Supplementary Data Table S1: Azithromycin (AZ) Treatment does not Affect Body (Rectal) Temperatures after LPS or PAM-amplified Cerebral Hypoxia-Ischemia (HI) in P7 Rats [a].

Group	Injection times (h after end of HI)	Pre-surgery	End of 8% O_2 exposure	15 min after hypoxia	60 min after hypoxia	120 min after hypoxia	24 h after hypoxia	48 h after hypoxia	72 h after hypoxia	96 h after hypoxia
LPS+HI [b]: 3- (AZ*3: 45, 22.5, 22.5 mg/kg/dose) vs. 5-dose (AZ*5: 45, 22.5, 22.5, 22.5, 22.5 mg/kg/dose)										
Saline	2, 24, 48, 72, 96	34.6±0.9	36.0±0.6	36.1±0.6	36.5±0.5	35.1±1.4	35.5±0.6	NA	NA	NA
AZ*3	2, 24, 48	34.8±0.8	35.8±1.0	36.1±0.6	36.6±0.4	35.6±0.7	35.7±0.6	NA	NA	NA
AZ*5	2, 24, 48, 72, 96	34.7±0.7	35.9±0.5	35.9±0.7	36.7±0.6	35.7±0.9	35.9±0.5	NA	NA	NA
LPS+HI [b]: Initial-dose time-dependence of AZ Neuroprotection (AZ*5: doses as above)										
Saline	2, 24, 48, 72, 96	34.7±1.0	35.6±0.5	35.3±0.6	35.9±0.7	34.9±0.7	35.2±0.7	35.8±0.5	35.0±0.4	35.5±0.4
AZ 1h	1, 24, 48, 72, 96	34.9±1.3	35.5±0.5	35.5±0.7	36.1±1.1	34.2±1.8	35.3±0.7	35.3±0.3	35.1±0.5	35.3±0.3
AZ 2h	2, 24, 48, 72, 96	34.8±1.1	35.3±1.0	35.5±0.4	35.8±0.7	34.8±0.9	35.2±0.6	35.3±0.5	35.1±0.5	35.3±0.3
AZ 4h	4, 24, 48, 72, 96	34.8±1.1	35.4±0.9	35.5±0.8	36.0±0.7	34.6±1.4	35.1±0.8	35.3±0.8	35.4±0.5	35.2±0.8
PAM+HI [c]: 3 (AZ*3) vs. 5-dose (AZ*5) Regimens (doses as above)										
Saline	2, 24, 48, 72, 96	35.1±0.7	34.8±1.0	35.3±0.4	36.1±0.5	35.6±0.7	35.3±0.5	35.3±0.5	35.5±0.3	35.3±0.7
AZ*3	2, 24, 48	34.7±0.9	35.6±0.4	35.4±0.4	36.1±0.4	35.5±0.8	35.6±0.3	35.4±0.2	35.7±0.5	35.4±0.5
AZ*5	2, 24, 48, 72, 96	35.1±0.9	35.7±0.4	35.7±0.5	36.1±0.4	35.6±0.7	35.6±0.3	35.6±0.4	35.5±0.7	35.4±0.4
PAM+HI [c]: Initial-dose time-dependence of AZ Neuroprotection (AZ*5: doses as above)										
Saline	2, 24, 48, 72, 96	35.2±0.3	35.3±0.8	35.4±0.7	35.8±0.6	35.2±1.0	35.0±0.7	35.1±1.2	35.8±1.1	34.0±2.4
AZ 1h	1, 24, 48, 72, 96	35.2±0.5	35.1±0.7	35.5±0.3	36.3±0.4	35.1±0.9	35.3±0.8	35.9±0.7	36.5±0	35.6±0.4
AZ 2h	2, 24, 48, 72, 96	35.0±0.4	35.5±0.9	35.3±0.6	36.2±0.4	35.4±1.2	35.1±0.9	36.2±0.7	36.2±0.7	35.6±0.4
AZ 4h	4, 24, 48, 72, 96	35.1±0.4	35.2±0.8	35.9±0.4	35.9±0.4	35.3±0.8	35.2±0.8	35.8±0.4	36.0±0.7	35.8±0.4

a: There was no temperature differences among treatment groups in any of the experiments, as evaluated by repeated-measures ANOVA.

