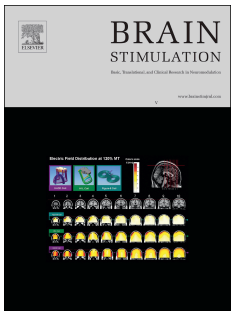

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TMS for staging and predicting functional decline in Frontotemporal Dementia

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Abstract

Objective: To evaluate if transcranial magnetic stimulation (TMS) measures correlate with disease severity and predict functional decline in frontotemporal dementia (FTD) phenotypes.

Methods: Paired-pulse TMS was used to investigate the activity of different intracortical circuits in 171 FTD patients (122 bvFTD, 31 avPPA, 18 svPPA) and 74 healthy controls. Pearson's correlations were used to analyze the association between TMS measures and disease severity, while multiple regression analysis was used to identify the best clinical or neurophysiological measure to predict functional decline at 12 months.

Results: We observed significant strong correlations between TMS measures [short interval intracortical inhibition-facilitation (SICI-ICF) and long interval intracortical inhibition (LICI)], and disease severity (evaluated with the FTLD-CDR) (all $r>0.5$, $p<0.005$).

SICI-ICF, short interval intracortical facilitation (SICF) and LICI were also significant predictors of functional decline, evaluated as the change in FTLD-CDR scores at 12 months (all $p<0.005$), while at the stepwise multiple regression analysis, SICI was the best predictor of disease progression, accounting for 72.5% of the variation in FTLD-CDR scores at 12 months (adjusted $R^2=0.72$, $p<0.001$).

Conclusions: The present study has shown that the dysfunction of inhibitory and facilitatory intracortical circuits, evaluated with TMS, correlates with disease severity and progression, accurately predicting functional decline at 12 months, better than any other investigated marker.

Introduction

Frontotemporal dementia (FTD) represents a progressive neurodegenerative disorder with overlapping clinical features, characterized by a wide spectrum of symptoms ranging from personality changes, behavioural disturbances, language deficits to the impairment of executive functions.[1] Three phenotypes have been described, namely the behavioural variant of FTD (bvFTD), the agrammatic variant of Primary Progressive Aphasia (avPPA) and the semantic variant of PPA (svPPA).[2,3]

The heterogeneity of clinical presentations has consistently precluded a straightforward staging of FTD and has generated substantial issues in predicting the clinical course of the disease, considering that the rate of functional decline can vary between patients.[4,5] Indeed, biological markers of disease severity and disease progression are critical for advising patients and caregivers, for evaluating potential disease modifying treatments in homogeneous groups, independently of clinical phenotype, and to better understand the disease pathophysiology.[6]

In this view, a recent study has shown that transcranial magnetic stimulation (TMS) intracortical connectivity measures considerably correlate with disease progression in patients with presymptomatic and symptomatic genetic FTD.[7] In particular, FTD is characterized by a significant decrease in intracortical facilitation (ICF), which represents a facilitation only partially mediated by glutamatergic NMDA receptors, and by a decrease of short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI), markers of postsynaptic inhibition mediated through the $GABA_A$ and $GABA_B$ receptors, respectively.

In the present work, we aimed to confirm TMS abnormalities in different FTD phenotypes, and to determine whether TMS intracortical connectivity measures could stage FTD and predict the rate of functional decline.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Informed consent was acquired from all participants in accordance to the Declaration of Helsinki. The local ethics committee of the Brescia Hospital approved the study (05.19.2015, #NP1965).

