

Reward and punishment enhance motor adaptation in stroke

Supplementary material

Supplementary table 1 Study calendar

Procedures	Visits		
	Day 1	Day 2	Day 3
Informed consent	X		
Medical history, physical examination, eligibility assessment	X		
Functional scales			
Barthel Index	X		
Fugl Meyer-Upper Limb	X		
Modified Ashworth scale	X		
MRC scale for muscle strength	X		
Cognitive tests			
Mini Mental State Examination	X		
Bells test	X		
Frontal Assessment Battery	X		
SPSRQ-20	X		
Stroop Test		X	
Apathy evaluation scale – clinician version		X	
Fatigue Severity scale		X	
Beck Depression Inventory			X
Apathy evaluation score – self administered			X
St Mary’s sleep questionnaire	X	X	X
VAS Alertness and Fatigue (after task)	X	X	X

MRC=Medical Research Council; SPSRQ-20=sensitivity to punishment and sensitivity to reward questionnaire; VAS=visual analogue scale.

Supplementary table 2 Factor loadings after varimax rotation for principal component analysis.

We can interpret these three components as patients' motor functional level (muscle strength, FMA-UL, spasticity, Barthel index), psychomotor functional level (BDI, FSS, AES-S, AES-C) and cognitive functional level (FAB and MMSE).

	Component		
	1	2	3
Muscle strength	0.878		
FMA-UL	0.847		
Spasticity	-0.824		
Barthel Index	0.603		
BDI		0.835	
FSS		0.830	
AES-S		0.576	
FAB			0.803
MMSE			0.737
AES-C		0.423	-0.595

Muscle strength=average Medical Research Council score measured from the shoulder flexors, elbow flexors and wrist extensors muscles; FMA-UL=Fugl-Meyer Assessment Upper-Limb score; Spasticity=averaged modified Ashworth scale score from the shoulder, elbow and wrist joints; BDI=Beck Depression Inventory; FSS=Fatigue Severity Scale; FAB=Frontal Assessment Battery; MMSE=Mini Mental State Examination; AES-S=Apathy Evaluation Scale self-administered version; AES-C=Apathy Evaluation Scale clinician version.

Supplementary table 3 Cognitive tests

	N (n=15)	R (n=15)	P (n=15)	<i>F</i> _(2,42)	p	Effect size
MMSE	27.5±0.7	28.4±0.5	28.1±0.4	0.77	0.468	0.036
FAB	14.3±0.7	15.1±0.5	15.1±0.5	0.74	0.485	0.034
Stroop Errors	1.3±0.4	2.3±0.7	2±0.6	0.66	0.521	0.031
Stroop time (s)	15.9±2.8	28.7±10.1	16.1±2.4	1.41	0.255	0.063
BDI	11.7±2	7.3±1.5	13.6±3	2.28	0.114	0.098
FSS	36.1±3.3	30±3.1	35.8±4.1	0.95	0.394	0.043
AES-C	32.5±1.8	27.1±2	29.7±2	1.83	0.172	0.08
AES-S	31.8±1.4	28.3±1.9	33±1.4	2.39	0.104	0.102
SP	5.1±0.6	3.3±0.5	5±0.6	2.76	0.075	0.116
SR	3.7±0.6	3.6±0.6	3.9±0.7	0.07	0.929	0.003
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A-VAS						
Day 1	7.2±0.6	7.7±0.6	6.7±0.6	0.77	0.466	0.036
Day 2	5.8±0.6	7.1±0.6	6.5±0.6	1.11	0.337	0.050
Day 3	6.6±0.5	7.5±0.5	6.7±0.5	0.81	0.454	0.037
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F-VAS						
Day 1	6.7±0.6	6.7±0.7	6.5±0.4	0.03	0.968	0.002
Day 2	5.7±0.4	6.5±0.8	7±0.5	1.22	0.306	0.055
Day 3	5.6±0.7	6.9±0.5	6.9±0.5	1.32	0.279	0.059
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Sleep hours						
Day 1	7.9±0.3	7.7±0.3	7.5±0.3	0.34	0.717	0.016
Day 2	7.7±0.2	8±0.4	7.9±0.3	0.28	0.757	0.013
Day 3	7.6±0.2	7.9±0.3	8.1±0.3	0.64	0.532	0.030

Values are depicted as mean \pm SEM. N=neutral; R=reward; P=punishment; MMSE=Mini Mental State Examination; FAB=Frontal Assessment Battery; BDI=Beck Depression Inventory; FSS=Fatigue Severity Scale; AES-C=Apathy Evaluation Scale clinician version; AES-S=Apathy Evaluation Scale, self-administered version; SP=sensitivity to punishment; SR=sensitivity to reward; A-VAS=alertness visual analogue scale; F-VAS=fatigue visual analogue scale; Sleep hours= overnight sleep prior each study day.

