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Evaluation of Neurofeedback Training in the Treatment of Parkinson's Disease: A Pilot Study

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SCIENTIFIC FEATURES

EVALUATION OF NEUROFEEDBACK TRAINING IN THE TREATMENT OF PARKINSON'S DISEASE: A PILOT STUDY

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We assess the effects of EEG biofeedback training on levodopa-induced dyskinesia (LID) in patients with Parkinson's disease (PD) using a sham feedback controlled study design. Nine subjects were randomized into either a treatment group or control group and underwent 24 sessions of either active feedback training or sham feedback. The training protocol aimed at increasing 8–15 Hz activity while inhibiting excess 4–8 Hz and 23–34 Hz activity at the C3-C4 derivation. There were no statistically significant differences baseline to post-active neurofeedback training as compared to sham feedback training in primary outcome measures assessing change in dyskinesia severity, nor in secondary outcome measures assessing change in clinical features of PD. Nonsignificant trends were observed in subjects' PD home diaries indicating a decrease in the severity of motor fluctuations. Baseline to post-training comparisons of secondary outcome measures in quantitative EEG analysis showed significant interaction effects within and between frontal and posterior regions, accompanied by decreases in 25–30 Hz (high beta) relative power, cross spectral power and phase resets per second activity, and significant increases in 8–12 Hz (alpha) relative power, cross spectral power, and coherence activity. These results indicate that EEG biofeedback training can affect the spectral EEG topography of individuals with PD and LID and that training to increase 8–15 Hz activity and decrease 23–34 Hz activity may have been associated with a nonsignificant decrease in dyskinesia severity and an improved sense of well-being.

INTRODUCTION

Individuals with Parkinson's disease (PD) have been shown to have characteristic bioelectrical aberrancies that correspond with Parkinsonian symptomatology and that may be sensitive to alteration through neurofeedback training. Studies utilizing local field potential recordings in patients in the untreated Parkinsonian state have found marked synchronized 11–30 Hz (Brown, 2003; Hammond, Bergman, & Brown,

2007; Marsden, Limousin-Dowsey, Ashby, Pollak, & Brown, 2001; Silberstein et al., 2003; Silberstein et al., 2005) and 4–10 Hz (Brown, 2003; Williams et al., 2002) oscillatory activity in the basal ganglia-thalamo-cortical circuit. In patients with advanced-stage PD, this activity is thought to be antikinetic in nature. Indeed, reductions in the amount of 11–30 Hz activity through the desynchronizing effect of either dopaminergic treatment or

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John Anderson owns and operates the Minnesota Neurotherapy Institute (St. Louis Park, MN), where he practices as a neurofeedback specialist. He also teaches a 3-day QEEG course once per year sponsored by Stens Corporation, the sole distributor for the EEG systems used in this study. This work was supported by Struthers Parkinson's Center.

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electrical stimulation at high frequencies have correlated with clinical improvement (Hammond et al., 2007; Kühn, Kupsch, Schneider, & Brown, 2006; Silberstein et al., 2005). When dyskinesia resulted from dopaminergic administration (Alonso-Frech et al., 2006) or surgical stimulation (Foffani et al., 2005), these depth recordings have found coherence in the 4–10 Hz band to be enhanced and coherence in the 13–20 Hz band to be significantly decreased.

The single case report that has been published on the effects of neurofeedback therapy on an individual with PD reported that training to increase 12–15 Hz activity over central electrode derivations was associated with a decrease in involuntary movements and an overall sense of well-being (Thompson & Thompson, 2002). Our center sought to examine the effects of EEG biofeedback training on levodopa-induced dyskinesia (LID) and other clinical features of PD using a sham-feedback-controlled study design. Based on these aforementioned findings, it was initially hypothesized that utilizing a protocol that aimed at increasing cortical 12–15 Hz activity while decreasing excess 4–10 Hz and 11–30 Hz activity over central electrode derivations would lead to a decrease in LID and possibly PD symptom severity.

METHODS

Study Design

This study utilized a partial cross-over design. Subjects were initially randomly assigned to

either the active training group or the control group and were blinded to their treatment condition. For the first half of the study, subjects in the active training group received neurofeedback training and subjects in the control group received sham feedback. After completing either 24 neurofeedback training or sham feedback sessions, subjects in both groups were unblinded, and the subjects in the control group went on to undergo 24 neurofeedback training sessions.

