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Vibrotactile coordinated reset stimulation for the treatment of Parkinson's disease

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Introduction of the treatment concept: Regular deep brain stimulation (rDBS) is the standard therapy for the treatment of medically refractory Parkinson's disease (PD) (Benabid et al., 2009). Notwithstanding its significant therapeutic effects, rDBS may cause side effects, characterized as rDBS-induced movement disorders (Baizabal-Carvallo and Jankovic, 2016). Abnormal neuronal synchrony is a hallmark of Parkinson's disease (Hammond et al., 2007). Coordinated reset (CR) stimulation was computationally developed to cause an "unlearning" of pathologically persistent synchrony and synaptic connectivity, thereby inducing long-lasting therapeutic effects (Tass and Majtanik, 2006; Tass, 2017). The CR approach was initially developed for DBS (Tass and Majtanik, 2006; Tass et al., 2012; Adamchic et al., 2014) and thereafter, employing vibratory CR stimuli enabled the development of vibrotactile CR (vCR) fingertip stimulation (Tass, 2017). Two recent clinical feasibility studies with vCR in PD patients demonstrated that delivery of vCR for four hours per day for 3^+ months is feasible, has no side effects, and leads to a clinically and statistically significant reduction of Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPRDS III) scores (Pfeifer et al., 2012). In one of these feasibility studies, electroencephalography (EEG) recordings demonstrated that cortical sensorimotor high beta power (21–30 Hz) at rest was significantly reduced after three months of daily vCR therapy (Pfeifer et al., 2021). Remarkably, in both studies MDS-UPDRS exams as well as EEG recordings were performed off medication, where PD medication was properly withdrawn for 12–48 hours prior to the patients' morning MDS-UPDRS exams and EEG recordings, depending on the PD medication's half-life. These encouraging results enable the development of a proof-of-concept study with vCR for the treatment of PD. In addition, these results highlight the potential for vibrotactile, non-invasive neuromodulation approaches employing dedicated multichannel stimulus patterns for the treatment of PD.

Target plasticity mechanism of CR: Already in the 19th century, Charcot observed that Parkinson's symptoms may decrease after long carriage trains or horseback rides (Tass, 2017). However, the overall effects of, e.g., whole-body vibration therapy on PD turned out to be limited and somewhat inconsistent (Dincher et al., 2019). To leverage the potential of vibration therapy, the CR approach (Tass and Majtanik, 2006) was adapted for the use of non-invasive, vibrotactile stimuli (Tass, 2017; Syrkin-Nikolau et al., 2018; Pfeifer et al., 2021). CR stimulation was initially developed computationally in the context of DBS, to specifically counteract abnormally persistent neuronal synchrony observed in PD, by administering brief high-frequency electrical pulse trains in a patterned sequence to cause desynchronization (Tass and Majtanik, 2006; Tass, 2017). By employing dynamic self-organization and synaptic plasticity principles, CR stimulation patterns aim at an "unlearning" of abnormal synaptic connectivity and pathologically persistent synchrony (Tass and Majtanik, 2006; Tass, 2017). Accordingly, therapeutic effects may outlast stimulation cessation.

Pre-clinical and clinical studies with CR-DBS: A few hours of electrical CR stimulation delivered to the subthalamic nucleus (STN) of parkinsonian non-human primates had both acute and sustained, weeks-long after-effects on motor function (Tass et al., 2012). In contrast, long-lasting after-effects were not observed with rDBS (Tass et al., 2012). By the same token, CR stimulation of the STN delivered to PD patients for four hours during three consecutive stimulation days led to a significant and cumulative reduction of beta-band activity in the STN local field potential and a correlated significant motor improvement (Adamchic et al., 2014).

Transition to non-invasive stimulation: It was hypothesized that CR's cumulative and long-lasting therapeutic effects should enable sustained therapeutic effects by delivering stimulation for only a few hours regularly or occasionally, specifically by non-invasive CR approaches (Tass, 2017). The large cortical representation of fingertips, the response properties of neurons in the cutaneous core of the human thalamic somatic sensory nucleus to skin vibration and computational predictions led to the development of vCR fingertip stimulation for the treatment of PD (Tass, 2017). To this end, brief electrical bursts invasively delivered to the STN were replaced by vibratory bursts, non-invasively delivered to the fingertips through a glove system (Tass, 2017; Syrkin-Nikolau et al., 2018; Pfeifer et al., 2021).

