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Letter to the Editor

Quantitative Evidence of Pathological Tremor Suppression after Functional Electrical Stimulation

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Dear Editor-in-Chief

Pathological tremor is defined as a rapid and rhythmic movement of a body part, involuntarily shown in individuals with neurological disorders (1). These patients revealed resting, action, and postural tremor with 4-12 Hz of oscillations interfering with activities of daily living. Thus, minimizing involuntary tremulous movements is an important goal for therapists and rehabilitation researchers.

Medications and deep brain stimulation (DBS) were often investigated for improving pathological tremor. However, only 50% of patients after medications revealed positive treatment effects on reducing tremor and DBS intervention has still very expensive cost and possible risks during brain surgery (2). One alternative protocol is functional electrical stimulation (FES) that uses electrodes on the skin for electrically stimulating the desired motor nerves improving a weak or paralyzed muscle. FES is economical, portable, and easily accessible device, and this could be a viable option for the suppression of pathological tremor via modulating and enhancing intrinsic muscle properties and feedback loops (3). Given that no one determined the comprehensive contribution of FES to pathological tremor, we conducted meta-analysis to provide the quantitative evidence of pathological tremor changes after FES interventions.

For study identification, we performed computerized literature searches using PubMed and Web of Science. Search keywords were: (a) functional electrical muscle stimulation and (b) tremor. Initial systematic literature search identified 83 potential articles, and we excluded 73 studies: (a) seven review article, (b) six animal studies, (d) 26 DBS articles, (e) 34 articles not related to our topic (e.g., simulation studies and no pathological tremor reported). Finally, total 10 studies met our inclusion criteria were analyzed (1-10).

Ten qualified studies included patients with Parkinson's disease, essential tremor, multiple sclerosis, and cerebellar tremor. Tremor changes were quantified by calculating changes in amplitude and power of tremor during either active movement or resting position. FES protocols were based on two different strategies (i.e., co-contraction vs. out-of-phase). Co-contraction strategy provides simultaneously continuous stimulation on antagonist muscles increasing the stiffness and viscosity of the tremulous limbs, and this co-activation reduces tremor oscillations. Out-of-phase strategy activates antagonist muscles when agonist muscles are involuntarily contracted. To compare effect sizes between the two different FES protocols, we performed moderator variable analysis.

A random effects model meta-analysis revealed a significant overall effect sizes across 10 included

studies (Hedges'g = 0.86 and $P < 0.001$; Fig. 1). Variability tests showed low level of heterogeneity ($Q = 14.43$ and $P = 0.11$; $I^2 = 37.61\%$). Further, publication bias was relatively minimal: (a) Begg and Mazumdar rank correlation: $P = 0.07$ and (b) three imputed values in a revised funnel plot (Fig. 2). Moderator variable analysis on two different FES protocols reported significant effect sizes. Specific results were: (a) co-contraction (Hedges'g = 0.85 and $P < 0.001$; $Q = 6.87$ and $P = 0.23$; $I^2 = 27.26\%$) and (b) out-of-phase (Hedges'g = 0.94 and $P = 0.02$; $Q = 7.41$ and $P = 0.06$; $I^2 = 59.52\%$).

Study	Subject	FES Protocol (joint)	Outcome Measure
Bo 2014 (1)	10 ET	Co-contraction (W/F) Fixed PW: 150 μs; Freq: 40 Hz	Δ in RMS ratio of tremor amplitude from active motion
Dosen 2014 (2)	4 PD, 1 ET	Out-of-phase (W/F) Online control system	Δ in ratio of tremor power from active motion
Gallego 2013 (3)	4 ET, 2 PD	Co-contraction (W) Online control system	Δ in ratio of integrated tremor power from active motion
Gillard 1999 (4)	3 PD	Out-of-phase (W/F) Online control system	Δ in tremor attenuation from active motion
Grimaldi 2011 (5)	1 PD, 1 ET, 1CT	Co-contraction (W/F/E) Fixed PW 100 μs; Freq: 30 Hz	Crest factor bt stim on and off from active motion
Heo 2015 (6)	18 ET	Co-contraction (W/F/E) Fixed PW 300 μs; Freq: 100 Hz	RMS of angular velocity bt stim on and off from active motion
Javidan 1992 (7)	6 MS, 4 PD, 3 ET	Out-of-phase (W/F) Online control system	Tremor power bt stim on and off from active motion
Jitkritsadakul 2015 (8)	34 PD	Co-contraction (W/F) Fixed PW 150 μs; Freq: 50 Hz	RMS of angular velocity bt stim on and off from resting position
Jitkritsadakul 2017 (9)	14 PD	Co-contraction (W/F) Fixed PW 150 μs; Freq: 50 Hz	RMS of angular velocity bt stim and sham from resting position
PopovicManeski 2011 (10)	4 PD, 3 ET	Out-of-phase (W/F) Online control system	Δ in RMS ratio of tremor amplitude from active motion

Abbreviations. bt: between; CT: cerebellar tremor; E: elbow; ET: essential tremor; F: fingers; FES: functional electrical stimulation; Freq: frequency; PD: Parkinson's disease; PW: pulse width; RMS: root-mean-squared; stim: electrical stimulation; W: wrist

Note. Each size of individual effects was proportional to their weight.
Red diamond indicates an overall effect size.
Positive (+) value denotes treatment effects on tremor.