Subjects

Ten subjects with PD initially enrolled in the study, with five randomly assigned to the active treatment group and five to the control group. During the course of the study, three subjects—one in the control group who completed one sham feedback session, and two in the treatment group who completed 10 and 14 neurofeedback training sessions, respectively—discontinued for personal reasons not related to the study. Two additional subjects were then enrolled into the active treatment condition. These nine subjects, with four in the control group and five in the treatment group, completed the study (Table 1).

Subjects were diagnosed with PD by their treating neurologist at our center. Diagnoses were confirmed by the study neurologist (SAP) based on previously published diagnostic criteria (Gelb, Oliver, & Gilman, 1999). Study inclusion criteria also required that the subjects experience LID at least 20% of the waking day and that they be on a stable dose of standard anti-Parkinsonian medications for at least 4

TABLE 1. Demographic Characteristics and Clinical Measures at Baseline

ID	Group	Age (years)	Sex	PD duration (years)	Medications (daily dose in mg)		
					L-Dopa	Pramipexole	Other
1	Control	41	F	8	600	1.5	300 amantadine
2	Control	40	F	12	700		200 amantadine
3	Control	52	M	7	1000		5.0 ropinirole
4	Control	52	M	9	1300		1200 entacapone
5	Active	71	F	11	750	2.0	600 entacapone
6	Active	60	F	7	700	5.0	
7	Active	64	M	12	1600	1.5	300 amantadine 1400 entacapone
8	Active	65	M	12	450		
9	Active	67	F	8	350		12.5 selegiline

weeks prior to initial clinic visit. Exclusion criteria included the presence of potential causes of secondary Parkinsonism; diagnosis of an atypical Parkinsonian syndrome; prior brain surgery for PD; or cognitive impairment that, in the investigator's opinion, limited the ability of the person to follow directions. Informed written consent for participation in the study was obtained from each subject according to a protocol approved by the Park Nicollet Institute Institutional Review Board.

Outcome Measures

The primary outcome measure was change in clinical measures of dyskinesia severity baseline to post neurofeedback training. These clinical measures included the total score of the Modified Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), performed at rest (AIMS Rest) and with cognitive load (AIMS CogLoad), and also the following items from the Parkinson's Disease Home Diary (Hauser et al., 2000): the average number of hours per day the subject felt "OFF" (OFF), the average number of hours per day the subject felt "ON" without dyskinesia (ONNODYS), the average number of hours per day the subject felt "ON" with nontroublesome dyskinesia (SOMEDYS), and the average number of hours per day the subject felt "ON" with troublesome dyskinesia (TROUBDYS). Completion of the PD Home Diary required that subjects recorded the length and severity of his or her dyskinesias for two consecutive 24-hr periods every other week during the study period.

Secondary outcome measures were change in overall clinical features of PD and QEEG analysis of change in resting-state cortical activity baseline to postneurofeedback training. Secondary outcome clinical measures included the Modified Hoehn and Yahr Staging Scale score (Hoehn & Yahr, 1967); Unified Parkinson's Disease Rating Scale sections I, II, III, IV; and total scores (Fahn, Elton, & Members of the UPDRS Development Committee, 1987). Quantitative EEG data collection was performed using a NeXus-32 channel EEG device with BioTrace +32 software (Mind Media BV, Roermond-Herten,

the Netherlands) in a resting, eyes-closed condition (24 bit A/D; 512 Hz; 1–800 Hz band-pass). Sintered Ag/AgCl electrodes (electrode impedances below 5000 ohm) were placed according to the 10:20 international system and referenced to linked ears. Two min of artifact free data were selected by visual inspection. Analysis was performed using NeuroGuide normative database software (Applied Neuroscience, Inc., St. Petersburg, FL; Thatcher, Walker, Biver, North, & Curtin, 2003) to generate Z scores for the 12 QEEG parameters (absolute power, relative power, cross spectral power (CSP), peak frequency, amplitude asymmetry, phase-resets per second, coherence, phase lag, phase shift duration, bursts per second, burst duration, interburst interval) in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), and high beta (25–30 Hz) frequency bands, adjusting for age. Details on calculations for these parameters can be found in previous publications (Thatcher, North, & Biver, 2005, 2008).

