Transcranial magnetic stimulation in ALS

Utility of central motor conduction tests

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ABSTRACT

Objective: To investigate transcranial magnetic stimulation (TMS) measures as clinical correlates and longitudinal markers of amyotrophic lateral sclerosis (ALS).

Methods: We prospectively studied 60 patients with ALS subtypes (sporadic ALS, familial ALS, progressive muscular atrophy, and primary lateral sclerosis) using single pulse TMS, recording from abductor digiti minimi (ADM) and tibialis anterior (TA) muscles. We evaluated three measures: 1) TMS motor response threshold to the ADM, 2) central motor conduction time (CMCT), and 3) motor evoked potential amplitude (correcting for peripheral changes). Patients were evaluated at baseline, compared with controls, and followed every 3 months for up to six visits. Changes were analyzed using generalized estimation equations to test linear trends with time.

Results: TMS threshold, CMCT, and TMS amplitude correlated ($p < 0.05$) with clinical upper motor neuron (UMN) signs at baseline and were different ($p < 0.05$) from normal controls in at least one response. Seventy-eight percent of patients with UMN (41/52) and 50% (4/8) of patients without clinical UMN signs had prolonged CMCT. All three measures revealed significant deterioration over time: TMS amplitude showed the greatest change, decreasing 8% per month; threshold increased 1.8% per month; and CMCT increased by 0.9% per month.

Conclusions: Transcranial magnetic stimulation (TMS) findings, particularly TMS amplitude, can objectively discriminate corticospinal tract involvement in amyotrophic lateral sclerosis (ALS) from controls and assess the progression of ALS. While central motor conduction time and response threshold worsen by less than 2% per month, TMS amplitude decrease averages 8% per month, and may be a useful objective marker of disease progression. *Neurology*® 2009;72:498-504

GLOSSARY

ADM = abductor digiti minimi; **ALS** = amyotrophic lateral sclerosis; **ANOVA** = analysis of variance; **CI** = confidence interval; **CMAP** = compound motor action potential; **CMCT** = central motor conduction time; **DTR** = deep tendon stretch reflex; **fALS** = familial ALS; **GEE** = generalized estimation equations; **LMN** = lower motor neuron; **MEP** = motor evoked potential; **PLS** = primary lateral sclerosis; **PMA** = progressive muscular atrophy; **sALS** = sporadic ALS; **TA** = tibialis anterior; **TMS** = transcranial magnetic stimulation; **UMN** = upper motor neuron.

ALS is diagnosed by finding clinical upper motor neuron (UMN) and lower motor neuron (LMN) signs. LMN dysfunction can be confirmed objectively through electromyography, whereas UMN dysfunction lacks a comparable established marker. Detection of subclinical UMN dysfunction would be helpful for diagnostic purposes, and objective markers of UMN dysfunction may also help clarify the relationship between ALS and its variants, including progressive muscular atrophy (PMA).

PMA has been diagnosed by the absence of clinical UMN signs in the presence of LMN findings for several years. However, autopsies on patients with clinically diagnosed PMA show corticospinal tract degeneration in half of the patients. Therefore, clinical examination alone does not disclose all relevant UMN pathology.¹⁻³

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Table 1 Demographic and clinical information					
	No.	Age at visit 1, y	M:F	Duration of illness: Onset to baseline visit, d	Site of onset, % bulbar/% limb
sALS	41	53 ± 11	30:11	852 ± 1,206	10/90
fALS	5	56 ± 13	0:5	1,251 ± 961	20/80
PLS	6	55 ± 9	2:4	2,398 ± 2,172	17/83
PMA	8	65 ± 13	8:0	789 ± 320	0/100
All UMN cases	52	53 ± 11	32:20	1,069 ± 1,387	12/88
All cases	60	55 ± 12	40:20	1,032 ± 1,298	10/90

When patients enrolled, the duration of disease from onset to baseline was less than 4 years, but patients were followed more than 4 years to satisfy PLS criteria.

sALS = sporadic amyotrophic lateral sclerosis; fALS = familial amyotrophic lateral sclerosis; PLS = primary lateral sclerosis; PMA = progressive muscular atrophy; UMN = upper motor neuron.