b: **LPS+HI**: The TLR4 agonist lipopolysaccharide (LPS, 0.05 mg/kg) was injected intraperitoneally (i.p.), 2.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 50 min 8% O_2 started (see Methods). Saline or AZ injections were i.p. (n=15-16/group).

c: **PAM+HI**: The TLR2 agonist Pam_3Cys-Ser-$(Lys)_4$ (PAM, 0.5 mg/kg) was injected i.p. 4.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 60 min 8% O_2 started (see Methods). Saline or AZ injections were i.p. (n=8/group).

NA: not available

Supplementary Data Table S2: Blood Glucose Concentrations [a] after Inflammation-Amplified Hypoxia-Ischemia are not Affected by Azithromycin Treatment

Model	Treatment group [b]	Pre-injection [b]	Post-injection [b]			
			1 h	2 h	4 h	24 h
LPS+HI [c]	NS	54±15	77±30	87±39	94±38	120±15
	AZ	60±23	87±35	103±45	105±41	113±41
PAM+HI [d]	NS	121±21	NA [e]	NA	NA	122±19
	AZ	127±23	NA	NA	NA	129±11

a: **Blood glucose** (mg/dL, mean±SD) was measured using the AimStrip Plus Blood Glucose Testing System and Test Strips (Germaine Laboratories, San Antonio, TX).

b: **Pre-injection** samples (ear puncture) were collected after the end of HI, immediately before i.p. injection of AZ 45 mg/kg or saline solution (NS). Post-injection samples were timed as indicated above.

c: **LPS+HI**: LPS, (0.05 mg/kg) was injected intraperitoneally (i.p.), 2.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 50 min 8% O_2 started (see Methods). NS or AZ injections were i.p. (n=12/group).

d: **PAM+HI**: Pam_3Cys-Ser-$(Lys)_4$ (PAM, 0.5 mg/kg) was injected i.p. 4.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 60 min 8% O_2 started (see Methods). NS or AZ injections were i.p. (NS, n=12; AZ, n=32).

e: **NA**: not available. Samples were only collected at 24 h after injection and not at the early time points because pre-injection blood glucose values were normal after PAM+HI.

Supplementary Data Table S3: Analysis of Sex-effects on AZ Treatment Efficacy in LPS+HI and PAM+HI Neonatal Rodent Models

	Saline					AZ [a]				
LPS+HI50 [b] (N=71)	Composite Score [d]		Deaths [e]	Survivors	Modified Composite Score [f]	Composite Score [d]		Deaths [e]	Survivors	Modified Composite Score [f]
	n	(Mean±SD)			(Mean±SD)	n	(Mean±SD)			(Mean±SD)
Female	14	10.1±6.0	3	11	12.8±2.8	19	23.3±7.1 †	1	18	24.6±4.4 †
Male	13	10.1±5.1	2	11	11.9±2.7	25	22.4±7.2 †	2	23	24.4±2.7 †
PAM+HI60 [c] (N=34)										
Female	6	5.7±6.3*	3	3	11.3±1.5	11	22.9±7.9* †	1	10	25.2±2.3 †
Male	7	12.1±1.3	0	7	12.1±1.3	10	26.2±2.7 †	0	10	26.2±2.7 †

a: **AZ:** For these analyses, in order to incorporate P35 and P21 outcome data, we only included AZ treatment regimens in which the initial 45 mg/kg i.p. injection was 2 h after the end of HI. Subsequent AZ doses (22.5 mg/kg) were injected at 24 and 48 h after HI (AZ*3: LPS+HI n=16, PAM+HI =8) and with additional doses at 72 and 96 h after HI (AZ*5: LPS+HI n=28, PAM+HI =13). All controls received saline injections at 2, 24, 48, 72, and 96 h after the end of HI (LPS+HI n=27, PAM+HI n=13).

b: **LPS+HI**: LPS, 0.05 mg/kg was injected 2.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 50 min 8% O_2 started (see Methods).

c: **PAM+HI**: PAM, 0.5 mg/kg, was injected. 4.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 60 min 8% O_2 started (see Methods).

d: **Composite scores** from both P35 and P21 outcome studies are included (see Methods); deaths receive Composite scores of 0.

e: **Deaths:** Only deaths that occurred >2 h after HI, i.e. after the start of treatment, are included.

f: **Modified composite scores**: these values are limited to animals that survive for the duration of the experiments and facilitate distinction between treatment effects on mortality vs. effects on function and brain injury in surviving animals.