Clinical assessments and QEEG analysis were performed baseline, post-sham feedback, and post-training. Clinical assessments were performed by the study neurologist (SAP), and QEEG analysis was conducted by the neurofeedback specialist (JA).

Treatment Intervention (Neurofeedback Training)

With the guide of the certified neurofeedback specialist, subjects received 30-min neurofeedback training or sham feedback sessions twice a week for 12 to 15 weeks or until they completed 24 sessions. Training sessions were recorded using a NeXus-4 DC amplifier with two individual EEG fast channels sampled at 512 samples per second using individual 24-bit analog to digital (A/D) converters for each channel. These channels were subsequently subtracted in the software and the resulting output was filtered using an IIR Elliptic 3rd order bandpass filter and converted to an amplitude signal used for training purposes.

Two channel difference training consisted of two separate individual monopolar EEG channels (A & B) with active sensors at the

C3 and C4 derivations (using the 10:20 international system), with reference sensors on the ipsilateral ears and a common ground placed at the C7 vertebra. Filters as previously described were set for 4–8 Hz (theta) and 23–34 Hz (high beta). Training reward frequencies focused on promoting increases in a 3 Hz wide bandpass within 8–15 Hz (alpha and low beta) amplitude with concurrent decreases in both 4–8 Hz and 23–34 Hz. Additional protocols included rewarding decreases in 4–8 Hz (theta) coherence for select participants.

For each training session, the subject reclined in a comfortable chair with feet up and eyes closed. Amplitude and coherence measures of the reward and inhibit frequencies were represented as audio feedback to the subjects. Operant contingencies were such that rewards were gained whenever the subject enhanced the chosen 3 Hz band within 8–15 Hz amplitude—or decreased 4–8 Hz theta coherence—while also maintaining reduced levels of theta and high beta amplitude on the inhibit channels. During each session, subjects were instructed to inform the neurofeedback technician (JA) when they felt any subjective improvement or worsening of their symptoms. The technician monitored temperature, galvanic skin response, and EEG results and observed the subjects for changes in physical manifestations of motor activity. As the overlaying objective was achievement of clinical benefit, reward frequencies were occasionally changed within individual sessions in an attempt to find the frequency that produced the greatest decrease in the physical manifestations of symptoms and corresponded with the client's own subjective self-report of improvement in feelings of physical well-being. For the majority of sessions for all subjects, the reward frequencies were focused within the 8–15 Hz range, primarily on 12–15 Hz.

For subjects in the sham condition, recordings were collected at the C3-C4 bipolar derivation. Subjects followed the same protocol as the active training group, except that instead of receiving auditory feedback on real-time recordings of their cortical activity, the auditory track they heard corresponded to a recording

from a previous session (i.e., there was no correlation between events taking place within the subject's EEG and the auditory feedback heard by the subject).

Statistical Analysis

Demographic differences between active treatment and control groups were evaluated at baseline using Mann-Whitney *U* Test. Training effects at each electrode were assessed by a 2×5 time (baseline vs. post-training) by frequency bands repeated measures analysis of variance with post hoc *t* tests with Bonferroni correction if analyses of variance were significant ($p < .05$). For statistical analyses, EEG values were averaged over groups of electrodes across the lateral and rostro-posterior axes corresponding to left frontal (FP1, F3, F7), right frontal (FP2, F4, F8), left central (C3), right central (C4), left parietal (P3), right parietal (P4), left posterior (T5, O1), right posterior (T6, O2), central (Cz), central-frontal (Fz), and central parietal (Pz). Treatment and control group differences were tested for each time period using a Wilcoxon rank sum test. Pre-post-training differences in clinical outcomes were tested using a Wilcoxon signed rank test. All analyses were done using SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Clinical Characteristics

At baseline, treatment and control groups were similar in respect to Modified Hoehn and Yahr Staging Scale staging; Unified Parkinson's Disease Rating Scale I, II, III, IV; and total scores, AIMS scores, average number of hours OFF, and average hours with troublesome dyskinesia. However, there were statistically significant differences between treatment and control groups at baseline in age (control group was younger; $p = .020$), the average number of hours ON without dyskinesia (higher in the treatment group than in the control group; $p = .030$), and the average number of hours of nontroublesome dyskinesia per day (lower

in the treatment group than the control group; $p = .030$).