Transcranial magnetic stimulation (TMS) is a neurophysiologic technique used to assess the function of central motor pathways. Standard TMS measures include motor threshold, central motor conduction time (CMCT), and motor evoked potential (MEP) amplitudes. There have been numerous studies of TMS in ALS for over 20 years, investigating a multitude of issues on UMN physiology, cortical excitability and inhibition, the utility of the silent period and other responses to detect early changes in ALS, and the relationship between the UMN and LMN, many of which have been contradictory.⁴⁻¹¹ Threshold, CMCT, and MEP are three useful measures of single pulse TMS; however, the diagnostic success of these nonspecific UMN measures varies widely from 16% to 100%.^{5,9,12-17} Reasons include different muscle recording sites, different methods of calculating CMCT,^{4,18} and different thresholds for defining diagnostic success (i.e., 1/4 sites prolonged vs 4/4).

The TMS MEP is activated through both UMN and LMN pathways after magnetic stimulation of the cortex. In ALS, TMS amplitudes are often attenuated or absent¹⁹⁻²¹; even patients with pseudobulbar features are prone to have small, desynchronized MEPs.¹² Reduced TMS MEP/M-wave amplitude ratio may be more closely correlated with pyramidal tract involvement than prolonged CMCT.²¹ There are fewer investigations of TMS amplitude compared to CMCT. One study found TMS amplitude abnormalities in only 16 of 54 patients with ALS (30%),⁵

whereas another found a significant difference between patients and controls at three recording sites, with amplitude reductions in almost all patients.¹⁹

The sensitivity of baseline TMS measures in ALS has been studied extensively, with mixed results, but there have been few longitudinal studies of TMS changes in ALS. Most reports showed no change in TMS threshold with time^{6,22,23} but one noted significant increase.¹⁷ CMCT has generally been reported to not increase with time.^{6,22,24} In a small series, TMS MEP amplitude and MEP/peripheral compound motor action potential (CMAP) ratio did not change with disease progression.²²

In this study, we report on TMS threshold, CMCT, and amplitude data that were not included in an overarching report on neurophysiologic, brain imaging, and clinical methods to quantify and track progression in patients with ALS.²⁵

METHODS Subjects. Patients with suspected ALS or ALS variants were evaluated for eligibility and enrolled through the Eleanor and Lou Gehrig MDA/ALS Research Center at Columbia University as previously described.²⁵ Qualifying patients included those with a suspected diagnosis according to El Escorial criteria²⁶ of sporadic or familial ALS (sALS and fALS), primary lateral sclerosis (PLS), and PMA. The study enrolled 60 patients, 23 of whom had evaluations spanning a minimum of four visits up to 1.5 years (table 1) and measured clinical variables as described.²⁵ Control data for CMCT baseline measures were from 33 normal subjects (mean ± SD age 44.8 ± 11.8 years) collected previously. All patients provided informed consent, and this study protocol was approved in accordance with Columbia University Medical Center Institutional Review Board guidelines.

Neuromuscular assessment. Clinical examination relevant to TMS testing at each baseline and follow-up visit consisted of height, forced vital capacity measurements, strength in 36 skeletal muscles including grip and pinch, muscle tone, deep tendon stretch reflexes (DTRs), pathologic responses (Babinski and Hoffmann), and finger and foot tapping speed. Examinations were performed by a senior neurologist and an experienced ALS clinical evaluator.²⁵

Electrophysiologic procedures. Motor conduction tests using TMS and peripheral spinal root stimulation were obtained at baseline and at 3-month intervals up to six visits. TMS was performed using a cap stimulator (Cadwell MES-10; Cadwell Inc., Kennewick, WA) at Cz recording from bilateral abductor digiti minimi (ADM) and tibialis anterior (TA) muscles in a belly-tendon arrangement with 1-cm disc electrodes at 100% machine output. Electrical spinal root stimulation was performed over C7 and L1 using a high voltage stimulator (Digitimer, Ltd., Hertfordshire, UK) at the same output settings across all visits for each patient. Supramaximal stimulation was not possible with either TMS or spinal nerve root stimulation.