Participants

In the present study, 176 patients were consecutively recruited from the Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy.
Patients were included in the present study only after fulling current clinical criteria for probable FTD, encompassing both bvFTD[3] (n=125) and the PPAs[2] (avPPA (n=33) and svPPA (n=18).
Exclusion criteria were defined as: *i*) use of drugs that could affect TMS variables, *ii*) history of head trauma, alcohol abuse, stroke or transient ischemic attack, or epilepsy; *iii*) presence of pacemaker or other cardiac devices, cochlear implants, or previous brain surgery, such as clipping of a cerebral aneurysm; *iv)* motor neuron disease, including amyotrophic lateral sclerosis, primary lateral sclerosis and progressive muscular atrophy, considering that patients with motor neuron disease may have intracortical connectivity abnormalities.[8,9]
5 patients out of 176 (n=3 bvFTD, n=2 avPPA) were excluded (2.8%), because carrying electronic implants (n=1) or motor cortex excitability was unreliable (n=4).
Moreover, 74 age-matched healthy controls were recruited among healthy volunteers as a control group (HC), for a total of 250 participants.
The diagnostic assessment consisted in the comprehensive evaluation of the past medical history, a complete neurological and neuropsychological assessment, and an MRI brain scan in all patients.
Disease severity was measured using the Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating (FTLD-CDR) scale sum of boxes[10], while behavioral disturbances were rated by

the Neuropsychiatric Inventory (NPI).[11] Basic Activities of Daily Living (BADL)[12] and Instrumental Activities of Daily Living (IADL)[13] were also considered.

In the majority of patients (67.3%.), CSF tau and $A\beta_{42}$ determinations (50.9%) or amyloid PET imaging (16.4%) were performed to exclude focal Alzheimer's disease (AD) pathology, as previously reported.[14] Briefly, a CSF AD-like profile was defined as tau≥400 ng/L and $A\beta_{42}$≤600 ng/L using an ELISA assay (INNOTEST, Innogenetics, Ghent, Belgium),[15] while PET amyloid imaging was acquired using 370 MBq (10 mCi) of [18F]-florbetapir and visual readings were performed by nuclear medicine physicians.

Genetic analysis identified 29 patients (17.0%) with pathogenic mutations (n=20 *Granulin* mutations, n=9 *C9orf72* expansions).

HC underwent a brief standardized neuropsychological assessment (Mini-Mental State examination ≥27/30); psychiatric or other neurological illnesses were considered as exclusion criterion.

None of the patients were treated with drugs that could have altered the cerebral cortex excitability in the previous three months.

Transcranial magnetic stimulation variables and protocols

For the purpose of the present study, we considered short interval intracortical inhibition and intracortical facilitation (SICI-ICF), long interval intracortical inhibition (LICI), short interval intracortical facilitation (SICF) and short latency afferent inhibition (SAI). These measures partially and indirectly reflect the activity of several neurotransmitter circuits: SICI reflects $GABA_A$, ICF glutamate, LICI $GABA_B$, SICF both $GABA_A$ and glutamate, and SAI acetylcholine.[16,17]

A TMS figure-of-eight coil (each loop diameter 70 mm – $D70^2$ coil) connected to a monophasic Magstim $Bistim^2$ system (Magstim Company, Oxford, UK) was employed for all TMS paradigms, as previously reported.[18] Electromyographic (EMG) recordings were performed from the first dorsal

interosseous (FDI) muscles using 9 mm diameter, Ag-AgCl surface-cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified and filtered at 20 Hz and 2 kHz with a sampling rate of 5 kHz.

Resting motor threshold (RMT) was determined on the left motor cortex as the minimum intensity of the stimulator required to elicit motor evoked potentials (MEPs) with a 50 μV amplitude in 50% of 10 consecutive trails, recorded form the right first dorsal interosseous muscle during full muscle relaxation.

SICI-ICF, SICF, LICI and SAI were studied using a paired-pulse technique, employing a conditioning-test design. For all paradigms, the test stimulus (TS) was adjusted to evoke a MEP of approximately 1 mv amplitude in the right first dorsal interosseous muscle.