Effect of Treatment

There were no statistically significant differences baseline to post-active neurofeedback training as compared to sham feedback training in primary outcome measures assessing change in dyskinesia severity (Table 2). Group analysis of PD Home Diary data indicated non-significant decreases in motor fluctuation and dyskinesia severity baseline to post-active training as compared to sham feedback. That is, although there was a 54.8% decrease in SOMEDYS in the control group after sham feedback as compared to a 17.3% decrease in the active training group, the decrease in controls was accompanied by a 9.4% decrease in ONNODYS as compared to no change in the active group, a 400% increase in TROUBDYS as compared to no change in the active group, and a 430% increase in OFF as compared to a 8.3% increase in the active group. After the control group crossed over and received active neurofeedback training, there was a 12.5% increase in ONNODYS, a 44% decrease in TROUBDYS, and OFF stayed

constant; although there was a 39.4% increase in SOMEDYS, it remained 37% below baseline levels (Table 2).

There were no statistically significant differences between baseline and post-active neurofeedback training as compared to sham feedback training in secondary outcome measures assessing change in clinical features of PD (Table 2). Baseline to post-training comparisons of secondary outcome measures in QEEG analysis showed significant differences in resting-state, baseline cortical activity among subjects. Within the relative power parameter, significant frequency band \times time interaction effects were detected in both right and left posterior and frontal regions ($p < .001$) and were accompanied by decreases in high beta activity across all four regions ($p < .001$) and by increases in alpha power in the right posterior region ($p = .005$; Figure 1). Similar interaction effects were also observed within the CSP parameter. Connections within and between right and left posterior regions and right and left frontal regions showed significant interaction effects ($p < .001$ for all eight regional derivation combinations) and were accompanied by decreases in high beta CSP and increases in

TABLE 2. Clinical Measures—Median (Range) Scores by Treatment Group

	Active group ^a		Crossover group ^b			Combined active treatment ^c	
	Pre	Post	Pre	Post-mock	Post-active	Pre	Post
AIMS Rest	7.0 (3–9)	4.0 (0–11)	4.5 (0–8)	2.0 (0–4)	3.5 (0–9)	6.0 (0–9)	4.0 (0–11)
AIMS Count	8.0 (3–14)	8.0 (2–13)	6.0 (0–12)	2.5 (0–15)	5.0 (0–8)	8.0 (0–14)	8.0 (0–13)
OFF	4.8 (3.3–5.8)	5.2 (1.5–6.5)	1.0 (0.0–6.8)	5.3 (0.0–9.3)	5.3 (0.0–9.0)	3.6 (0.0–6.8)	5.1 (0.0–9.0)
ONNODYS	9.5 (8.5–11.5)	9.6 (2.8–13.5)	5.3 (0.8–6.5)	4.8 (1.3–8.5)	5.4 (1.3–9.5)	7.5 (8.5–11.5)	7.8 (1.3–13.5)
SOMEDYS	2.3 (0.0–3.8)	1.9 (0.0–7.1)	7.3 (4.0–10.3)	3.3 (2.3–4.8)	4.6 (3.5–5.0)	3.9 (0.0–10.3)	4.0 (0.0–7.1)
ONTROUBDYS	0.0 (0.0–0.0)	0.0 (0.0–1)	0.5 (0.0–8.6)	2.5 (0.0–7.5)	1.4 (0.0–3.3)	0.0 (0.0–8.6)	0.0 (0.0–3.3)
H&Y	2.5 (2–3)	2.5 (2–3)	2.5 (2.5–2.5)	2.3 (2.0–2.5)	2.3 (2.0–2.5)	2.5 (2–3)	2.5 (2–3)
UPDRS I	3 (1–6)	3 (1–6)	2 (1–4)	2 (1–3)	0.5 (0–2)	2 (1–6)	2 (0–6)
UPDRS II	10 (9–7)	13 (10–19)	14 (7–22)	13.5 (7–23)	11 (2–24)	10 (7–22)	13 (2–24)
UPDRS III	20 (18–23)	25 (18–32)	17 (4–42)	10.5 (6–41)	7.5 (5–32)	20 (4–42)	20 (5–32)
UPDRS IV	7 (4–10)	7 (3–11)	7.5 (6–13)	8 (6–14)	8 (7–15)	7 (4–13)	7 (3–15)
UPDRS TOT	42 (38–48)	46 (40–55)	46 (29–59)	41.5 (29–57)	35 (25–46)	42 (29–59)	43 (25–55)