Figure Longitudinal tracings from a sample patient with sporadic amyotrophic lateral sclerosis from prestudy through visits 1 to 6

Amplitude and time are standardized across all visits. (A) Transcranial magnetic stimulation (TMS) motor evoked potential (MEP) responses from cortical stimulation over the vertex. Traces are from the right and left abductor digiti minimi (ADM) (A1 and A2), right and left tibialis anterior (TA) (A3 and A4). (B) Peripheral MEP responses stimulating over the cervical spine to the right and left ADM (B5 and B6), and lumbar spine to the right and left TA (B7 and B8).

Resting TMS threshold to the ADM was recorded as the minimum stimulus intensity producing consistent MEPs with peak-to-peak amplitudes greater than 50 μ V in at least 5 of 10 consecutive stimulations.²⁷ Stimulation was increased in 1% to 2% increments of maximum stimulator output until threshold was obtained.

CMCT was calculated through subtraction of the minimal spinal root stimulation latency from the upper spine (for the arms) and lower spine (for the legs) from the minimal latency achieved by cortical stimulation.

TMS and peripheral MEPs were recorded at an amplifier gain of 5 mV per division with high and low pass filters set at 10 Hz and 10 kHz. Latencies and amplitudes were determined manually at a sensitivity of 200 μ V/division with a time base of 10 msec/division. Multiple TMS and electrical spinal stimuli were applied to obtain at least two identical trials at each stimulation site to confirm reproducibility.

Amplitudes were calculated from baseline to highest negative peak of the MEP responses at each visit for both TMS and electrical spinal recordings (figure). When stimulus artifact obscured the signal baseline, the MEP amplitude was measured from the negative peak to an interpolated baseline point directly below. TMS and peripheral amplitudes were collated by a technician blinded to the patient and visit number.

Data analysis. Baseline analyses included all patients ($n = 60$). One-way analyses of variance (ANOVAs) were performed comparing the four diagnostic groups (sALS, PLS, PMA, and fALS). In the case of a significant ANOVA result, Tukey post hoc analyses were performed to determine which groups differed. Additionally, sALS, PLS, and fALS were collapsed into a single UMN group. t Tests were used to compare UMN vs PMA groups, and bulbar vs limb onset groups. Pearson product-moment correlation coefficients were used to correlate CMCT and threshold stimulation value, and clinical variables at baseline. Partial correlations were performed to determine the relationship between the TMS amplitudes and clinical variables, controlling for peripheral MEP amplitudes.

CMCT was dichotomized into normal and abnormal categories for the purpose of assessing diagnostic sensitivity. CMCT was rated as abnormal when two SD greater than the average of the control group. The CMCT in the control group was 7.8 ± 1.5 msec to the ADM, 13.5 ± 1.6 msec to the TA. Amplitudes were not dichotomized. The diagnostic category fALS was ex-

cluded from amplitude analyses due to missing data and low sample size ($n = 5$).

Longitudinal change in TMS measures were analyzed using generalized estimation equations (GEE) to test linear trends as the percent change with time. Each patient's data were treated as a cluster with repeated measurements at different visits, and used in an exchangeable working correlation matrix.^{28,29} Peripheral MEP amplitude measures were included as covariates when assessing change in TMS amplitudes over time. Interactions of time with diagnostic group (UMN vs PMA) and site of onset (bulbar vs limb) also were investigated.