Supplementary table 4 Healthy controls demographics and cognitive tests

	Controls (n=15)
Sex (male)	10 (66.7)
Age (years)	62.5 \pm 3.7
Education (years)	17.2 \pm 0.7
Dominant side (right)	14 (93.3)
Cognitive tests	
Mini Mental State Examination	29.1 \pm 0.3
Frontal Assessment Battery	18 \pm 0.8
Stroop errors	1.6 \pm 0.6
Stroop time (s)	11 \pm 1.8
Beck Depression Inventory	7.3 \pm 1.9
Fatigue Severity Scale	23.1 \pm 3.6
AES-C	27.7 \pm 1.6
AES-S	29.4 \pm 2
Sensitivity to Punishment	3.4 \pm 0.7
Sensitivity to Reward	3.8 \pm 0.5
A-VAS	
Day 1	7.3 \pm 0.4
Day 2	7.5 \pm 0.4
Day 3	7.1 \pm 0.6
F-VAS	
Day 1	7.5 \pm 0.4
Day 2	7.3 \pm 0.4
Day 3	7.2 \pm 0.5
Sleep (hours)	
Day 1	6.8 \pm 0.1
Day 2	6.9 \pm 0.2
Day 3	6.7 \pm 0.3

Values are depicted as mean \pm SEM. AES-C=Apathy Evaluation Scale clinician version; AES-S=Apathy Evaluation Scale, self-administered version; A-VAS=alertness visual analogue scale; F-VAS=fatigue visual analogue scale.

Supplementary table 5 Patient's movement times and reaction times

	Movement Time (ms)			Reaction Time (ms)		
	N	R	P	N	R	P
Day 1	408 \pm 25	482 \pm 37	472 \pm 30	569 \pm 36	465 \pm 36	514 \pm 41
ANOVA	$F_{(2,42)}=1.6, p=0.204, \eta^2=0.073$			$F_{(2,42)}=1.9, p=0.161, \eta^2=0.083$		
Day 2						
Baseline	362 \pm 18	447 \pm 40	401 \pm 24	545 \pm 39	428 \pm 37	480 \pm 37
Adaptation	400 \pm 35	472 \pm 44	436 \pm 36	495 \pm 32	406 \pm 36	470 \pm 33
Washout	386 \pm 24	450 \pm 41	414 \pm 25	539 \pm 26	419 \pm 36	490 \pm 40
ANOVA	G: $F_{(2,42)}=1.4, P=0.255, \eta^2=0.063$			G: $F_{(2,42)}=2.7, P=0.081, \eta^2=0.113$		
	Ph: $F_{(2,84)}=3.9, p=0.025, \eta^2=0.084$			Ph: $F_{(2,84)}=3.5, p=0.033, \eta^2=0.078$		
	G*Ph: $F_{(4,84)}=0.1, p=0.964, \eta^2=0.007$			G*Ph: $F_{(4,84)}=0.6, p=0.633, \eta^2=0.03$		
Day 3						
Baseline	332 \pm 23	425 \pm 42	393 \pm 20	502 \pm 33	409 \pm 34	508 \pm 37
Readaptation	395 \pm 40	453 \pm 34	390 \pm 29	494 \pm 32	406 \pm 36	470 \pm 33
Washout	371 \pm 23	412 \pm 29	368 \pm 26	519 \pm 29	409 \pm 30	472 \pm 31
ANOVA	G: $F_{(2,42)}=1.4, p=0.246, \eta^2=0.065$			G: $F_{(2,42)}=2.6, p=0.084, \eta^2=0.111$		
	Ph: $F_{(2,84)}=3.2, p=0.045, \eta^2=0.071$			Ph: $F_{(1.7,73.8)}=1.5, p=0.237, \eta^2=0.034$		
	G*Ph: $F_{(4,84)}=1.5, p=0.206, \eta^2=0.067$			G*Ph: $F_{(3.5,73.8)}=1.4, p=0.234, \eta^2=0.064$		

Values depict the mean \pm SEM determined for each subject by averaging over consecutive epochs. For each kinematic parameter, a mixed ANOVA compared group (G: N, R, P) and phase (Ph: Baseline, Adaptation/Readaptation, Washout) for each day. Greenhouse-Geisser or Huynh-Feldt corrections are shown when sphericity was violated. N=neutral; R=reward; P=punishment group.

