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BRIEF COMMUNICATION

Sensorimotor rhythm neurofeedback as adjunct therapy for Parkinson's disease

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Abstract

Neurofeedback may enhance compensatory brain mechanisms. EEG-based sensorimotor rhythm neurofeedback training was suggested to be beneficial in Parkinson's disease. In a placebo-controlled study in parkinsonian nonhuman primates we here show that sensorimotor rhythm neurofeedback training reduces MPTP-induced parkinsonian symptoms and both ON and OFF scores during classical L-DOPA treatment. Our findings encourage further development of sensorimotor rhythm neurofeedback training as adjunct therapy for Parkinson's disease which might help reduce L-DOPA-induced side effects.

Introduction

L-DOPA treatment for Parkinson's disease (PD) may have significant long-term side effects.[1] Real-time electroencephalography (EEG)-based neurofeedback, as a voluntary operant conditional training for self-regulation of brain function, was applied to treat epilepsy,[2] anxiety,[3] substance abuse,[4] and attention deficit/hyperactivity disorder (ADHD).[5] Sensorimotor rhythm (SMR) neurofeedback training can reduce susceptibility to epilepsy in cats.[6] SMR, an oscillatory thalamocortical rhythm of synchronized brain activity of 12–17 Hz above the sensorimotor cortex, is suppressed during contralateral motor performance or motor imagery.[7] Trained modulation of premovement SMR affects motor performance in healthy humans.[8] In a case study in a PD patient SMR neurofeedback combined with respiration-based biofeedback reduced L-DOPA dose and improved PD symptoms.[9,10] As the MPTP marmoset monkey is a well-validated model for PD,[11–13] and marmoset monkeys are able to voluntarily control SMR by neurofeedback training,[11] we here study the impact of SMR neurofeedback training on MPTP-induced parkinsonian symptoms and on OFF and ON scores during classical L-DOPA treatment in a placebo-controlled study in MPTP marmoset monkeys.

Material and Methods

Animals

We included 10 healthy adult (age 2–4) common marmoset monkeys (*Callithrix jacchus*) of both sexes (5F/5M) (325–425 g) from BPRC's colony. Monkeys were experimentally naïve, pair-housed in spacious cages, under intensive veterinary care and controlled conditions compliant with European Community guidelines,[11] daily fed with standard monkey-chow (Special Duit Services, Witham, Essex, UK), fruits, vegetables and ad libitum

water supply, equally divided over both groups concerning age, gender and facility room. The Institute's Ethics Committee approved study protocol and experimental procedure.

Experimental design

Monkeys were freely moving, implanted with two epidural sensorimotor cortex bioelectric bipolar electrodes for real time telemetric EEG registration and subcutaneous bioelectric chest electrodes for electrocardiogram (ECG) recording.[11] Three weeks after EEG surgery half the monkeys (n = 5, 3F/2M) had 1–2 SMR neurofeedback trainings per week to positively reinforce SMR EEG spindles by food rewards. Training sessions were finished after 35 rewards or after 30 min. EEG power spectra were calculated online from 1.28 sec EEG epochs.[11] Detection of characteristic 12–17 Hz SMR spindles (spectral EEG power below 11 V^2 Hz at 9 and 20 Hz and beyond 23 V^2 Hz for 11–18 Hz) triggered a positively reinforcing release of a marshmallow-like reward.[11] Once rewards were quickly achieved, training rate was reduced to 1/week till end of study. Control monkeys (n = 5, 2F/3M) were exposed to same training sessions receiving same amounts of rewards but not related to brain activity. After 9–12 training sessions PD was induced in all monkeys by five daily 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, Sigma Aldrich, USA) subcutaneous injections (total dose: 8 mg/kg). After disease stabilization, all monkeys were treated with L-DOPA (Madopar, 12.5 mg/kg p.o. BID for 3 weeks, Arabic Gum powder, Fagron Ltd, UK).[14] Finally, anesthetized monkeys were euthanized for pathological examination.