First-in-human vCR study: In a first-in-human study, five idiopathic PD patients were treated with vCR fingertip stimulation for four hours per day on three consecutive days (Syrkin-Nikolau et al., 2018). Four of these patients were completely off medication during the three stimulation days and the subsequent (stimulation-free) assessment visits, whereas one patient remained on medication during the entire protocol. In the four patients staying off medication, kinematic assessments demonstrated an improvement of gait and bradykinesia during stimulation days and at the 1-month follow-up visit after cessation of stimulation (as assessed off medication). However, no significant changes were obtained in blinded video UPDRS III scores, though notably, video ratings did not allow for assessment of rigidity and speech. The patient remaining on medication revealed a similar improvement. Without sham stimulation conditions, placebo effects could not rigorously be ruled out, although their contribution to the long-lasting improvement was less likely (Syrkin-Nikolau et al., 2018).

Months-long pilot studies with vCR: Pfeifer and colleagues performed two months-long clinical feasibility studies with improved vibration amplitude (see below) to investigate the effect of regular vCR fingertip stimulation (study 1) and noisy vCR fingertip stimulation (study 2) on PD motor symptoms (Pfeifer et al., 2021). For regular vCR, vibratory bursts were delivered at periodic stimulus times. In contrast, for noisy vCR the stimulus timing had a moderate jitter (± 23.5%) of the inter-stimulus intervals. The jitter was introduced based on the computationally based hypothesis that sufficient jitter may improve the long-lasting desynchronization and, hence, long-term clinical outcome (Pfeifer et al., 2021). For both regular and noisy vCR, vibrotactile stimulation was delivered to fingertips 2–5 of both hands (excluding the thumbs).

vCR study 1: In the feasibility pilot study (Pfeifer et al., 2021), six patients with clinically diagnosed mild to moderate idiopathic PD, further classified as tremor-dominant (n = 4), postural instability/gait difficulty (n = 1), and intermediate (n = 1), received noisy vCR stimulation for 3 months. To assess acute vCR effects at the outset of treatment, on the first vCR treatment day, patients received twice 2 hours

of vCR. MDS-UPDRS III scores were taken before and after the in total four hours of vCR. Patients remained off medication until after the second MDS-UPDRS III exam. MDS-UPDRS III scores were significantly reduced after the four hours of vCR (paired-samples *t*-test, *N* = 6, *t*(5) = 4.297, *P* = 0.008, SD = 4.56). By the same token, axial symptom subscores also showed a significant acute effect (*t*(5) = 4.719, *P* = 0.005, SD = 1.211). To assess whether the acute vCR effects were clinically significant, acute reduction of MDS-UPDRS III scores were compared with the minimal clinically important differences (MCID) of the MDS-UPDRS III. Although patients remained off medication, five out of six patients showed a clinically significant acute reduction of MDS-UPDRS III scores exceeding the MCID (3.25) (green bars, **Figure 1A**). Cumulative vCR effects were studied by comparing off medication MDS-UPDRS III scores before and after the 3-month vCR therapy, revealing a significant reduction of MDS-UPDRS III scores (paired-samples *t*-test, *N* = 6, t(5) = 2.890, *P* = 0.034, SD = 5.93). In particular, all patients showed a clinically significant cumulative reduction of MDS-UPDRS III scores after three months of vCR treatment (orange bars, **Figure 1A**). EEG recordings performed off medication before (**Figure 1B**) and after (**Figure 1C**) the 3-month noisy vCR therapy revealed a significant decrease in cortical sensorimotor high beta power (21–30 Hz) at rest (paired-samples *t*-test, t(4) = 3.012, *P* = 0.030, SD = 0.015). In addition, Levodopa equivalent daily dose was reduced on average by 7.82% after the 3-month vCR therapy.

vCR study 2: The 6^{+} months feasibility case series study in three patients with idiopathic PD was performed to investigate the long-term cumulative effects of vCR (Pfeifer et al., 2021). Off medication MDS-UPDRS III scores were obtained before vCR therapy and approx. every 3 months for 1–3 days during each follow-up visit. Patients 1 and 2 received regular vCR, while patient 3 (recruited from study 1, which had to be terminated after three months because of COVID-19) received noisy vCR. All three patients showed sustained cumulative therapeutic effect as demonstrated by a significant linear decrease of the off medication MDS-UPDRS III scores (two-tailed Pearson's correlation, **Figure 1D–F**) as well as off medication tremor subscores. In addition, in patient 1 the off medication subscore for bradykinesia and rigidity displayed a significant linear decrease. The Hohn and Yahr (HY) scales remained at HY2 on medication for patient 1, went from HY4 on medication (pre-vCR) to HY2 on medication (with vCR) for patient 2, decreased from HY3 (pre-vCR) off medication to HY2 (with vCR) off medication for patient 3. In patient 2, gait improved from consistent use of cane and occasional use of wheelchair to walking without assistance. Medication levels (assessed by Levodopa equivalent daily dose) stably remained on a pre-vCR level in patient 1, decreased from 2700 mg/d to 900 mg/d in patient 2 and from 920 mg/d to 820 mg/d in patient 3 in the course of the vCR therapy. Patient videos can be downloaded as supplementary material (Pfeifer et al., 2021).

