Measuring the Influence of Prefrontal and Premotor Subregions on Primary Motor Cortical Excitability in Healthy Controls and Huntington's Disease: A Dual Coil, Paired-Pulse TMS Study

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Background

- The **prefrontal cortex** and **premotor cortex** are essential **for motor planning and execution [1].** However, the precise mechanisms by which these regions interact with each other and modulate primary motor cortex (M1) excitability are not understood [2].
- Early-stage Huntington's Disease (HD) is characterized by **white matter deficits** in the **corpus callosum [3]**, indicating **compromised interhemispheric connectivity** between motor, premotor, and dorsolateral prefrontal cortex (DLPFC) regions. These connectivity disruptions could potentially serve as **biomarkers for preclinical Huntington's Disease Gene Expansion Carriers (pHDGECs),**
- **Dual-coil paired-pulse Transcranial Magnetic Stimulation (ppTMS)** is a non-invasive technique capable of evaluating **causal interactions** between **cortical regions** and detecting **neural network dysfunction[2].**

Objectives

To assess how **prefrontal** and **premotor** regions affect the **contralateral motor cortical excitability** in healthy controls (HCs) and pHDGECs.

Methods

Participants

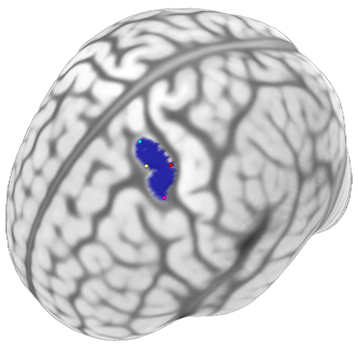
- Healthy Controls (n=15).
- Pre-manifest HD (n=3) (Confirmed HDGECs, 40+ CAG repeats).
- Relatives in HD Families (to be recruited).

Neuroimaging Data Collection

- T1 MPRAGE sequence, voxel size 1.0 × 1.0 × 1.0 mm (Siemens PRISMA 3T MRI).
- Registration of T1 images to MNI-152 brain using manual identification of anterior and posterior commissures.
- Overlay Glasser atlas [4].

Target Selection

- Premotor regions (6a, 6d), DLPFC regions (8av, 46, p9-46v), and a traditionally craniometrically measured dorsal premotor region (2.5 × 1 cm anteromedial to APB hotspot)(mesPMd) [2].
- **Centroid calculation**: Arithmetic mean of the vertices for each polygon target.