Note. AIMS = Modified Abnormal Involuntary Movement Scale performed at rest (AIMS Rest) and with cognitive load (AIMS CogLoad); OFF = average number of hours per day “off” medication; ONNODYS = average hours per day “on” medication with no dyskinesia; SOMEDYS = average number of hours per day “on” medication with nontroublesome dyskinesia; TROUBDYS = average hours per day “on” medication with troublesome dyskinesia; H&Y = modified Hoehn and Yahr Staging; UPDRS = Unified Parkinson’s Disease Rating Scale (sections I, II, III, IV & TOTAL scores).

^an = 5.

^bn = 4.

^cn = 9.

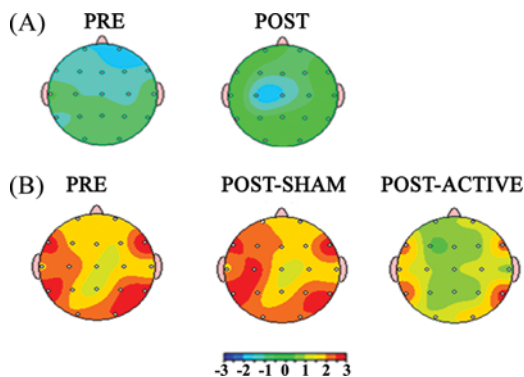


FIGURE 1. Topographic maps of relative power Z scores (A) within the alpha frequency band baseline and post-active training for one subject and (B) in the high beta frequency band baseline, post-sham feedback, and post-active feedback training for another subject. (Color figure available online.)

alpha CSP ($p < .005$ for both frequency bands in all eight regional derivations combinations). Within the coherence parameter, significant interaction effects were observed in left frontal-right posterior linked derivations ($p = .001$), accompanied by increases in alpha coherence ($p < .01$). Finally, within the phase resets per second (PRPS) parameter significant interactions were observed in right posterior-left posterior linked derivations ($p = .047$) and were accompanied by decreases in alpha ($p < .001$) and high beta PRPS activity ($p < .001$; Figure 2); decreases in alpha PRPS activity were also observed in right posterior-right posterior derivations ($p < .001$).

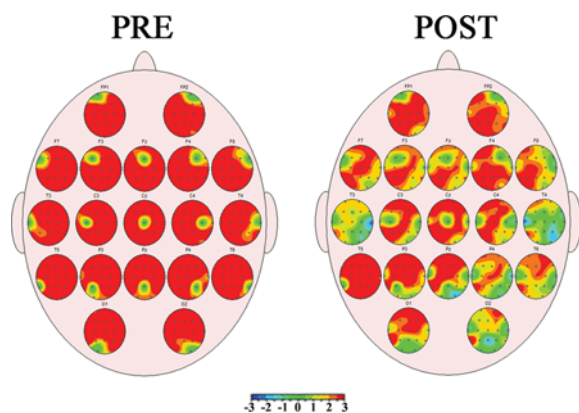


FIGURE 2. Topographic maps of high beta phase resets per second Z scores baseline and post-active training for one subject. (Color figure available online.)

DISCUSSION

We did not detect statistically significant clinical benefit for subjects receiving neurofeedback training, suggesting no objective benefits of the therapy. However, there were trends within the data that could be interpreted as showing positive effects. Diaries kept by study subjects during the course of the training indicated non-significant decreases in motor fluctuations and dyskinesia severity that were maintained with active training compared to sham feedback training. These changes, apparent in group analysis of the diaries, were also reflected in individual diary data (Figure 3). These differences were accompanied by significant changes in subjects' resting state cortical activity baseline to post-active neurofeedback training.

