the remaining parameters from the full six-parameter model. Standardized coefficients are from the two-term model fitted to z-scored variables. Under standard errors clustered by examination day, Size and CH remain significant at $p = 2.0 \times 10^{-17}$ and $p = 1.7 \times 10^{-14}$ and the velocity and latency terms remain non-significant.

c. Partial correlations and derived quantity

Relationship	Partial correlation	p value	Interpretation
NPi and Size, controlling for CH	-0.912	9.5×10^{-15}	Index falls as resting diameter rises at fixed constriction
NPi and CH, controlling for Size	+0.808	2.6×10^{-9}	Index rises with constriction at fixed diameter

From the two-term model, 7.53 percentage points of additional constriction are required to offset each millimeter of resting pupil dilation.

Supplementary Table 2 | Agreement between the Neurological Pupil index and average constriction velocity.

Classification	n	Percent of captures	Resting diameter, mean (range), mm
Agree, both normal	1	2.8	not applicable
Agree, both abnormal	21	58.3	not applicable
Disagree, index normal and velocity sluggish	6	16.7	2.96 (2.47 to 3.99)
Disagree, index abnormal and velocity brisk	8	22.2	5.40 (4.81 to 5.88)
Disagree, total	14	38.9	

Each of the 36 captures with a complete component vector was classified independently by index, normal at 3.0 or above, and by average constriction velocity, brisk at 0.8 mm/s or above. The resting diameter ranges of the two disagreement groups do not overlap (Mann-Whitney $p = 0.002$). Across the same captures the index and average constriction velocity were uncorrelated (Pearson $r = 0.001$, $p = 0.99$; Spearman $r = 0.273$, $p = 0.11$).

Supplementary Table 3 | Change-point analysis of the reactivity series.

	Right eye	Left eye
Readings entering the analysis	121	118
Maximum likelihood split	between day 3.8 and day 3.9	between day 0.8 and day 1.8
Reactive rate before the split	0.030 (3 of 100)	0.021 (2 of 96)
Reactive rate after the split	0.286 (6 of 21)	0.318 (7 of 22)
Maximised log-likelihood	-26.04	-23.48
Support interval, splits within 2 log-likelihood units	day -53.3 to day 5.1 (10 candidate splits)	day -55.2 to day 1.8 (7 candidate splits)
Readings between day -71 and day 0	23	22

Single-split Bernoulli model fitted by maximum likelihood over all possible split points, with time measured from each eye's own procedure. The procedure dates were not supplied to the model. Both maximum likelihood estimates fall within 4 days of the corresponding procedure, but the support interval extends backwards through the 52-day and 54-day intervals during which no readings were obtained, because moving the split through an unobserved interval costs almost no likelihood. The analysis therefore does not localize onset more precisely than the observation schedule already does and is not used as evidence of onset timing in the main text.

Supplementary Table 4 | Pupillometry observation schedule.

Interval	Eye	Readings	Study days sampled	Reactive readings	Maximum NPi
Acute, to study day 25	right	70	21	3	3.8
	left	72	22	2	4.6
Fixed baseline, 71 days before treatment	right	23	7	0	1.3
	left	22	6	0	2.5
After treatment, to day 45	right	28	22	6	4.4
	left	24	20	7	4.1

Sampling was clinically determined rather than scheduled. Within the fixed baseline, readings fall on study days 24, 25, 26, 40, 41, 42 and 94 in the right eye and 25, 26, 40, 41, 42 and 96 in the left. Because the baseline window is measured from each eye's own procedure to the hour, study day 24 in the right eye and study day 25 in the left are divided between the acute and baseline blocks, and are counted in both rows; no reading meeting the criterion falls on the baseline side of either division. The largest observation gap is 52 days in the right eye and 54 days in the left, both between study day 42 and the day of the procedure, corresponding to the period of inpatient rehabilitation. No data were imputed; intervals without readings reflect absence of assessment.

Supplementary Table 5 | Pre-treatment readings meeting the criterion, in context.

Eye	Study day	NPi	Other readings in the same eye that day	Range of those readings	Any other reading at 3.0 or above
left	1	4.6	10	0.0 to 1.0	no
left	2	3.7	14	0.0 to 2.0	no
right	2	3.7	14	0.0 to 0.0	no
right	23	3.8	2	0.6 to 0.8	no
right	24	3.4	3	0.5 to 0.7	no

All five readings meeting the criterion before treatment fall within the first 24 days after the hemorrhage. Each was an isolated value: on every occasion the same eye was sampled 3 to 15 times that day and every other reading fell below the criterion, most at or near zero. For comparison, after treatment the criterion was met on consecutive sampled days, on study days 99 to 101 in the right eye and on 7 of the 8 days sampled between study day 98 and study day 107 in the left. No reading met the criterion in the 71 days immediately preceding treatment.