Supplementary table 6 Patient's velocity and online corrections

	Max V (cm/s)			Max V %			Online corrections		
	N	R	P	N	R	P	N	R	P
Day 1	27 \pm 2	24 \pm 2	24 \pm 1	82 \pm 3	70 \pm 4	74 \pm 2	-0.1 \pm 0.3	-1 \pm 0.3	-0.1 \pm 0.3
ANOVA	$F_{(2,42)}=1.3$, $p=0.276$, $\eta^2=0.059$			$F_{(2,42)}=3.5$, $p=0.04$, $\eta^2=0.142$			$F_{(2,42)}=2.8$, $p=0.071$, $\eta^2=0.118$		
Day 2									
Baseline	29 \pm 2	26 \pm 3	27 \pm 2	86 \pm 3	75 \pm 4	82 \pm 2	0.3 \pm 0.02	0.05 \pm 0.04	0.04 \pm 0.04
Adaptation	29 \pm 3	25 \pm 3	26 \pm 2	79 \pm 4	68 \pm 5	76 \pm 3	1.8 \pm 0.5	2.8 \pm 0.8	2.6 \pm 1.1
Washout	28 \pm 2	26 \pm 2	26 \pm 2	86 \pm 3	78 \pm 5	84 \pm 3	-0.2 \pm 0.4	2.2 \pm 0.6	0.3 \pm 0.5
ANOVA	G: $F_{(2,42)}=1.6$, $p=0.564$, $\eta^2=0.027$			G: $F_{(2,42)}=2$, $p=0.146$, $\eta^2=0.088$			G: $F_{(2,42)}=2.3$, $p=0.114$, $\eta^2=0.098$		
	Ph: $F_{(1,7,71)}=0.3$, $p=0.694$, $\eta^2=0.007$			Ph: $F_{(1,8,74.8)}=29$, $p<0.001$, $\eta^2=0.408$			Ph: $F_{(1,7,73.3)}=15.8$, $p<0.001$, $\eta^2=0.273$		
	G*Ph: $F_{(3,4,71)}=0.7$, $p=0.982$, $\eta^2=0.003$			G*Ph: $F_{(3,6,74.8)}=0.3$, $p=0.849$, $\eta^2=0.015$			G*Ph: $F_{(3,5,73.3)}=1.5$, $p=0.2$, $\eta^2=0.069$		
Day 3									
Baseline	32 \pm 2	27 \pm 3	27 \pm 2	87 \pm 3	78 \pm 4	83 \pm 3	0.01 \pm 0.0	-0.03 \pm 0.03	0.02 \pm 0.01
Readaptation	31 \pm 3	25 \pm 2	29 \pm 2	80 \pm 4	70 \pm 5	79 \pm 3	1.7 \pm 0.8	2.7 \pm 0.8	2.8 \pm 0.9
Washout	30 \pm 2	27 \pm 2	30 \pm 2	86 \pm 3	81 \pm 5	86 \pm 3	-0.1 \pm 0.3	0.6 \pm 0.6	-0.1 \pm 0.5
ANOVA	G: $F_{(2,42)}=1.2$, $p=0.319$, $\eta^2=0.053$			G: $F_{(2,42)}=1.5$, $p=0.241$, $\eta^2=0.065$			G: $F_{(2,42)}=0.9$, $p=0.427$, $\eta^2=0.04$		
	Ph: $F_{(2,84)}=0.2$, $p=0.791$, $\eta^2=0.006$			Ph: $F_{(1,8,77.6)}=22.7$, $p<0.001$, $\eta^2=0.351$			Ph: $F_{(1,4,60)}=17.8$, $p<0.001$, $\eta^2=0.298$		
	G*Ph: $F_{(4,84)}=1.7$, $p=0.153$, $\eta^2=0.076$			G*Ph: $F_{(3,7,77.6)}=0.9$, $p=0.418$, $\eta^2=0.045$			G*Ph: $F_{(2,8,60)}=0.5$, $p=0.681$, $\eta^2=0.023$		

Values depict the mean \pm SEM for each subject by averaging over consecutive epochs. For each parameter, a mixed ANOVA compared group (G: N, R, P) and phase (Ph: Baseline, Adaptation/Readaptation, Washout) for each day. Greenhouse-Geisser or Huynh-Feldt corrections are shown when assumption of sphericity was violated. Max V=peak velocity; Max V%, time point in movement (%) when peak velocity occurred; Online corrections= difference between angular error at peak velocity and angular endpoint error. N=neutral; R=reward; P=punishment.