In the two feasibility studies (study 1 and study 2) in eight patients with idiopathic PD, no side effects were observed. Both regular vCR and noisy vCR turned out to be well-tolerated and caused sustained cumulative improvement of motor performance as assessed by off medication MDS-UPDRS III scores (Pfeifer et al., 2021). The significant reduction of high beta-band power in the sensorimotor cortex observed in study 1 indicates that noisy vCR is effectively reducing beta band activity at the cortical level, in this way contributing to an improvement of motor ability (Pfeifer et al., 2021). The clinical results and widespread EEG findings indicate that the therapeutic effects of vCR stimulation were not limited to sensory brain regions directly related to the fingertips. In particular, the clinical vCR effects imply that the desynchronizing vCR effects spread to other areas of the brain, especially motor areas (Pfeifer et al., 2021). Comparison with a sham control condition is required to disentangle vCR effects from placebo contributions. However, the longitudinally uniform improvement, together with effects well exceeding known placebo levels after 6 months, and the strong vCR effects on tremor make it unlikely that the observed pronounced improvements can be attributed to only placebo effects (Pfeifer et al., 2021).

Parameter settings for vCR stimulation: Sequences of vibratory stimuli (with 250 Hz vibration frequency and 100-ms duration) were delivered at a rate of 1.5 Hz, corresponding to a 667 ms cycle (Tass, 2017; Syrkin-Nikolau et al., 2018; Pfeifer et al., 2021). During a sequence, each fingertip of fingers 1–4 was stimulated exactly once, where both hands were stimulated in a mirrored manner. Sequence order was randomly varied. Inter-stimulus intervals were constant (for regular vCR) or subject to moderate jitter (for noisy vCR). In regards to vibration amplitude, CR is a multi-channel stimulation that requires neuronal sub-populations to be stimulated separately, thereby avoiding larger overlap between the different stimulated sub-populations (Tass and Majtanik 2006; Tass, 2017). Accordingly, pre-clinical studies in parkinsonian monkeys showed that CR-DBS delivered to the STN was significantly more effective, in fact causing a month-long therapeutic after-effect, with a third of the stimulus pulse amplitude used for rDBS than when using the very rDBS amplitude (Tass et al., 2012). Correspondingly, in the months-long vCR feasibility studies 1 and 2, to enhance vCR effects, perceptually weak vibration peak amplitudes (0.06–0.10 mm) were used (Pfeifer et al., 2021). Consequently, vCR at weak vibration amplitudes was not perceived as distracting or unpleasant, and patients were able to pursue different daily activities, including watching TV, making calls and going for a walk (Pfeifer et al., 2021). In contrast, in the first-in-human vCR study perceptually strong, potentially distracting vibration peak amplitudes (0.35 mm) were utilized (Syrkin-Nikolau et al., 2018).

vCR and neurodegeneration: Different fields of research focus on PD pathophysiology (uncovering circuit mechanisms related to symptoms) and PD pathogenesis (devoted to molecular and cellular neurodegeneration mechanisms). However, PD pathophysiology and pathogenesis may mutually interfere (McGregor and Nelson, 2019; Haelterman et al., 2019). In fact, abnormal neuronal activity and synaptic connectivity may crucially contribute to ongoing pathogenesis in PD, inducing a vicious circle giving rise to oxidant stress and mitochondrial impairment, ultimately resulting in a bioenergetic crisis and the death of dopamine neurons in the substantia nigra (Haelterman et al., 2019; McGregor and Nelson, 2019). By the same token, therapy-induced changes of synaptic connectivity may affect disease spread (Braak et al., 2003). Accordingly, vCR-induced long-lasting reduction of abnormal activity and connectivity may not only have an impact on PD pathophysiology but also on the underlying pathogenesis. However, future pre-clinical and clinical studies will have to further elucidate vCR's mechanism of action. Apart from its translational prospects, vCR may also provide a tool to study causal links between PD pathophysiology and pathogenesis, mediated by targeted modulation of plasticity.