For SICI and ICF, the conditioning stimulus (CS) was adjusted at 70% of the RMT, employing multiple interstimulus intervals (ISIs), including 1, 2, 3, 5 ms for SICI and 7, 10, 15 ms for ICF.[19,20] For SICF, the CS intensity was set to 90% RMT, delivering the CS after the TS, at ISIs of 1, 1.3, 2.1, 2.5, 3.3 and 4.1 ms.[21] LICI was investigated by implementing two supra-threshold stimuli, with the CS adjusted at 130% of the RMT, employing ISIs of 50, 100 and 150 ms.[22] SAI was evaluated employing a CS of single pulses (200 μs) of electrical stimulation delivered to right median nerve at the wrist, using a bipolar electrode with the cathode positioned proximally, at an intensity sufficient to evoke a visible twitch of the thenar muscles.[23] Different ISIs were implemented (-4, 0, +4, +8 ms), which were fixed relative to the N20 component latency of the somatosensory evoked potential of the median nerve.

For each ISI and for each protocol, ten different paired CS-TS stimuli and fourteen control TS stimuli were delivered in all participants in a pseudo randomized sequence, with an inter trial interval of 5 secs (±10%).

The conditioned MEP amplitude, evoked after delivering a paired CS-TS stimulus, was expressed as percentage of the average control MEP amplitude. Stimulation protocols were conducted in a randomized order. Audio-visual feedback was provided to ensure muscle relaxation during the entire experiment and trials were discarded if EMG activity exceeded 100 μV in the 250 ms prior to TMS stimulus delivery. Less that 5% of trials were discarded for each protocol. All of the participants were capable of following instructions and reaching complete muscle relaxation; if, however the data was corrupted by patient movement, the protocol was restarted and the initial recording was rejected.

Statistical analysis

Demographic and clinical characteristics at baseline were compared using one-way analysis of variance (ANOVA) or Chi-Square's test. EMG TMS evoked responses were compared using one-way ANCOVA (for RMT) or two-way mixed ANCOVA (for SICI-ICF, SICF, LICI and SAI) with GROUP as between-subjects factor and ISI as within-subjects factor, including sex, age (in years) at evaluation and disease duration (in years) as covariates. Moreover, to assess the effect of cortical atrophy on TMS measures, we used MRI imaging data to quantify the shortest Cartesian distances from the scalp to the left M1 hand representation. We performed the same two-way mixed ANCOVA covariating also for the scalp-to-cortex distance.

Mauchly's test was used to check for sphericity violation, applying Greenhouse-Geisser epsilon determinations. If a significant interaction was observed, considering the differences in sample size between groups, differences were evaluated with Welch's ANOVA and the Games-Howell *post hoc* test was applied to test differences at each ISI.

Pearson's correlation coefficient was used to investigate any association between individual TMS measures, demographic and clinical characteristics. Linear regression analyses were subsequently

implemented to characterize the relationship between each variable and functional decline in patients with follow-up evaluations (ΔFTLD-CDR score at 12 months compared to baseline). Ultimately, a stepwise multiple regression analysis was used to identify the most fitting explanatory variable/s for functional decline.

Data availability

All study data, including study design, protocol, statistical analysis plan and results are available from the corresponding author, B.B., upon reasonable request.

Results

Participants

One hundred twenty-two bvFTD (age 65.7±9.0), thirty-one avPPA (age 67.7±8.8) and eighteen svPPA (age 63.0±7.8) patients, and seventy-four HC (age 64.0±11.5) were included in the present study. Demographic and clinical characteristics are reported in **Table 1**.

Neurophysiological measures in bvFTD, avPPA and svPPA

Repeated measures ANCOVA highlighted a significant ISI×GROUP interaction for SICI-ICF [F(7.5,592.4)=36.4, p<0.001, partial η^2=0.32, ε=0.41] and SICF [F(11.4,813.5)=12.8, p<0.001, partial η^2=0.15, ε=0.76].

For LICI there was only a significant main effect for GROUP [F(3.0,215.0)=11.3, p<0.001, partial η^2=0.13], but not for ISI or a significant ISI×GROUP interaction.

For SAI we observed only a significant main effect for ISI [F(2.2,496.7)=7.6, p<0.001, partial η^2=0.03, ε=0.73], but not for GROUP or a significant ISI×GROUP interaction.