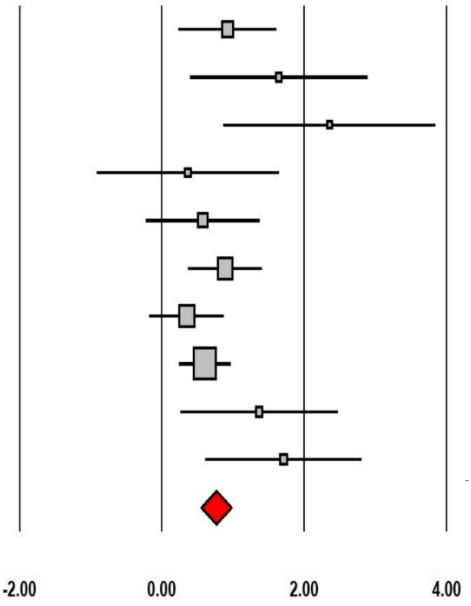

Fig. 1: Experimental characteristics and meta-analytic findings

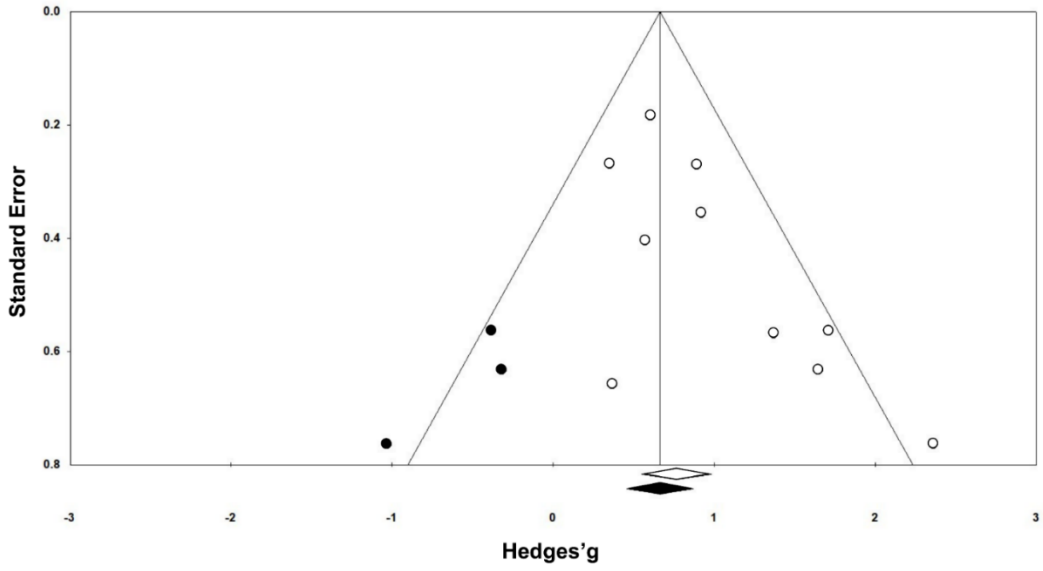

Fig. 2: A revised funnel plot after trim and fill technique

The current meta-analytic findings on 113 patients support a proposition that FES intervention effectively reduced the level of tremor with minimal heterogeneity levels. Moderator variable analysis identified similar treatment effects of FES between co-contraction and out-of-phase strategies. However, the effect size for out-of-phase strategy needs to be cautiously interpreted because of relatively medium level of heterogeneity that might be influenced by different control system modulating timing of stimulating antagonist muscles. To the best of our knowledge, our meta-analytic results are the first to report overall positive effects of FES on pathological tremor. However, small number of participants, the absence of control groups, short-term treatment effects only reported, and potential fatigue and discomfort of stimulated muscles remain as limitations. As shown in a prior study that reported the effectiveness of a new Tremor's Glove incorporating tremor detection module and FES on PD patients (9), developing more convenient and adjusted FES system and identifying individualized stimulation protocols may contribute to optimizing the suppression of pathological tremor.

Conflict of interest

The author declares that there is no conflict of interest.

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