[i] $C_x = \frac{\sum_{i=1}^{n} x_i}{n}$

[ii] $C_y = \frac{\sum_{i=1}^{n} y_i}{n}$

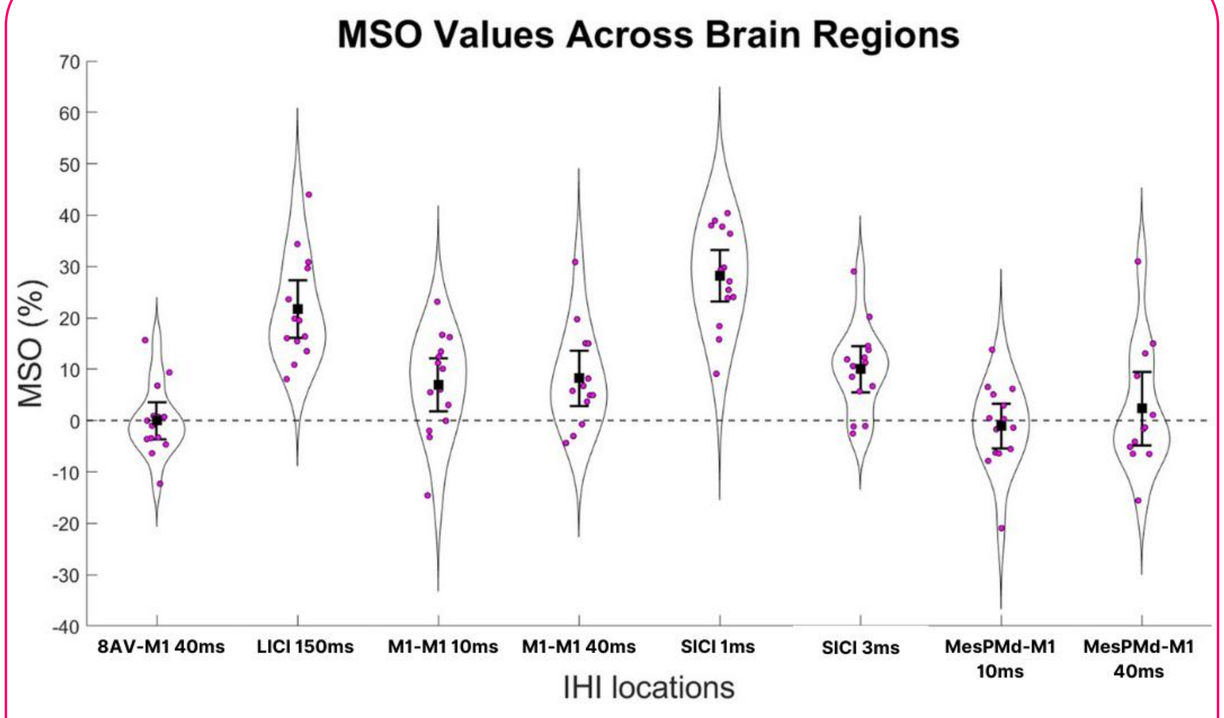
[ii] $C_z = \frac{\sum_{i=1}^{n} z_i}{n}$

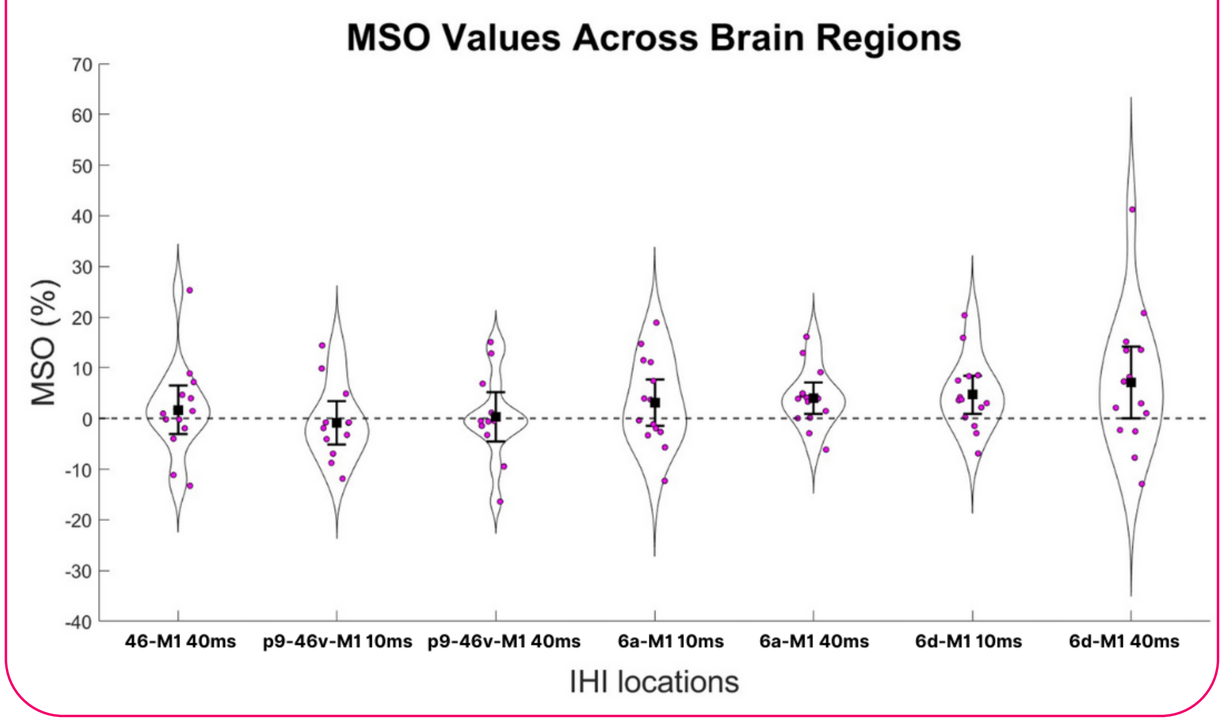
Figure One. Illustration of the process for determining centroid coordinates Cx , Cy , and Cz on a 3D brain model, showing marked extreme points connected to the computed centroid.