Including only patients with a quantifiable scalp-to-cortex distance at MRI, and thus excluding healthy controls, we observed similar results for SICI-ICF, F(4.2,264.8)=2.06, p=0.018, η^2=0.03, ε=0.35 and SICF, F(7.259.8)=0.95, p=0.038, η^2=0.05, ε=0.72.

We did not observe a significant interaction at the one-way ANCOVA for RMT.

Post hoc differences, with Bonferroni corrections for multiple comparisons, between groups and at every ISI for each neurophysiological protocol are reported in **Fig. 1**.

Association of neurophysiological measures and clinical characteristics

We evaluated the association between baseline clinical characteristics and neurophysiological measures (i.e. SICI, ICF, SICF and LICI) (see **Table 2**).

For this purpose, we considered mean SICI (1, 2, 3 ms), mean ICF (7, 10, 15 ms), mean SICF ratio (ratio 1.3/3.3 ms) and mean LICI (50, 100, 150 ms) values.

Disease severity, as measured by FTLD-CDR, was significantly associated with SICI (r=0.64, p<0.001), ICF (r=-0.50, p<0.001) and LICI (r=0.73, p<0.001) (see **Fig. 2**). Comparable results were obtained when MMSE scores were considered (SICI, r=-0.78, p<0.001; ICF, r=0.52, p<0.001; and LICI, r=-0.81, p<0.001). A comparable correlation was observed for both IADL or BADL and TMS parameters (see **Table 2** for single correlations).

A significant association between disease duration and SICI (r=0.37, p<0.001), ICF (r=-0.53, p<0.001), LICI (r=0.35, p<0.001) and SICF (r=-0.39, p<0.001) was observed.

Behavioral disturbances, as measured by NPI, significantly correlated with ICF (r=-0.17, p=0.039).

Neurophysiological measures as predictors of functional decline

A linear regression analysis was run to understand the effect of demographic/clinical and neurophysiological measures on functional decline, evaluated with the ΔFTLD-CDR score at 12 months compared to baseline. This was performed only on subjects with a follow-up evaluation (n=82).

We observed that baseline functional measures, as FTLD-CDR (β=0.47, p<0.001, adjusted R^2=0.21) and MMSE scores (β=-0.56, p<0.001, adjusted R^2=0.31) were significantly associated with functional decline. Moreover, the presence of a genetic mutations was also associated with faster decline (β=0.25, p=0.027, adjusted R^2=0.05).

Regarding neurophysiological measures, we observed a significant association of SICI (β=5.63, p<0.001, adjusted R^2=0.72), ICF (β=-0.33, p=0.003, adjusted R^2=0.10), SICF (β=-0.47, p<0.001, adjusted R^2=0.36), and LICI (β=0.48, p<0.001, adjusted R^2=0.22) with functional decline but not for RMT or SAI (see **Table 3**).

We then applied a stepwise multiple regression analysis including all variables with a $p<0.100$ at univariate analysis. Only SICI (β=5.0, $p<0.001$) and SICF (β=-1.36, p=0.004) were retained in the stepwise multiple regression model, which significantly predicted functional decline at 12 months ($p<0.001$, adjusted R^2=0.73).

Including only SICI in the linear regression analysis model, which was the most significant variable, it accounted for 72.5% of the variation in ΔFTLD-CDR scores at 12 months with adjusted R^2=0.72, a large size effect according to Cohen.[24] Thus, the predicted functional decline at 12 months' time may be calculated with the following formula:

Predicted ΔFTLD-CDR at 12 months = -1.616 + (5.629 × average SICI).

For example, for an average SICI of 0.60, there will be a predicted decrease in FTLD-CDR scores of 1.8 (95% CI, 1.2-2.1) points per year; for an average SICI of 0.8 a predicted decrease of 2.9 (95% CI 2.6-3.2) points per year, while for an average SICI of 1.0 a predicted decrease of 4.0 (95% CI 3.7-4.3) points per year (see **Fig. 3**).