Behavioral observations and measurements

Blinded ratings of parkinsonian signs (immobility, muscle rigidity, rest tremor, apathy, inadequate grooming), between 0 (normal/healthy) and 4 (severely affected), were performed in the monkeys' home cages every morning, i.e. 15 h post L-DOPA dose during treatment phase (OFF scores), and during the last 10 days also 2 h post dose (ON scores).[15] Body weight was measured every week and every time before drug administration and expressed relative to individual baseline (i.e. average of 4 subsequent pre-study days). Before noon monkeys' emotional mood was assessed with the Human Threat Test (HTT)[16] before (baseline), three times during the training phase and five times during L-DOPA treatment. Baseline was set to 100%. For HTT, during a two-minute period monkeys' postures and jumps were scored as fear related or relaxed and expressed as ratio between number of relaxed postures and jumps relative to total number.[16] All observations were made by two cross-validated blinded technicians.

Pathology

Dopamine positive neurons of the *Substantia nigra pars compacta (SNpc)* were counted with tyrosine hydroxylase immune reactive (TH-IR) staining by a blinded technician.[15,16]

Statistics

Animal group size N was based on statistical power calculation with simple between group t-tests: $N = 2(Z\alpha/2 + Z\beta)^2 * (SD/ES)^2$ with α=0.05, $Z\alpha/2 = 1.96$, β=0.2 (80% power), $Z\beta$=0.84. Parkinsonian score as primary outcome measure, SD=8 (based on previous experiments), effect size 16 yielded $N = 4$ (assuming normal distribution) and $N = 5$ (adjusted to student t distribution).

For HTT, body weight, ON scores (also compared with OFF scores) and pathology a between-group comparison was performed with independent t -tests with Welch's correction. Variance between groups was similar for body weight ($F = 1.944$, DFn = 13, Dfd = 13, $P = 0.2439$), HTT ($F = 2.120$, DFn = 8, Dfd = 8, $P = 0.3083$), L-DOPA effect ($F = 2.236$, DFn = 9, Dfd = 9, $P = 0.2465$) and pathology ($F = 2.114$, DFn = 4, Dfd = 4, $P = 0.2439$). OFF scores were analyzed with linear mixed-effects model fit by residual maximum likelihood estimations (REMLs). Performance improvement in each session was expressed as increase in the slope of the curve. $P < 0.05$ was considered significant.

Results

EEG Effects

Figure 1 shows raw sensorimotor cortex EEG signals without (Fig 1A) and during SMR neurofeedback training (Fig 1B). Food rewards were triggered by EEG epochs with characteristic SMR spindles. Representative power spectra during SMR neurofeedback training showed pronounced SMR peaks, whereas controls showed random EEG spectra (Fig 2). In one control monkey electrode failure impeded EEG recordings, but it completed the control training protocol.

Symptoms' progression and adjunct treatment

Blinded ratings showed less severe parkinsonian symptoms in neurofeedback-trained monkeys compared to controls during PD induction (Fig 3A) and reduced

