Recruitment Characteristics of Evoked Responses to Transcranial Magnetic Stimulation in Adults with Spastic Cerebral Palsy

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Introduction

Cerebral Palsy (CP)

- Involves a non-progressive insult to the fetal or infant brain[1]
- CP is common, 2-2.5/1000[2]
- 90% have spasticity as their primary motor impairment[3]

Voluntary Motor Impairments in CP include

- Weakness[4], Slow force generation & relaxation[5], Co-contraction[6]

OBJECTIVE: To explore descending motor pathways in adults with spastic CP using transcranial magnetic stimulation (TMS).

Most studies using TMS in CP have been done in children/adolescents and only at very low intensities.

Here we examined the full recruitment characteristics of responses evoked in the voluntarily-active soleus muscle by TMS in adults with spastic CP and neurologically intact (NI) peers.

Common Methods

Participants were seated with their knee flexed & ankle secured (90º).

The more impaired leg was targeted (TL) in the CP group.

Soleus voluntary EMG & motor evoked potentials (MEPs) were recorded.

Maximal voluntary activation (MVA) was calculated from the highest 1s of soleus activation during maximal plantarflexion, averaging the highest 2 trials.

Background EMG prior to TMS was quantified over 100ms.

A Magstim 200 or BiStim & a batwing coil were used to deliver TMS.

Peak-to-peak amplitude was determined for each motor evoked potential (MEP).

Most data was not normally distributed. Therefore groups were compared using a Mann-Whitney test with the median (range) reported.

Participants

CP & NI groups had similar age and gender distributions.

If consistent responses could not be elicited from the cortex contralateral to the TL, TMS was applied to activate the ipsilateral pathway.

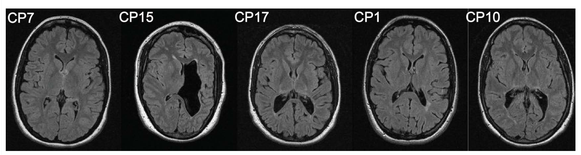
ID	Sex	Age	TL	Pathway	MRI	GFMCS	MRC	mAsh
CP1	F	21	R	Contra	PVWMI +	I	5	0
CP2*	M	32	R	Ipsi	CM/PVWMI ++	I	4	3
CP3	M	26	L	Contra	PVWMI ++	I	5	1+
CP4*	F	32	R	Contra	---	II	5	1+
CP6*	M	49	L	Ipsi	PVWMI ++	III	3	3
CP7	F	28	L	Contra	Normal	II	5	1
CP8	F	33	R	Ipsi	DGMI/PVWMI ++	III	4	3
CP9	F	21	L	Contra	PVWMI ++	III	1	1
CP10	M	28	L	Contra	CM/PVWMI +	II	2	0
CP11*	F	19	L	Contra	CM/PVWMI ++	IV	2	1
CP12*	M	24	R	Contra	PVWMI +	IV	2	1
CP14	F	39	L	Contra	Normal	III	1	1+
CP15*	F	52	R	Ipsi	CVA/PVWMI +++	II	1	2
CP16	F	57	R	Contra	PVWMI +	I	5	0
CP17	M	32	R	Contra	PVWMI ++	II	4	1
CP18	F	35	L	Contra	PVWMI ++	IV	1	2
CP19	M	42	R	Contra	PVWMI +	III	2	1
CP n=17	F: 59% M: 41%	32 (19-57)	R:9 L:8	Contra:13 Ipsi: 4	PVWMI: 87% CM: 19% DGMI: 6% CVA: 6% Normal: 13%	I: 24% II: 29% III: 29% IV: 18% V: 0%	3.1 ± 1.6	1.4 ± 1.0
NI n=15	F: 60% M: 40%	28 (19-59)	R:12 L: 3	Contra: 15 Ipsi: 0				

* Indicates taking medication known to impact TMS acutely

GMFCS: Gross Motor Functional Classification System

MRC: Medical Research Council Scale for Plantarflexor Muscle Strength, mAsh: modified Ashworth Scale