Discussion

In the present study, we observed a significant impairment of specific neurophysiological measures in FTD patients compared to HC. These findings confirm previous reports of an impairment in intracortical inhibitory and excitatory circuits, which largely rely on GABAergic and possibly glutamatergic transmission, in patients with FTD.[7,14,25–29]

These changes seem to reflect the pharmacological abnormalities which are now clearly associated with FTLD, particularly in serotonin, dopamine, GABA and glutamate, possibly reflecting the underlying pathological process.[30,31] In particular, we observed a significant impairment in SICI and LICI, which indirectly and partially depend on $GABA_A$ and $GABA_B$ergic transmission, respectively, and an impairment in ICF, which partly relies on glutamatergic circuits, in all FTD phenotypes. For the first time, we have observed a significant impairment in SICF, which could be explained by the degeneration of both inhibitory and facilitatory circuits. As expected, SAI, a marker of cholinergic transmission was comparable between different FTD phenotypes and HC, since cholinergic dysfunction is not part of the FTD pathology.

This study has also shown that FTD phenotypes have divergent intracortical circuits abnormalities, with both bvFTD and avPPA showing a significantly greater impairment than patients with svPPA, in particular for SICI. This somewhat confirms a previous report in which patients with svPPA showed a reduced intracortical inhibition,[25] in line with the pathological distribution of atrophy in this group of patients, particularly in the anterior temporal lobes, compared to patients with bvFTD and avPPA which show a greater involvement of the frontal lobes.[32] This could also be secondary to the different underlying neuropathology, as patients with svPPA more often are associated with an underlying TDP-43 pathology, while avPPA and bvFTD patients conceal both Tau and TDP-43 pathology.[33] However, in previous studies we observed a significant impairment of SICI and ICF also in patients with *GRN* or *C9orf72* mutations, which have an underlying TDP-43 pathology.[7,26,29]

Considering the asymmetry in cortical atrophy which characterize FTD patients, measures were also adjusted for scalp-to-cortex distances,[34] which have been shown to correlate with motor thresholds, showing comparable results.

Overall, these results could inevitably raise important implications for pharmacologic therapies, to an extent similar to what has been accomplished in AD with cholinergic therapy or in Parkinson's disease with dopaminergic therapy.

We have also observed that neurophysiological measures were variably associated to disease severity, disease duration, independence in activities of daily living, cognitive decline and neuropsychiatric disturbances, further emphasizing the parallelism with pathological burden of disease and the disruption of intracortical circuits.

Predicting the clinical course or progression in FTD remains problematic and several studies have identified markers of poor outcome, as the presence of a known pathogenic mutation,[35,36] an early age at disease onset,[36] increased frontal and temporal atrophy,[37,38] increased tau or neurofilaments levels in cerebrospinal fluid (CSF),[39,40] and the presence of concurrent motor neuron disease.[41] However, several of these observations have not been confirmed or have led to conflicting results, while others have been shown to account for only a small variation in disease progression.

On the contrary, in this study we have observed that intracortical connectivity measures obtained by TMS may predict more than 70% of the variation in FTLD-CDR scores at 12 months' time, showing to be the best markers of disease progression, more than genetic status or disease severity at baseline.

This is of fundamental importance for counselling patients and caregivers regarding the rate of functional decline, which is still speculative in daily clinical practice.

In line with these results, neurophysiological measures of intracortical inhibition (SICI), have been shown to be reduced in patients with amyotrophic lateral sclerosis (ALS), which is part of the FTLD-ALS spectrum disorder, being independently associated with a shorter survival.[42] Parallelly, also in Alzheimer's disease, cortical plasticity, evaluated with TMS, has been shown to correlate with disease severity and to predict disease progression better than any other neuropsychological measure.[43]

We acknowledge that this study entails some limitations. First, although excluding patients with an AD-like CSF profile, we did not have pathological confirmation of each diagnosis. Secondly, the prediction of functional decline using TMS variables was performed on the whole cohort of FTD patients, not taking into account the different phenotypes which have somewhat different baseline levels of SICI and ICF. This was necessary because of the relatively small number of patients with avPPA and svPPA with follow-up evaluations. However, the different phenotypes were not significant at the univariate linear regression model. Moreover, we did not consider laterality in TMS evaluations, considering that patients with FTD frequently have a very prominent asymmetrical cortical atrophy. Lastly, this a single center study, and results should be confirmed in larger multicenter studies and with longer follow-up evaluations.