Supplementary Table 6 | Inventory of within-patient analyses.

Analysis	Specification	Right eye	Left eye
Primary comparison	Fisher exact, fixed baseline against after treatment	0/23 against 6/28, p = 0.027	0/22 against 7/24, p = 0.010
Primary comparison, eyes combined	Fisher exact	0/45 against 13/52, p = 0.00015	
Day-block bootstrap	whole days resampled, 20,000 replicates	+21.4 points (7.4 to 37.5)	+29.2 points (12.5 to 47.8)
Bayesian comparison	beta-binomial, Beta(1,1) prior	P = 0.990; difference 19.3% (3.4 to 36.8)	P = 0.997; difference 26.6% (8.3 to 46.4)
Reactive rate by epoch	Wilson 95 percent intervals	Table 1	Table 1
Onset, peak, last	first, highest and last reading meeting the criterion	day 4; 4.4 on day 4; day 39	day 2; 4.1 on day 4; day 11
Run structure	sampled days meeting the criterion	6 of 22 days, longest run 3 days	7 of 8 days from day 2 to 11, then 0 of 12
Isolation of pre-treatment readings	other readings in the same eye on the same day	Supplementary Table 5	Supplementary Table 5
Between-eye association	Spearman on readings acquired at the same timepoint	before 0.66 (n = 94, 0.53 to 0.76); after 0.14 (n = 24, -0.28 to 0.52); Fisher z = 2.68, p = 0.007	
Between-eye discordance	days on which either eye met the criterion	7 of 10 days involved one eye only	
Time of day	logistic regression of reactivity on hour	p = 0.67	p = 0.67
Repeat-scan dispersion	median within-session standard deviation	before 0.21; after 1.06	before 0.28; after 1.36
Dispersion before against after	standard deviation of all readings, Levene test	0.77 to 1.38, p = 0.003	0.78 to 1.45, p < 0.001
Change-point	single-split Bernoulli maximum likelihood	Supplementary Table 3	Supplementary Table 3

Intervals are 95 percent and are presented descriptively. No adjustment for multiplicity was prespecified or applied.

Supplementary Table 7 | Steady-state visual evoked potential session register.

Study day	Day relative to first procedure	Eyes stimulated	Plot full scale, µV	Dominant channel	Peak band, Hz	Organized response
68	-27	both	10	O1	5 to 10	no, O1 only
91	-4	both	1.0	O2, weak	5 to 10	borderline
98	+3	both	8.0	O1 and O2 comparable	5 to 16	yes
139	+44	both	2.5	balanced	5 to 15	yes
140	+45	both	0.6	O2 and Oz	5 to 12	yes
140	+45	left	0.6	O2	5 to 10	yes
140	+45	right	2.5	Oz	5 to 10	yes

Recorded from occipital channels O1, O2 and Oz. Records exist only as photographic captures of the device frequency-domain output, with no numeric export, and archived images survive for two of the seven captures, at study day 91 and study day 98; both are provided with Supplementary Data 1, and the remaining sessions are recorded in the contemporaneous session log only. Device plots are automatically scaled and the full-scale value differs between sessions, so absolute amplitudes are not comparable across rows and are not reported. An organized response was defined as concordant peaks above the plotted noise floor in at least two occipital channels within a common frequency band. There were 5 recording sessions yielding 7 captures, of which 3 sessions and 5 captures follow treatment; no recording was obtained between study day 98 and study day 139. No monocular recording exists from before treatment. Within a plot the three channel traces are overlaid rather than offset, so relative channel amplitudes are approximate. An organized response was defined as concordant peaks above the plotted noise floor in at least two occipital channels within a common frequency band.

Supplementary Data 1 | De-identified pupillometry and evoked potential datasets. One workbook with four data sheets and a README. NPi_series holds all 239 automated pupillometry readings. Device_captures holds the source-of-record capture table, 40 captures with the eight displayed parameters, derived quantities and verification provenance. SSVEP_sessions reproduces the register given as Supplementary Table 7, and SSVEP_source_images records which captures have an archived device screen image and what each shows. Calendar dates are replaced by study days throughout, and no patient, device or operator identifier is included.