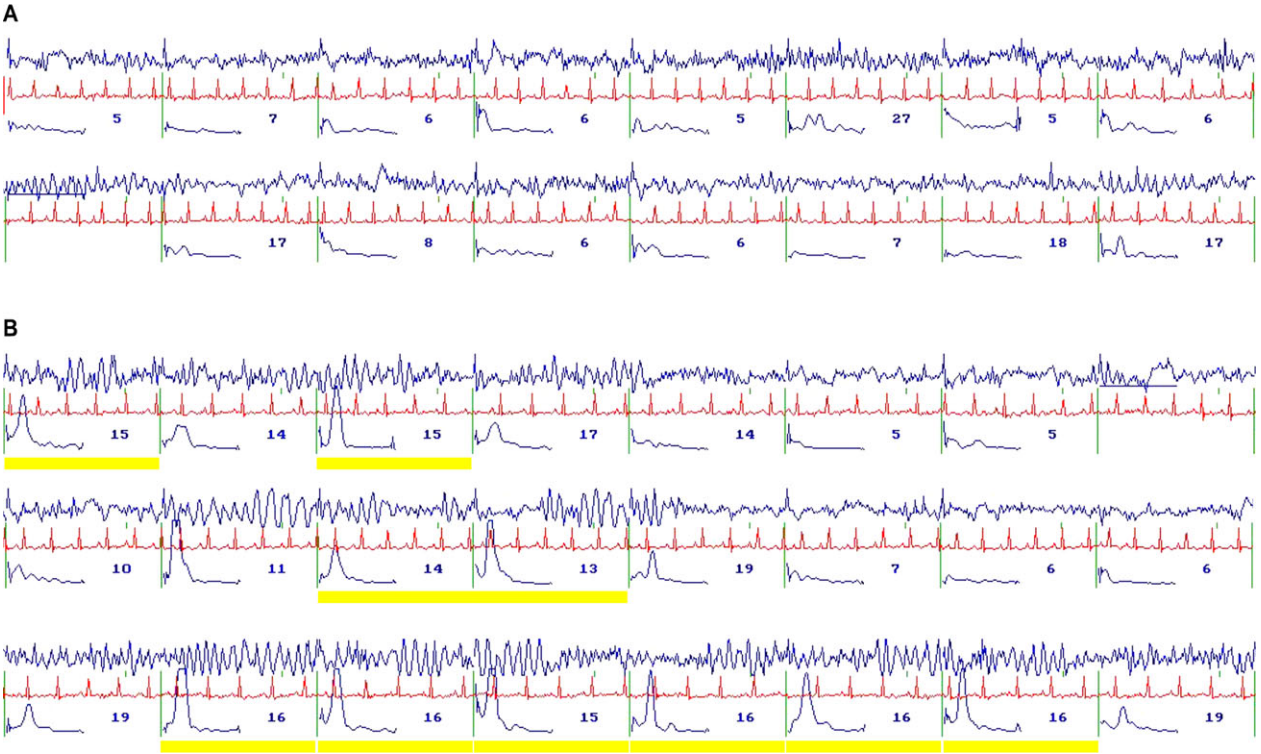

Figure 1. EEG (blue curves) with power spectra underneath (blue, from 1.28-s epochs separated by green lines, axes equally scaled, numbers indicating peak frequency) and ECG (red curves) during (A) control (two traces) and (B) SMR neurofeedback training (three traces). Yellow bars indicate epochs with SMR spindles. No power spectrum calculation for noisy epochs (horizontal blue lines in second and third trace).

scores during the stabilization phase compared to controls. During identical L-DOPA treatment, both ON and OFF scores were significantly reduced in neurofeedback-trained monkeys compared to controls, respectively (Fig 3A). Note, even OFF scores in neurofeedback-trained monkeys were significantly smaller than ON scores in controls (Fig 3A).

Secondary parameters

The MPTP-induced decline in body weight was smaller in neurofeedback-trained monkeys (Fig 3B). HTT revealed a mood increase owing to the monkeys' handling before PD induction in both groups (Fig 3C). During L-DOPA treatment control monkeys' mood fell below baseline, whereas neurofeedback-trained monkeys improved. Heart rate varied between 240-300 beats/min and 220–250 beats/min in control and in neurofeedback-trained monkeys, respectively.

Pathology

Both groups had a > 50% cell loss of TH-IR positive SNpc neurons compared to healthy controls ($P < 0.01$), without difference between neurofeedback ($n = 5$) and control group ($n = 5$) (40.75 ± 4.76% vs. 34.56 ± 6.93% cell survival, t -test with Welch's correction, $t = 0.7361$, df = 7.092, $P = 0.4853$).

Discussion

We showed that SMR neurofeedback reduces MPTP-induced parkinsonian symptoms and body weight loss in monkeys compared to control monkeys. Both groups had no difference in TH-positive SNpc neurons, ruling out neuroprotective effects. SMR neurofeedback training might enhance compensatory mechanisms, comparable with presymptomatic PD compensation[17,18] or paradoxical movement.[19] We found that during L-DOPA treatment, ON and OFF scores were significantly smaller in SMR neurofeedback-trained monkeys compared to controls, respectively. Intriguingly, OFF scores in SMR monkeys were even significantly smaller compared to ON scores in controls. Future studies should address the impact of the selected frequency band (here 12–17 Hz) to demonstrate SMR specificity and help elucidate the role of controversially discussed basal ganglia-thalamocortical rhythms.[20–24] We showed that SMR neurofeedback