Our findings suggest that the imbalance between GABA and possibly glutamatergic transmission, evaluated indirectly with TMS, is associated with increased disease severity and to a poor prognosis. The noninvasive *in vivo* monitoring of intracortical connectivity using TMS may provide not only relevant prognostic information but could be used to stratify patients in clinical trials and to evaluate the effects of novel disease modifying therapies.

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Tables

Table 1. Demographic, clinical and neurophysiological characteristics of included patients.

	bvFTD	avPPA	svPPA	HC	*p*-values
Patients (n)	122	31	18	74	-
Age (years)	65.7±9.0	67.7±8.8	63.0±7.8	64.0±11.5	n.s
Gender (% female)	38.4%	63.6%	55.6%	60.8%	0.008
Disease duration (years)	3.3±2.6	2.7±1.9	3.2±2.6	-	n.s
Education (years)	9.7±4.4	10.8±4.0	11.5±5.0	11.2±4.4	n.s
FTLD-CDR	6.9±4.6	6.2±5.0	5.4±5.2	-	n.s
MMSE	21.0±8.1	19.7±9.2	22.6±8.2	-	n.s
1 mV MEP (% MSO)	0.55±0.11	0.54±0.10	0.54±0.13	0.55±0.11	n.s.
RMT (% MSO)	0.45±0.09	0.45±0.09	0.46±0.09	0.45±0.09	n.s
SICI	0.88±0.43	0.97±0.43	0.63±0.43	0.29±0.17	<0.001
ICF	0.82±0.19	0.77±0.23	0.91±0.29	1.45±0.22	<0.001
SICF	0.78±0.39	0.89±0.38	0.78±0.26	1.42±0.49	<0.001
LICI	0.85±0.52	0.85±0.56	0.82±0.58	0.29±0.16	<0.001
SAI	0.56±0.13	0.54±0.16	0.55±0.11	0.51±0.10	n.s.

Demographic and clinical characteristics, and neurophysiological parameters are expressed as mean ± SD; resting motor threshold is expressed as ratio of the MSO; SICI, ICF, SICF, LICI and SAI are represented as ratio of mean motor evoked potential (MEP) amplitude related to the control MEP.

bvFTD = behavioral variant frontotemporal dementia; avPPA = agrammatic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; HC = healthy controls; FTLD-CDR = frontotemporal lobar degeneration-modified clinical rating scale sum of boxes; MMSE = Mini Mental State Examination; 1 mV MEP = intensity of the MSO at which approximately 1 mV was recorded; RMT = resting motor threshold; MSO = percentage of maximal stimulator output; SICI = mean short interval intracortical inhibition (1, 2, 3 ms); ICF = mean intracortical facilitation (7, 10, 15 ms); SICF = mean ratio at 1.3 and 3.3 ms; LICI: mean long interval intracortical inhibition (50, 100, 150 ms); SAI = mean short latency afferent inhibition (0, $^{+}$4 ms); MEP = motor evoked potential; n.s. = not significant.

**p*-values for Welch's ANOVA (*post hoc* tests with Games-Howell correction) or Chi-Square's test, as

appropriate.

Table 2. Pearson's correlations between neurophysiological parameters and demographic-clinical characteristics.