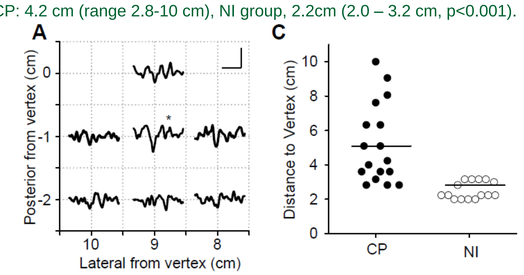
PVWMI: periventricular white matter injury, CM: cerebral malformation, DGMI: deep gray matter injury, CVA: stroke



1. Hotspot

The optimal cortical location for stimulating the soleus (hotspot) was found while participants performed a 20 %MVA plantarflexion contraction.

A. Example averaged MEPs from CP1 at and near the hotspot (*).
B. Each individual's hotspot in Cartesian coordinates.
C. The **distance** from vertex is larger in the CP group, p<0.001.
CP: 4.2 cm (range 2.8-10 cm), NI group, 2.2cm (2.0 – 3.2 cm, p<0.001).



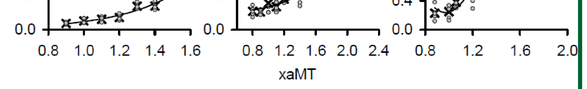
The hotspots in the CP group are more varied & more distant from the vertex than for the NI group.

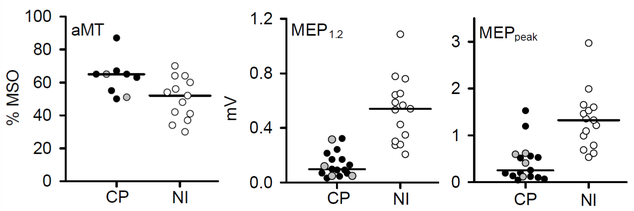
2. Stimulus Recruitment Curves

The relationship between stimulation intensity & MEP amplitude was studied at 20% MVA.

Methods: 5 MEPs were measured at each intensity.

Results: In all NI participants, MEP amplitudes increased until reaching a peak beyond which MEPs plateaued or decreased.
In most individuals with CP (15/17 including CP4), MEPs increased up to 100 %MSO.
aMT = the active motor threshold = the lowest stimulation intensity producing a discernable MEP in 3/5 trials. Analyzed for participants tested with the same stimulator. aMT is higher in CP, p=0.03.
$MEP_{1.2}$ = the magnitude of MEPs at 1.2 xaMT is smaller in CP, p<0.001.
MEP_{Peak} = the magnitude of the largest MEPs is smaller in CP, p<0.001.





CP: 66 (50-87) %MSO
NI: 52 (30-70) %MSO

CP: 0.10 (0.03-0.32) mV
NI: 0.54 (0.21-1.09) mV

CP: 0.26 (0.05-1.53) mV
NI: 1.32 (0.53-2.97) mV

Comparing Apples to Apples?
Peak-intensity = the intensity producing the largest MEPs is similar between groups, p=0.95. CP: 1.6 (1.1-2.2), NI: 1.6 (1.4-2.1) xaMT.

Latencies = time of onset soleus MEPs is similar between groups, suggesting we are indeed activating the corticospinal tract in CP, not alternative pathways, p=0.96. CP: 30 (20-38), NI: 30 (27-37) ms. At 30ms, its likely the TMS activated the fast corticospinal tract in both groups.

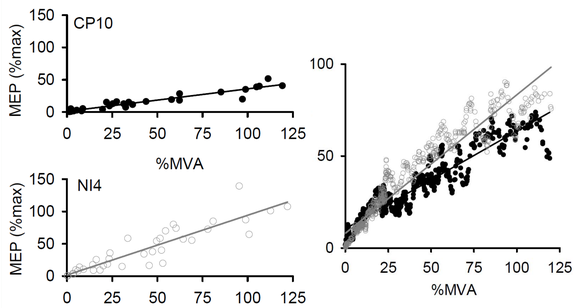
Recruitment of corticospinal pathways is reduced in the soleus in participants with CP contracting at 20% MVA.

3. Voluntary Facilitation of MEPs

The relationship between voluntary activation and MEP amplitude was explored at two stimulation intensities: 1.2 xaMT & Peak-Intensity..