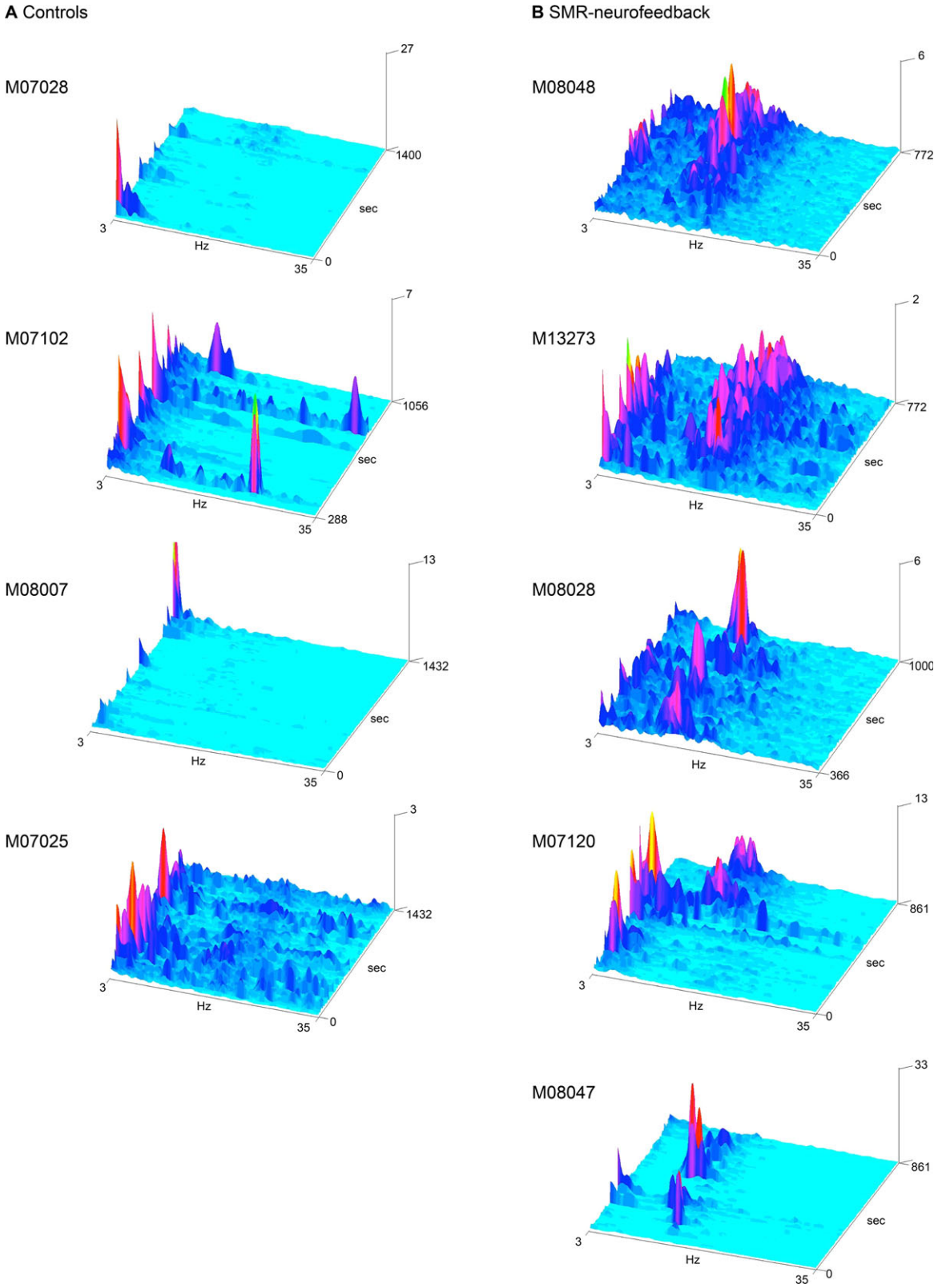

Figure 2. Time-varying power spectra of 30-min EEG recordings in monkeys with (A) control (n = 4) and (B) SMR neurofeedback training (n = 5) normalized by highest individual peak for each monkey. Only neurofeedback-trained monkeys had pronounced 12–17 Hz SMR peaks.