TMS Data Collection

- Automated threshold hunting used for dual-site ppTMS protocol [5].
- Ten interhemispheric inhibition (IHI) and three intracortical inhibition measures (M1-M1, M1-6a, M1-6d, M1-8AV, M1-p9 to 46v, M1-46).
- Conditioning stimulus (CS) applied to motor, pre-motor, and DLPFC regions.
- Test stimulus (TS) applied to dominant hemisphere M1 (lowest stimulation intensity for MEPs).
- Short (10ms) and long (40ms) Interstimulus intervals for IHIs.
- Short and long intracortical inhibition measures.

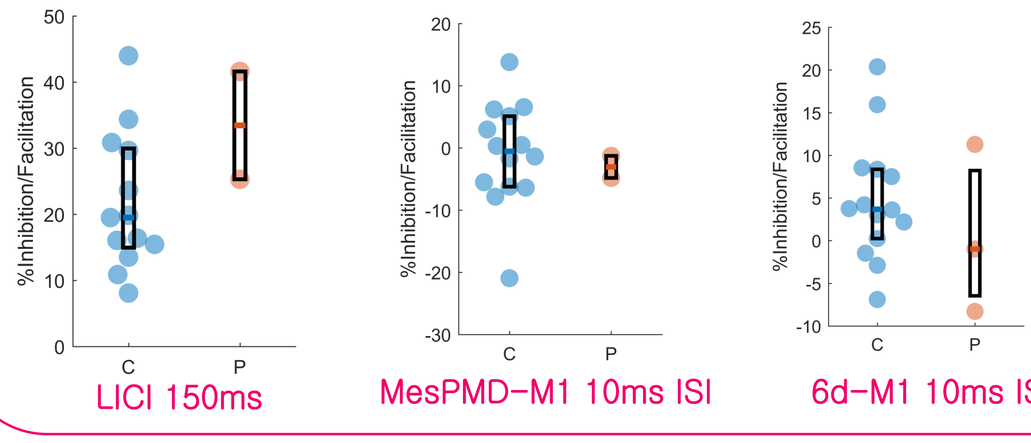
Results





Measure	Condition (ms)	p-value	Significance
6a-M1	10	0.2958	Not Significant
6a-M1	**40**	**0.0166**	**Significant**
6d-M1	**10**	**0.0166**	**Significant**
6d-M1	40	0.0676	Not Significant
8av-M1	40	0.7148	Not Significant
46-M1	40	0.5016	Not Significant
P9-46v-M1	10	0.4697	Not Significant
P9-46v-M1	40	0.791	Not Significant
M1-M1	**10**	**0.0295**	**Significant**
M1-M1	**40**	**0.0046**	**Significant**
SICI 1	**1**	**0.000122**	**Significant**
SICI 3	**3**	**0.0017**	**Significant**
mesPMD-M1	10	0.7148	Not Significant
mesPMD-M1	40	0.9697	Not Significant
LICI	**150**	**0.0002**	**Significant**

Pilot pHDGECs Analysis



Discussion

- Significant effects of 6a and 6d premotor regions on M1 excitability during IHI.
- SICI (1 ms and 3 ms), and LICI (150 ms), showed significant effects.
- 6a and 6d premotor regions play a role in modulating M1 excitability and pilot results suggest that LICI may be a sensitive indicator of premanifest HD.

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