Supplementary table 7 Targets and force-field directions selected after day 1

	N (n=15)	R (n=15)	P (n=15)
Targets			
25° and 65°	2 (13.3)	2 (13.3)	1 (6.7)
115° and 155°	8 (53.3)	6 (40)	2 (13.3)
205° and 245°	4 (26.7)	3 (20)	5 (33.3)
295° and 335°	1 (6.7)	4 (26.7)	7 (46.7)
Force-field direction (CW)	3 (20)	2 (13.3)	10 (66.7)

Values are depicted as number of patients and the percentage this relates to in terms of each group (%). N=neutral; R=reward; P=punishment; CW=clockwise.

Supplementary table 8 Within-subject variability. Variability (SD of angular error at peak velocity) was similar across the three patient groups (one-way ANOVA).

	N	R	P	<i>F</i>_(2,42)	p	Effect size
Day 1	12.7 \pm 1	13.7 \pm 0.7	12.8 \pm 0.9	0.33	0.717	0.016
Day 2-3	9.4 \pm 1	9.8 \pm 0.6	9 \pm 0.6	0.30	0.733	0.015
Early adaptation	9.4 \pm 1	11.4 \pm 0.7	9 \pm 0.5	3.03	0.059	0.126
Late adaptation	9.4 \pm 1	9.1 \pm 0.7	9.2 \pm 0.7	0.03	0.968	0.002
Early readaptation	9.6 \pm 0.9	11.1 \pm 0.7	10 \pm 0.9	0.78	0.462	0.036
Late readaptation	9.4 \pm 1.6	9.1 \pm 0.6	8.2 \pm 0.5	0.39	0.678	0.018

Values are depicted as mean \pm SEM, effect size is η^2 (eta squared). N=neutral; R=reward; P=punishment; Day 1=overall variability during the baseline day; Day 2-3=overall variability during day 2 and 3; Early adaptation=variability first block (50 trials) of adaptation on day 2; Late adaptation=variability last block of adaptation day 2; Early readaptation=variability first block of adaptation day 3; Late readaptation=variability last block of adaptation day 3.

Supplementary table 9 Within-subject variability in healthy controls

Variability	Controls (n=15)
Day 1	8.3 ± 1.5
Day 2-3	6.1±0.2
Early adaptation	8.2±0.4
Late adaptation	5.7±0.4
Early readaptation	8.2±0.5
Late readaptation	5.3±0.3

Values are depicted as mean ± SEM. Day 1=overall variability during the baseline day; Day 2-3=overall variability during day 2 and 3; Early adaptation=variability first block (50 trials) of adaptation on day 2; Late adaptation=variability last block of adaptation day 2; Early readaptation=variability first block of adaptation day 3; Late readaptation=variability last block of adaptation day 3.

One-way ANOVA between the three stroke groups and the healthy controls showed the followings:

- Day 1, $F_{(3,56)}=8.43$ $p<0.001$, $\eta^2=0.311$
- Day 2-3, $F_{(3,56)}=7.17$, $p<0.001$, $\eta^2=0.278$
- Early adaptation, $F_{(3,56)}=4.04$, $p=0.011$, $\eta^2=0.178$
- Late adaptation, $F_{(3,56)}=6.5$, $p=0.001$, $\eta^2=0.257$
- Early readaptation, $F_{(3,56)}=2.3$, $p=0.085$, $\eta^2=0.110$
- Late readaptation, $F_{(3,56)}=4.2$, $p=0.010$, $\eta^2=0.183$