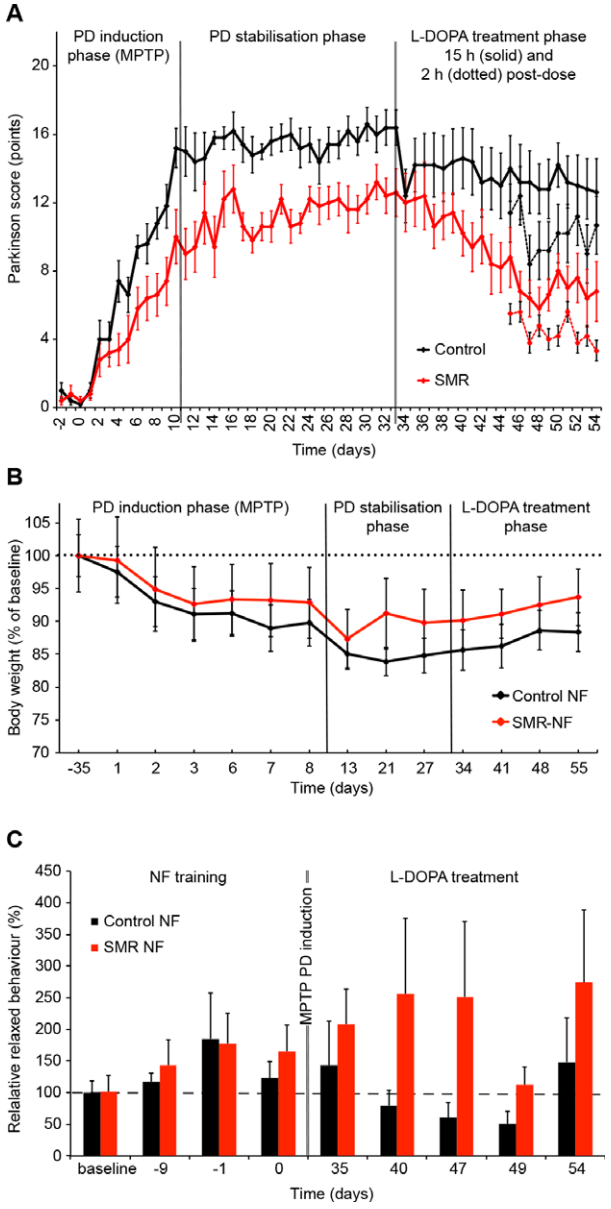

Figure 3. (A) MPTP-induced averaged parkinsonian scores (±SE, $n = 5$ per group) were alleviated during PD induction (left, first MPTP injection on day 0) and reached lower levels during disease stabilization (middle) in neurofeedback monkeys (red curve) compared to controls (black curve) (resp. slope: $P = 0.0077$ and intercept: $P = 0.0234$). Neurofeedback interacted synergistically with L-DOPA treatment OFF scores (right) compared to controls (solid lines; slope: $P < 0.0001$) and improved the ON scores (dashed lines; *t*-test with Welch's correction: $P < 0.0001$, two-tailed). SMR monkeys' OFF scores were significantly smaller than controls ON scores (*t*-test with Welch's correction: $P < 0.0001$, two-tailed). (B) Normalized body weight reduction was significantly greater in controls (black) compared to SMR neurofeedback (SMR NF) monkeys (red) (mean ± SE, $n = 5$ per group, unpaired *t*-test with Welch's correction, $t = 2.176$, df=23.58; $P = 0.0398$, two-tailed). Dotted line indicates pre-MPTP baseline. (C) Averaged HHT score (±SE, $n = 5$ per group) at baseline, during SMR/control neurofeedback (NF) training (left) and combined with L-DOPA (started on day 34). SMR trained monkeys had significantly improved HTT scores compared to controls (unpaired *t*-test with Welch's correction, $t = 2.936$, df = 14.17; $P = 0.0107$, two-tailed).

reduced monkeys' heart rate close to anesthesia levels (206–245 beats/min)[25] and improved HTT mood scores,[16] in accordance with findings in normal humans.[10]

In conclusion, SMR neurofeedback is a promising adjunct approach for further development as treatment for PD motor symptoms to lower the L-DOPA-induced side effects.

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Author Contribution

I.P. and P.T. (when he was affiliated with Research Center Juelich, and Cologne University, Germany) designed the study. I.P supervised the project. R.V. prepared the experimental setup. D.E. collected the data. J.W. performed and analyzed the histology. R.V., I.P., and P.T. analyzed the data. I.P., J.W. and P.T. discussed the findings. I.P. and P.T. wrote the paper.