Outlook – clinical trials: In summary, the encouraging results revealed by Pfeifer et al. (2021) enabled the development of an ongoing randomized double-blind sham-controlled proof-of-concept study with vCR for the treatment of PD (ClinicalTrials.gov identifier: NCT04877015) and an upcoming dose-finding study to optimally reduce daily stimulation dose for ease of use and compliance, enabling vCR to be administered, e.g., for a total of three hours per day during the first weeks, ultimately decreasing to a

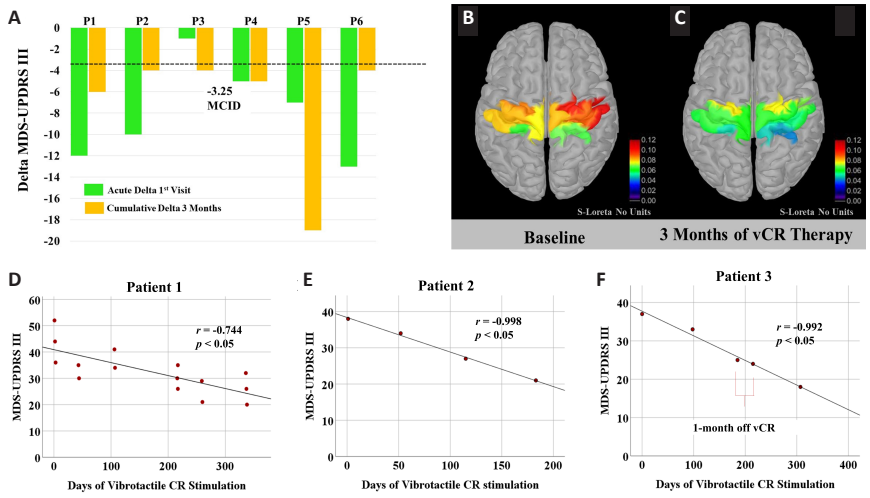

Figure 1 | **Acute, cumulative and long-lasting off medication clinical and EEG effects of VCR stimulation.**

(A) Clinical significance of acute and cumulative vCR therapy outcomes were assessed by comparing Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) score changes [i.e., Delta MDS-UPDRS III = post-vCR MDS-UPDRS III minus pre-vCR MDS-UPDRS III] with minimal clinically important differences (MCID = –3.25, dashed line) for all six patients (P1,…,P6). Green bars illustrate reduction of MDS-UPDRS III on the first visit (afternoon score minus morning score) to measure acute effects after 4 hours of vCR therapy. Five out of six patients showed a clinically significant acute reduction of MDS-UPDRS III while staying off medication. Orange bars correspond to the reduction of MDS-UPDRS III after 3 months of vCR therapy (3-month score minus baseline score). All patients displayed a clinically significant reduction of MDS-UPDRS III scores after the 3-month vCR therapy. (B, C) Relative power for the high beta (21–30 Hz) band in the sensorimotor cortex obtained from at-rest EEG recordings performed off medication at baseline (B) and after 3 months (C) of vCR therapy revealed by standardized low-resolution brain electromagnetic tomography (sLORETA). High beta relative power significantly decreased after the 3-month vCR treatment. (A–C) All MDS-UPDRS III ratings and EEG recordings were performed off medication and belong to study 1. (D–F) VCR study 2: In all three patients, off medication morning MDS-UPDRS III scores decreased in the course of the vCR treatment as reflected by significant negative correlations between MDS-UPDRS III scores and days of vCR therapy (Patient 1 (D), $r = –0.744$, $P = 0.001$; Patient 2 (E), $r = –0.998$, $P = 0.002$; Patient 3 (F), $r = –0.992$, $P = 0.001$). In patient 3 (F) the MDS-UPDRS III score was slightly decreased after the preplanned 1-month vCR pause between 6 and 7 months. (D–F) All MDS-UPDRS III ratings were obtained off medication and belong to study 2. Reprinted with permission from Pfeifer et al. (2021).

total of only a few hours per week after a few months. Furthermore, these results indicate that vCR may ultimately provide a safe and tolerable non-pharmacological and non-invasive treatment option for PD patients. Acute and long-lasting effects were tested after delivering vCR off medication (Syrkin-Nikolau et al., 2018; Pfeifer et al., 2021) as well as on medication (Pfeifer et al., 2021). However, in future clinical applications vCR should be delivered most conveniently, not requiring medication withdrawal. vCR stimulation might also be applied to the treatment of other brain disorders characterized by abnormal neuronal synchrony, e.g., movement disorders, such as essential tremor and dystonia, as well as epilepsies.

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