Supplementary table 10 Kinematic parameters for healthy controls

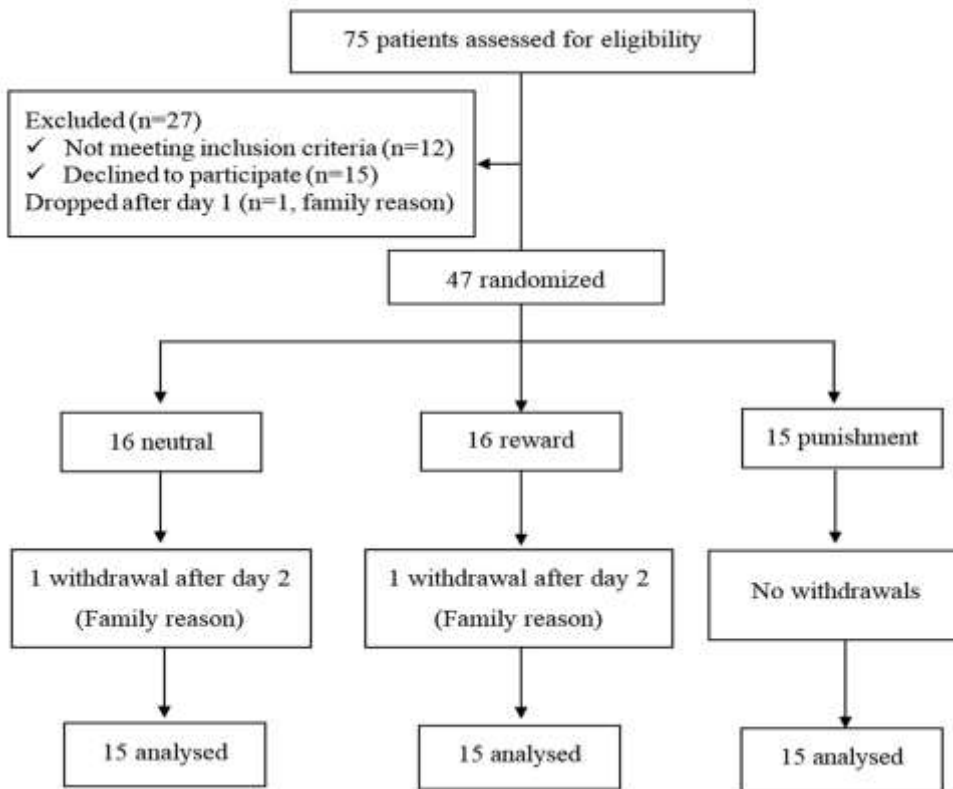
	MT (ms)	RT (ms)*	Max V (cm/s)	Max V %	Online corrections
Day 1	411±13	342±12	23±0.7	71±2*	-0.3±0.3
Day 2					
Baseline	358±17	327±11	27±2	78±3	0±0.01
Adaptation	365±19	319±12	28±2	71±3	2.8±0.5
Washout	363±15	343±13	26±2	78±2	0.5±0.3*
Day 3					
Baseline	353±16	331±11	27±2	81±3	0.002±0.01
Readaptation	371±18	326±10	26±2	73±3	2.2±0.6
Washout	371±15	331±9	26±1	79±2	-0.2±0.3

Values depict the mean ± SEM determined for each subject by averaging over consecutive epochs. MT=movement time; RT=reaction time; Max V=peak velocity; Max V %=time point in movement (%) when peak velocity occurred; Online corrections=difference between angular error at peak velocity and angular endpoint error. *Significant difference compared to stroke groups (one-way ANOVA).

One-way ANOVA between patients and healthy controls showed the followings significant results:

- RT Day 1, $F_{(3,56)}=8.42$, $p<0.001$, $\eta^2=0.311$
- RT Baseline day 2, $F_{(3,56)}=7.7$, $p<0.001$, $\eta^2=0.291$
- RT Adaptation, $F_{(3,56)}=6.9$, $p<0.001$, $\eta^2=0.271$
- RT Washout day 2, $F_{(3,56)}=7.7$, $p<0.001$, $\eta^2=0.294$
- RT Baseline day 3, $F_{(3,56)}=7.6$, $p<0.001$, $\eta^2=0.289$
- RT Readaptation, $F_{(3,56)}=6.5$, $p=0.001$, $\eta^2=0.258$
- RT Washout day 3, $F_{(3,56)}=9.2$, $p<0.001$, $\eta^2=0.331$

- Max V % day 1, $F_{(3,56)}=3.16$, $p=0.032$, $\eta^2=0.145$
- Online corrections washout day 2, $F_{(3,56)}=5.2$, $p=0.003$



Supplementary figure 1 Patients enrolment. The reasons for exclusion of patients from the study were: incapability to perform the task due to excessive weakness (n=5 patients); cardiorespiratory impairment (n=3); cerebellar stroke (n=2); significant peripheral motor problems (n=1); significant sleep disturbance (n=1).