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Failed Attempt with Paired Associative Stimulation to Separate Functional and Organic Dystonia

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No neurophysiological assessments are available to distinguish between functional and organic dystonia. Paired associative stimulation (PAS) is an established technique to study plasticity in dystonia utilizing a timed interaction between two synchronous stimuli to the motor cortex. We designed a study after Quartarone et al. ¹ with modifications aimed to develop PAS into a clinically useful test. Instead of 90 stimuli pairs every 20 seconds (0.05 Hz) for a stimulation time of 30 minutes, we used 600 stimuli pairs given continuously over 2 minutes at 5Hz, also a methodology introduced by Quartarone et al. referred to as rapid repetitive PAS (rPAS) ². We believed that rPAS, by decreasing testing time, minimizes

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DISCLOSURES:

Employment:

Vesper Ramos, MD has employment with Pfizer, Inc. over the past year.

Advisory boards, partnerships, honoraria, royalties, others:

Mark Hallett, MD serves as Chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Editorial Board of approximately 20 journals, and received royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, and Elsevier. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand dystonia, Allergan for studies of methods to inject botulinum toxins and for a treatment trial, and Medtronic, Inc. for a study of DBS for dystonia.

The rest of the authors have nothing to disclose.

transcranial magnetic stimulation (TMS) target displacement and fatigue effects in both subject and experimenter. We also employed motor recruitment curves, which more accurately measure synaptic plasticity in musicians³, with good-to-excellent test-retest reliability in our group⁴. Data from the Quartarone et al. study¹ on the change in motor evoked potential (MEP) amplitude from baseline to 30 minutes after PAS (T30), with alpha of 0.05, two-sided paired t-test, standard deviation of 0.5, effect size 1.6, and power of 80% gave us an initial subject size estimate of 6 per arm. We then planned to re-power after.

Seven patients with primary focal dystonia, six patients with clinically established functional dystonia, and six age-matched healthy volunteers were enrolled. A patient with organic dystonia was withdrawn because we could not get reliable MEPs. Motor recruitment curves were obtained with TMS pulses at random-order intensities from 20 to 100% of maximum stimulator output at 0.01 Hz. Fifteen TMS pulses at the intensity at which one can obtain 50% of the MEP-MAX (S50) were then delivered to record baseline MEP amplitudes. rPAS was given with 200-microseconds electrical stimulus to the median nerve at 200% perceptual threshold, followed by TMS (80% resting motor threshold) to motor hotspot 25 ms later. Motor recruitment curves and 15 MEPs at S50 were then recorded immediately (T0), 30 minutes (T30) and 1 hour (T60) after rPAS.

rPAS outcome measures using S50 intensity were not significantly different across the groups (Figure 1). Using our primary outcome measure of change from baseline in MEP using S50 intensity at T30, re-powering yielded an impractical number of participants per group to detect group differences. Motor recruitment curve parameters (bottom, MEP-MAX, S50 and K), obtained after normalizing MEP amplitudes to the MEP max and applying logarithmic transformation, were also not different across the groups.

The patient cohort was limited to those who could undergo rPAS safely, excluding any seizure history, or taking medication that lowers seizure threshold. No blinding measures were instituted. Neuronavigation for better assurance of localization of the target for TMS and Val66Met brain-derived neurotrophic factor⁵ and catechol-o-methyltransferase⁶ status of participants could be useful as these genetic factors play a role in PAS response. With these limitations, emphasizing the small sample size, we found that methods here cannot be used to easily separate subjects into organic or functional dystonia.

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AUTHORS' ROLES

1. Research project: A. Conception, B. Organization, C. Execution;
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Abbreviations

MEP	motor-evoked potentials
PAS	paired associative stimulation
rPAS	repetitive paired associative stimulation
S50	stimulation intensity at which one can obtain 50% of the maximal response
TMS	transcranial magnetic stimulation

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Figure 1.

Effects of rapid paired associative stimulation as measured by percentage of baseline immediately after (T0), 30 minutes after (T30) and 60 minutes after (T60) with two different muscles (A) abductor pollicis brevis and (B) first dorsal interossei.

MEP- motor-evoked potentials

rPAS- rapid paired associative stimulation