		Age	Dis. duration	FTLD-CDR	MMSE	BADL	IADL	NPI
SICI	***r***	0.12	**0.37**	**0.64**	**-0.78**	**0.35**	**0.42**	0.15
	p	0.059	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.062
ICF	***r***	**-0.14**	**-0.53**	**-0.50**	**0.52**	**-0.38**	**-0.44**	**-0.17**
	p	**0.036**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.039**
SICF	***r***	-0.012	**-0.39**	-0.14	0.09	-0.10	-0.08	0.06
	p	0.881	**<0.001**	0.074	0.250	0.503	0.322	0.479
LICI	***r***	-0.01	**0.35**	**0.73**	**-0.81**	**0.43**	**0.53**	0.16
	p	0.868	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.060

Dis. Duration = disease duration; FTLD-CDR = frontotemporal lobar degeneration-modified clinical rating scale sum of boxes; MMSE = Mini Mental State Examination; BADL = basic activities of daily living; IADL = instrumental activities of daily living; NPI = neuropsychiatric inventory; SICI = mean short interval intracortical inhibition (1, 2, 3 ms); ICF = mean intracortical facilitation (7, 10, 15 ms); SICF = mean short interval intracortical facilitation ratio (1.3/3.3 ms); LICI: mean long interval intracortical inhibition (50, 100, 150 ms). Significant values are reported in bold-face.

Table 3. Univariate linear regression model and multivariate regression model for predictors of functional decline (ΔFTLD-CDR score at 12 months compared to baseline).

	Univariate				Multivariate			
	B	**SE_B**	***β***	***p*-values**	***B***	**SE_B**	***β***	***p*-values**
Age	0.00	0.03	0.00	0.988	-	-	-	-
Sex	0.18	0.56	0.32	0.747	-	-	-	-
Phenotype	-0.30	0.40	-0.08	0.457	-	-	-	-
Genetic mutation	1.04	0.46	0.25	0.027	0.23	0.26	0.06	0.374
Disease duration	-0.05	0.13	-0.04	0.721	-	-	-	-
Education	-0.06	0.07	-0.09	0.408	-	-	-	-
FTLD-CDR	0.26	0.06	0.47	<0.001	0.01	0.05	0.02	0.833
MMSE	-0.18	0.03	-0.56	<0.001	0.04	0.04	0.13	0.338
RMT (% MSO)	-1.96	3.28	-0.07	0.551	-	-	-	-
SICI	5.63	0.39	0.85	<0.001	5.23	0.59	0.83	<0.001
ICF	-3.92	1.27	-0.33	0.003	-0.31	0.80	-0.03	0.703
SICF	-3.47	0.76	-0.47	<0.001	-1.19	0.49	-0.16	0.017
LICI	2.36	0.50	0.48	<0.001	0.24	0.51	0.05	0.638
SAI	3.18	2.37	0.16	0.184	-	-	-	-

FTLD-CDR = frontotemporal lobar degeneration-modified clinical rating scale sum of boxes; MMSE = Mini Mental State Examination; RMT = resting motor threshold; MSO = percentage of maximal stimulator output; SICI = mean short interval intracortical inhibition (1, 2, 3 ms); ICF = mean intracortical facilitation (7, 10, 15 ms); SICF = mean short interval intracortical facilitation ratio (1.3/3.3 ms); LICI: mean long interval intracortical inhibition (50, 100, 150 ms); SAI = mean short latency afferent inhibition (0, $^{+}$4 ms); B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient.

Legend to Figures

Figure 1. Neurophysiological parameters in bvFTD, avPPA, svPPA and healthy controls.

Legend. (A) Short-interval intracortical inhibition (SICI) at ISI 1, 2, 3, 5 and intracortical facilitation (ICF) at ISI 7, 10, 15 ms, (B) short-interval intracortical facilitation (SICF) at ISI 1, 1.3, 2.1, 2.5, 3.3, 4.1 ms, (C) long-interval intracortical inhibition (LICI) at ISI 50, 100, 150 ms, (D) short-latency afferent inhibition (SAI) at ISI -4, 0, +4, +8 ms, in bvFTD, avPPA, svPPA and HC. Data are represented as a ratio to the unconditioned motor evoked potential amplitude; error bars represent standard errors. bvFTD = behavioral variant frontotemporal dementia; avPPA = agrammatic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; HC = healthy controls; MEP = motor evoked potential; ISI = inter stimulus interval