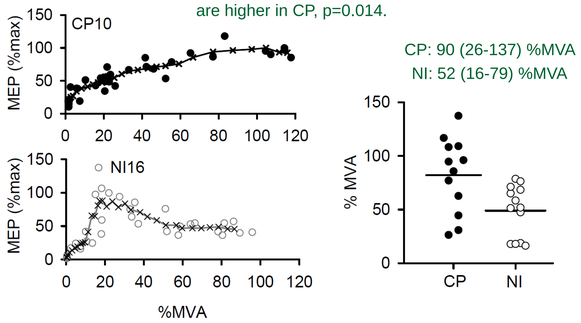
Methods: At each intensity: 5 trials at rest, >20 trials with graded contractions.
MEPs were normalized to the individuals maximum MEP that could be evoked at either intensity (max of 5 consecutive MEPs when plotted against %MVA).
Linear portions of the relationship for each group were evaluated using a Mixed Effects Model w/ their coefficient and 95th confidence intervals compared.

Results: At 1.2 xaMT the entire relationship between %MVA & MEP was linear.
The rate of increase in MEP as a function of voluntary activation (i.e. the slope between background activation and MEP) was lower in the CP group.
CP: β=0.52 (0.48-0.56)
NI: β=0.76 (0.72-0.81)



At Peak-Intensity, only the section of the relationship <20%MVA was consistently linear & included in the model.
The rate of increase in MEP as a function of voluntary activation was lower in the CP group.
CP: β=2.1 (1.7-2.5)
NI: β=3.4 (3.1-3.8)

Plateau = the activation level at which MEPs reached at least 90% of the individual's maximum. The plateau's are higher in CP, p=0.014.



CP: 90 (26-137) %MVA
NI: 52 (16-79) %MVA

4. Role of Muscle Atrophy?

CP group is weaker as shown by lower maximal voluntary activation (**MVA**) over 1s during maximum plantarflexion.
CP: 26 (7-85) uV, NI: 185 (73-297) uV, p<0.001.
M_{max} was also smaller in the CP group.
CP=5.1 (1.3-9.8) mV, NI=9.8 (4.5-12.2) mV, p=0.002.
All MEP amplitude findings were unchanged by expressing the MEP amplitudes as a percentage of M_{max}.

5. Effect of Medication?

Many medication that impact neurotransmitters or neuromodulators such as anticonvulsants or antidepressants are known to impact TMS when taken as a single dose.
The impact of chronic use is unknown.
6 participants with CP utilized these medication (gray solid dots).
They were not outliers.
Excluding their data did not change any findings.

Discussion

Functional excitability of the corticospinal pathway and the ability to modulate that excitability is reduced in adults with spastic CP.

Consistent with previous work in kids with CP[7], participants with CP in this study showed hotspots displaced relative to NI peers.

Adults w/ CP have higher thresholds for MEP activation and lower amplitude MEPs. Lower amplitudes are found at both a relatively low test intensity, standardized relative to the participant's aMT, and at a higher test intensity producing the participant's peak amplitude. Therefore decreased excitability is found from the earliest recruited components of the corticospinal tract through to the higher threshold elements.

Adults with CP also have a decreased ability to voluntarily modulate corticospinal excitability as revealed by a weaker relationship between voluntary muscle activity and MEP amplitudes even when controlling for the available range of excitability (i.e. their own maximal MEPs). This suggest reduced ability to increase excitability voluntarily.

The source of the decreased excitability was not identified in this study, but it likely stems from reduced voluntary enhancement of cortical and/or spinal excitability.

Significance
Reduced excitability of the corticospinal pathway throughout the recruitable range and reduced voluntary modulation within that range furthers our understanding of the mechanisms contributing to motor impairments in people with spastic CP, particularly those with bilateral lesions.

This can lead to impaired neuromuscular activation, which has been demonstrated to be a main contributor to motor weakness[4], making it a prime target for neurorehabilitation. Evaluating the impact of treatments on the full range of impairments during functional contractions as demonstrated here can further help assess neurorehabilitation programs and the target individuals for each program.

References & Acknowledgments

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