RESULTS Thirty-six of the 60 patients completed two or more follow-up visits, and 11 finished all six follow-up visits spanning a period of 1.5 years, including prestudy baseline visits (table 1).

Threshold baseline. Baseline TMS thresholds were greater in UMN than in PMA, but did not reach significance ($38 \pm 9\%$ vs $31 \pm 6\%$, $p = 0.058$). There was no difference in TMS threshold by site of disease onset. When compared with clinical and physiologic variables, ADM threshold values correlated significantly with finger tapping rate, the brachioradialis DTR, ipsilateral CMCT, and TMS amplitudes (table 2).

Threshold change over time. TMS thresholds increased among all cases and UMN cases by 1.8% per month ($p < 0.0001$). Among the eight PMA cases available for analysis, threshold did not change significantly, nor were any trends apparent in that group.

CMCT baseline. CMCT at baseline did not correlate with patient age or duration of disease. CMCT to the TA was prolonged relative to controls among patients with sALS (mean = 24.0 msec, 95% confidence interval [CI] = 19.7–28.3 msec; $p < 0.0005$) and patients with fALS (mean = 23 msec, 95% CI = 17.7–28.3 msec; $p = 0.01$). TA CMCT also was prolonged in the combined UMN group (sALS, fALS, and PLS, $p < 0.0005$) compared to control values to the TA (mean = 13.5 msec, 95% CI = 12.0–15.0 msec). CMCT to the ADM showed no difference between patients and controls.

There was no CMCT difference among the four diagnostic groups or between patients with bulbar vs limb onset. The combined UMN patients had significantly longer CMCTs to both arms and legs compared with PMA patients. Dichotomized CMCT values revealed that 78% (41/52) of UMN patients had at least one prolonged central conduction, and 13% (7/52) had CMCT prolongation to all four limbs. Four of the eight PMA cases (50%) had prolonged CMCT to the TA.

CMCT to the ADM correlated significantly with increased DTRs in the brachioradialis, as well as decreased finger dexterity. CMCT to the TA correlated

Table 2 Clinical and physiologic correlations					
		CMCT*		TMS amplitude*	
	Threshold* ADM	ADM	TA	ADM	TA
DTR					
Brachioradialis	+0.28	+0.34	—	−0.34	—
Biceps	NS	+0.32	—	NS	—
Triceps	NS	+0.29		−0.32	—
Knee	—	—	+0.34	—	NS
Ankle	—	—	+0.33	—	NS
Babinski	—	—	+0.38	—	NS
Hoffmann		+0.45	—	−0.47	—
Dexterity					
Finger tapping	−0.53	−0.32	—	+0.61	—
Foot tapping	—	—	NS	—	+0.55
Strength					
Pinch	NS	NS	—	NS	—
Grip	NS	NS	—	+0.35	—
First dorsal interosseous	NS	NS	—	NS	—
Abductor pollicis brevis	NS	NS	—	NS	—
Inversion	—	—	NS	—	+0.41
Dorsiflexion	—	—	NS	—	+0.48

Significance level set at two-tailed $p < 0.05$.

*Pearson correlation coefficients.

*Partial correlation coefficients, controlling for peripheral amplitude.

ADM = abductor digiti minimi; CMCT = central motor conduction time; TA = tibialis anterior; TMS = transcranial magnetic stimulation; DTR = deep tendon reflex; NS = not significant.

with increased patellar and ankle DTRs. There was no correlation between CMCT and muscle strength measures. Patients with a Babinski sign had longer CMCT to the TA than those without findings (29.5 ± 15.7 msec compared to 20.5 ± 10.2 msec), and those with positive Hoffmann signs had longer CMCT to the ADM (18.2 ± 14.6 msec compared to 7.5 ± 0.7 msec). CMCT and clinical correlations are summarized in table 2.