*,†: In LPS-amplified HI, there were no outcome differences in composite scores between males and females; AZ was neuroprotective in both sexes († $p<0.0001$). In PAM amplified HI, females were more severely affected (*) in controls and AZ-treated groups. AZ (†) improved outcomes substantially in both sexes - by 2-way ANOVA factoring group and sex, † $p<0.0001$ for treatment, and * $p=0.017$ for sex, with no treatment*sex interaction effect. Modified Composite scores, limited to surviving animals, did not differ between sexes.

Supplementary Data Table S4: Sensorimotor Testing Results on P21 are Consistent with Results on P35 [a]

	NS	**AZ*3** [b]	**AZ*5** [b]
LPS + HI [c]			
Forepaw Placing Score (/10)			
P21	1.5±1.5*	6±3	9±2.5
P35	1±1.5	6.5±3	9±2.5
Grip Strength L/R ratio			
P21	0.5±0.2	0.7±0.3	0.8±0.2
P35	0.5±0.2	0.6±0.2	0.8±0.2
PAM + HI [d]			
Forepaw Placing (/10)			
P21	2±1.5	8±0.5	8±3.5
P35	0.5±1	8±1	9±3.5
Grip Strength L/R ratio			
P21	0.4±0.2	0.9±0.1	0.8±0.3
P35	0.3±0.2	0.7±0.2	0.8±0.3

*: All cells are mean±SD. Forepaw placing scores are rounded to the nearest 0.5 because this is an ordinal variable in which the smallest score increment is 0.5; in contrast grip strength ratio is a continuous variable and values are rounded to the nearest 0.1.

a: For both LPS+HI and PAM+HI there was no significant difference between mean P21 and mean P35 vibrissae-stimulated forepaw placing scores or L/R grip traction strength ratios, in any treatment group, by 2-way ANOVA factoring group and age, with $p<0.0001$ for treatment, but p=NS for age (P21 vs. P35), by Tukey's multiple comparisons test.