Similar to the previous case report (Thompson & Thompson, 2002), by training to increase 8–15 Hz activity through C3-C4 difference training, we observed nonsignificant decreases in dyskinesia severity as recorded in PD home diaries and an increase in subjects' self-reported sense of well-being (anecdotal observation made by the neurofeedback specialist and study neurologist based on subjects' self reports). In our study, this was accompanied with significant increases in alpha relative power, CSP, and coherence—and a decrease in alpha PRPS—observed in frontal and posterior regions in baseline to post-QEEG comparisons.

Of interest, we found that training to decrease 4–8 Hz coherence led to immediate self-reported worsening of PD symptoms and a decreased sense of well-being (this training strategy was immediately ceased once such discomfort or worsening was reported). We initially utilized this training protocol as previous studies found excess 4–10 Hz coherence in the untreated Parkinsonian state (Brown, 2003; Williams et al., 2002) and increases in the 4–10 Hz peak frequency when individuals with PD were given levodopa treatment that resulted in dyskinesia (Alonso-Frech et al., 2006). It is unclear what our finding of self-reported diminishment of well-being associated with training to decrease theta coherence indicates.

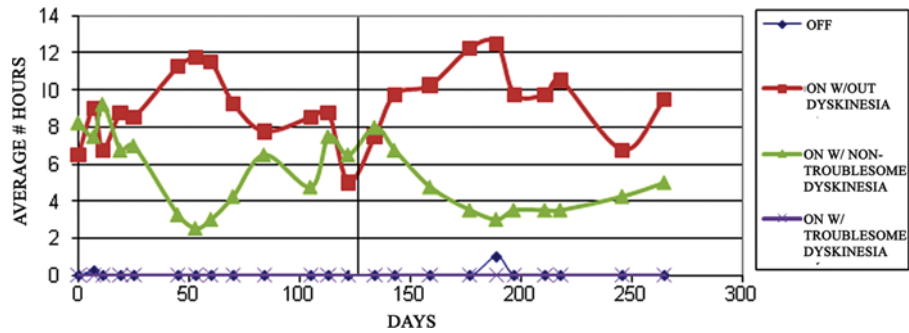


FIGURE 3. PD Home Diary record from one subject. Note. Line at Day 130 represents crossover from the sham feedback condition to active feedback training. (Color figure available online.)

Excess beta and high beta activity have previously been found to be associated with increased severity of Parkinsonian symptoms, particularly over midline derivations (Brown, 2003; Hammond et al., 2007; Marsden et al., 2001; Silberstein et al., 2003; Silberstein et al., 2005). Post-training, we observed decreases in high beta relative power, CSP, and phase resets per second activity within and between frontal and posterior regions. Conceivably, this decrease may have been associated with training to inhibit excess 23–34 Hz activity. As with the observed changes within the alpha frequency band, it is unknown why these changes in resting-state cortical activity were observed only within and between frontal and posterior regions, or whether there would have been more clinical benefit had similar changes occurred and been detected across midline-linked derivations.

The discrepancy between the failure to achieve statistically significant clinical benefit and the theoretically “positive” changes in the QEEG may be additionally attributable to several factors, including the small sample size used, the sensitivity of the outcome measures, and/or the occasional variability in the treatment protocol. Although major treatment strategies were similar across subjects, individualization of treatment protocols across a relatively short period may have interfered with the appearance of significant clinical differences. Also, the significantly greater age and lower baseline dyskinesia of the treatment group relative to the control group may have

contributed to the lack of significant effect on dyskinesia severity.

This was the first sham-controlled study of neurofeedback training in PD. Overall, LID was not influenced significantly by neurofeedback training, and PD symptoms did not change. However, results indicate that EEG biofeedback training can affect the spectral EEG topography of individuals with PD and LID, and that training to increase 8–15 Hz activity and decrease 23–34 Hz activity may have been associated with a nonsignificant decrease in dyskinesia severity and an improved sense of well-being. We believe that neurofeedback training in the treatment of PD with LID is an avenue worth further exploration using better powered studies and possibly more sensitive clinical outcome measures.

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