CMCT change over time. Averaged across all cases, CMCT to the TA increased by an average of 0.9%

per month ($p = 0.016$). The interaction between upper vs lower MN involvement and time was significant such that UMN cases had greater TA CMCT increase than did PMA cases. The increase in CMCT in PMA cases was not significant when analyzed independently.

CMCT to the ADM did not show significant increase over time. Peripheral conduction times remained unchanged in UMN cases. However, in PMA cases peripheral conduction times for both the ADM and TA increased between 0.5% and 0.6% at each successive visit ($p < 0.005$).

Amplitude baseline. A one-way ANOVA revealed significant amplitude differences among the diagnostic groups. Tukey HSD post hoc comparisons indicated that PLS had significantly larger, more polyphasic, and dispersed TMS amplitudes than sALS in the TA. Peripheral amplitudes for PLS, however, were neither polyphasic nor dispersed, and were significantly larger than all other diagnostic groups (sALS, fALS, PMA) in the ADM (table 3). There was no difference in baseline amplitude between bulbar and limb onset groups.

Partial correlations between clinical signs and baseline TMS amplitudes, controlling for peripheral amplitudes using the latter as covariates in the GEE model, showed significant positive relationships between baseline TMS amplitudes, dexterity, and strength. There was a negative relationship between the brachioradialis and triceps DTRs and TMS amplitude to the ADM. Similarly, patients with positive Hoffmann signs had lower TMS amplitudes to the ADM (2.4 ± 1.2 mV compared to 1.0 ± 1.3 mV). Partial correlation results of Hoffmann sign presence vs TMS amplitude to the ADM, controlling for peripheral amplitude, was also significant (table 2). In the legs, TMS amplitudes correlated directly with foot tapping as well as dorsiflexion and inversion strength.

Amplitude change over time. TMS amplitude changes over time were analyzed controlling for the peripheral MEP amplitude at each visit by including peripheral amplitude data as a covariate in the GEE model. Across all cases, there was a decrease in TMS amplitude to the ADM of 2.8% per month ($p < 0.0001$) as well as decrease in TMS amplitude to the TA of 8.0% per month ($p < 0.05$) after controlling for the corresponding peripheral amplitude decreases. Amplitude decreases were found in both UMN and PMA cases analyzed separately. TMS amplitude drop to the ADM and TA in PMA was greater than in UMN cases, but the effect did not reach significance.

	TMS amplitude ADM (mV)	TMS amplitude TA (mV)	ADM peripheral amplitude (mV)	TA peripheral amplitude (mV)
sALS	1.3 ± 1.2	$0.7 \pm 0.8^*$	$2.1 \pm 1.9^*$	3.0 ± 2.6
fALS	1.4 ± 2.2	0.9 ± 1.0	$2.6 \pm 1.9^*$	2.5 ± 2.2
PLS	2.7 ± 2.0	2.2 ± 2.4	6.3 ± 2.2	5.2 ± 2.7
PMA	2.3 ± 0.8	1.0 ± 0.5	$2.4 \pm 1.6^*$	2.2 ± 2.5

*Significantly smaller than corresponding PLS amplitude.

TMS = transcranial magnetic stimulation; MEP = motor evoked potential; ADM = abductor digiti minimi; TA = tibialis anterior; sALS = sporadic amyotrophic lateral sclerosis; fALS = familial amyotrophic lateral sclerosis; PLS = primary lateral sclerosis; PMA = progressive muscular atrophy.

DISCUSSION We demonstrate that central motor conduction tests using single pulse TMS can both detect corticospinal tract involvement in ALS and measure disease progression, in agreement with reviews of TMS methods.^{7,9} Three measures from this study (TMS threshold, CMCT and TMS amplitude) revealed differences at baseline and showed changes in patients with ALS over time. TMS amplitude was abnormal and worsened at a greater rate than either threshold or CMCT.