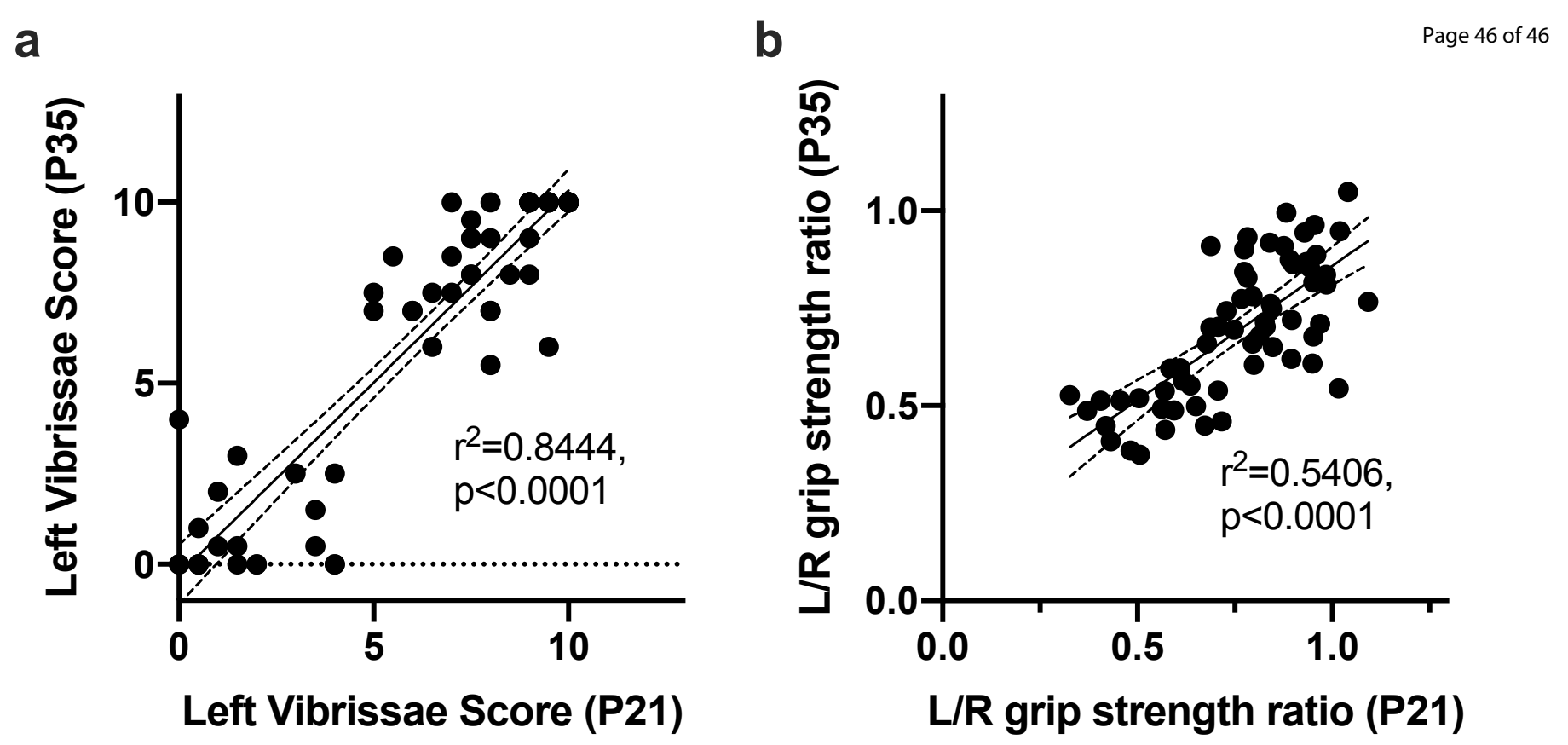
b: **AZ Treatment Groups**: AZ 45 mg/kg injected i.p. 2 h after the end of HI. Subsequent AZ doses (22.5 mg/kg) were injected at 24 and 48 h after HI (AZ*3), and with additional doses at 72 and 96 h after HI (AZ*5). NS controls received saline injections at 2, 24, 48, 72, and 96 h after the end of HI.

c: **LPS+HI**: LPS, (0.05 mg/kg) was injected intraperitoneally (i.p.), 2.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 50 min 8% O_2 started (see Methods). Saline or AZ injections were i.p. (n=15-16/group).

d: **PAM+HI**: Pam_3Cys-Ser-$(Lys)_4$ (PAM, 0.5 mg/kg) was injected i.p. 4.5 h prior to right carotid artery ligation, and 1.5 h later, exposure to 60 min 8% O_2 started (see Methods). Saline or AZ injections were i.p. (n=8/group).

Supplementary Data Figure S1: Close Relationship Between Sensorimotor Testing Results on P21 and P35

Combining results from all experiments (both LPS+HI and PAM+HI) in which performance was assessed in the same animal at both P21 and P35, left forepaw vibrissae-stimulated placing scores (**a**) and L/R grip strength ratios (**b**) were compared in each animal, between P21 and P35, by simple linear regression; animals that died before P35 were not included. There were very strong relationships between animals' results at P21 and P35. For the forepaw placing score (**a**), the best-fit slope was 1.06 [95% Confidence Interval (CI) 0.95-1.18, $p<0.0001$, $r^2 = 0.84$]. For the L/R grip strength ratio (**b**) the best-fit slope was 0.69 [95% CI 0.53-0.85, $p<0.0001$, $r^2 = 0.54$].


a
Left Vibrissae Score (P35)
10
5
0
0
5
10
Left Vibrissae Score (P21)
r2=0.8444,
p<0.0001
b
L/R grip strength ratio (P35)
1.0
0.5
0.0
0.0
0.5
1.0
L/R grip strength ratio (P21)
r2=0.5406,
p<0.0001