Conflict of Interests

The authors declare no competing financial interests.

References

1. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448–458.
2. Egner T, Sterman MB. Neurofeedback treatment of epilepsy: from basic rationale to practical application. Expert Rev of Neurotherapeutics 2006;6:247–257.

3. Moore NC. A review of EEG biofeedback for anxiety disorders. Clin Electroencephalogr 2000;31:1–6.
4. Cannon R, Sokhadze T, Trudeau D. EEG Biofeedback as a treatment for substance use disorders: review, rating of efficacy, and recommendations for further research. Appl Psychophysiol Biofeedback 2008;33:1–28.
5. Fox DJ, Tharp DF, Fox LC. Neurofeedback: an alternative and efficacious treatment for Attention Deficit Hyperactivity Disorder. Appl Psychophysiol Biofeedback 2005;30:365–373.
6. Sterman MB, Egner T. Foundation and Practice of Neurofeedback for the treatment of Epilepsy. Appl Psychophysiol Biofeedback 2006;31:21–35.
7. Roth SR, Sterman MB, Clemente CD. Comparison of EEG correlates of reinforcement, internal inhibition and sleep. Electroencephalogr Clin Neurophysiol 1967;23:509–520.
8. McFarland DJ, Sarnacki WA, Wolpaw JR. Effects of training pre-movement sensorimotor rhythms on behavioral performance. J Neural Eng 2015;12:066021.
9. Thompson M, Thompson L. Biofeedback for movement disorders (dystonia with Parkinson's disease): theory and preliminary results. J Neurotherapy 2002;6:51–70.
10. Thompson M, Thompson L. Improving quality of life using biofeedback plus neurofeedback. Neuroconnections 2011;Winter:18–21.
11. Philippens IHCHM, Vanwersch RAP. Neurofeedback training on sensorimotor rhythm in marmoset monkeys. NeuroReport 2010;21:328–32.
12. Eslamboli A. Marmoset monkey models of Parkinson's disease: which model, when and why? Brain Res Bull 2005;68:140–149.
13. Philippens IHCHM. Non-human primate models for Parkinson's disease. DDT: Disease Models 2009;5:105–111.
14. Fox SH, Henry B, Hill MP, et al. Neural mechanisms underlying peak-dose dyskinesia induced by levodopa and apomorphine are distinct: evidence from the effects of the alpha(2) adrenoceptor antagonist idazoxan. Mov Disord 2001;16:642–650.
15. Philippens IHCHM, Wubben JA, Finsen B, 't Hart A. Oral treatment with the NADPH oxidase antagonist apocynin mitigates clinical and pathological features of parkinsonism in the MPTP marmoset model. J Neuroimmune Pharmacol 2013;8:715–26.
16. van Vliet SA, Vanwersch RA, Jongsma MJ, et al. Neuroprotective effects of modafinil in a marmoset Parkinson model: behavioral and neurochemical aspects. Behav Pharmacol 2006;17(5–6):453–462.
17. Appel-Cresswell S, de la Fuente-Fernandez R, Galley S, McKeown MJ. Imaging of compensatory mechanisms in PD. Curr Opin Neurol 2010;23:407–412.
18. Bezard E, Gross CE, Brotchie JM. Presymptomatic compensation in Parkinson's disease is not dopamine-mediated. Trends Neurosci 2003;26:215–221.
19. Glickstein M, Stein J. Paradoxical movement in Parkinson's disease. Trends Neurosci 1991;14: 480–482.
20. Doyle LM, Kühn AA, Hariz M, et al. Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. Eur J Neurosci 2005;21:1403–1412.
21. Pollok B, Kamp D, Butz M, et al. Increased SMA-M1 coherence in Parkinson's disease - Pathophysiology or compensation? Exp Neurol 2013;247:178–181.
22. Leblois A, Meissner W, Bioulac B, et al. Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism. European J Neurosci 2007;26:1701–1713.
23. Leblois A, Boraud T, Meissner W, et al. Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. The J Neurosci 2006;26:3567–3583.
24. Beudel M, Brown P. Adaptive deep brain stimulation in parkinson's disease. Parkinsonism Relat Disord 2016;22: S123–S126.
25. Davies JA. Some aspects of the physiology of the anaesthetised marmoset. Lab Anim 1969;3:151–156.