TMS amplitude change, adjusting for peripheral change, was three to eight times greater per month than CMCT or threshold. Though neither motor cortex nor spinal roots could be stimulated supra-maximally, this was corrected using peripheral changes in MEP amplitude in the GEE model, and TMS/peripheral amplitude ratios. The differentially greater changes on TMS amplitude in ALS could be due to diminished number of cortical motor neuron cell bodies, axonal loss, desynchronization, and conduction abnormalities affecting long tract axons.

Though other longitudinal studies reported no significant CMCT prolongation over time,^{6,22,24} we found most patients had a prolonged baseline CMCT that gradually but significantly increased in UMN patients. We believe we were able to demonstrate this effect because our sample size was larger and data collection period was longer than previous studies. PMA patients revealed less prolonged CMCTs at baseline compared to UMN patients, and did not demonstrate longitudinal changes in this measure, possibly because PMA progresses slower than other ALS subtypes.⁴ Nevertheless, CMCT can be abnormal in purely LMN clinical syndromes^{14,17} and histopathologic and immunochemical studies reveal UMN pathology in LMN patients.^{1,2} We found that CMCT was prolonged in 50% of our patients without clinical UMN signs.

CMCT correlated with hyperreflexia and loss of dexterity, presence of Hoffmann and Babinski signs, but not with strength measures. Thus, CMCT abnormalities parallel some clinical UMN findings, and could be used to mark UMN dysfunction.^{14,24} The lack of correlation between CMCT and strength, however, suggests that CMCT does not measure pathophysiologic mechanisms of strength. LMN dysfunction may be the primary cause of weakness in ALS.³⁰ Motor unit number estimation correlates well with muscle strength, but not with UMN signs such as dexterity.²⁵ We found that TMS amplitude correlated strongly with hyperreflexia, dexterity, and strength. However, TMS amplitude did not correlate with Hoffmann or Babinski signs, suggesting that these release responses are

modulated by different UMN pathways than strength and dexterity.

There are several limitations to this study. The average age of our normal controls, used to compare differences in baseline CMCT, was 10 years younger than in our patients. This could diminish the strength of our findings. While we did not find a significant difference between patient age and baseline CMCT, this was likely due to the wide range of abnormal CMCT in ALS. Patient data only were factored into the GEE longitudinal analyses of threshold, CMCT, and TMS amplitude; control data were not obtained over time. We also did not analyze the ADM or TA MEP after peripheral nerve stimulation as another measure of lower motor neuron involvement. These probably would not have changed our results of up to 8% change in TMS amplitude. However, it would be important to determine the sensitivity of TMS amplitude in detecting UMN changes, as well as establish longitudinal findings in age-matched controls.

Other concerns may be that minimal F-wave latency methods may be better at determining peripheral conduction times in comparison to magnetic paravertebral stimulation.^{4,9} However, our subtraction of method used high voltage electrical root stimulation, which arguably provided a more focused stimulus than a paravertebral magnetic pulse. We did not test bulbar or proximal muscles such as the masseter or biceps brachii where subclinical abnormalities may occur earlier and more reliably in ALS.^{31,32}

Future investigations should study longer ALS disease progression by incorporating patients at the earliest stages of disease using GEE to analyze TMS amplitudes and peripheral changes. It would be important to assess TMS amplitude longitudinally, after controlling for peripheral MEP changes, using GEE in normal controls and patients with peripheral neuropathy. Advanced electrophysiologic methods³³⁻³⁵ might be helpful in parsing out the contributions of central and peripheral motor pathology. Combining TMS with routine EMG and nerve conduction studies, macro-EMG, and motor unit number estimation³⁶ of the same muscles in patients with ALS may determine more precisely the relative contributions of UMN and LMN to TMS findings in ALS over time.

AUTHOR CONTRIBUTIONS

M.X. Tang, Department of Biostatistics and Sergievsky Center, Columbia University, conducted the statistical analyses.

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2. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639–1643.
3. Gross RA, Johnston KC. Levels of evidence: taking *Neurology*® to the next level. *Neurology* 2008;72:8–10.

Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.