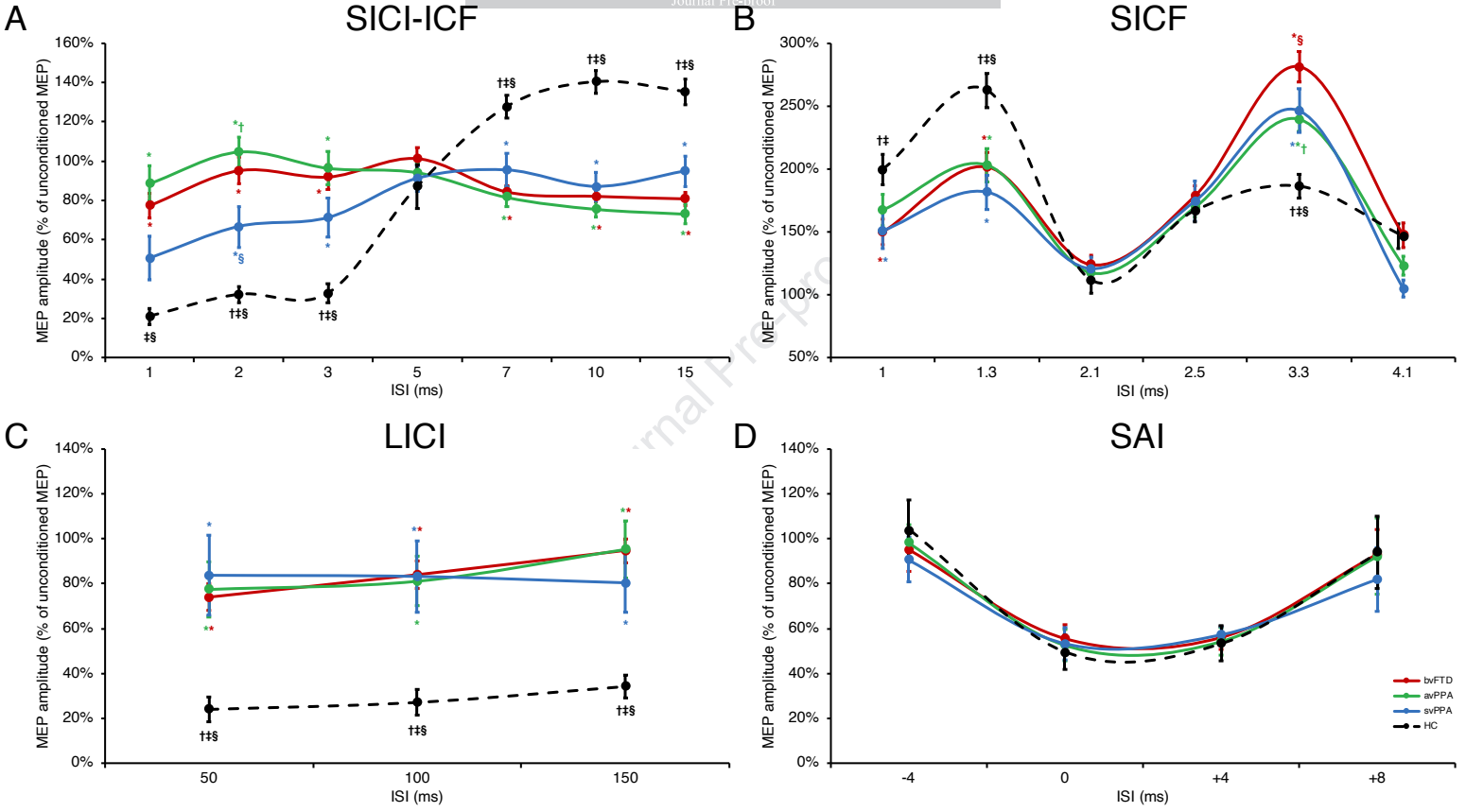
*p<0.05 vs HC; †p<0.05 vs svPPA, ‡p<0.05 vs bvFTD, §p<0.05 vs avPPA using Welch's ANOVA (*post hoc* tests with Games-Howell correction).

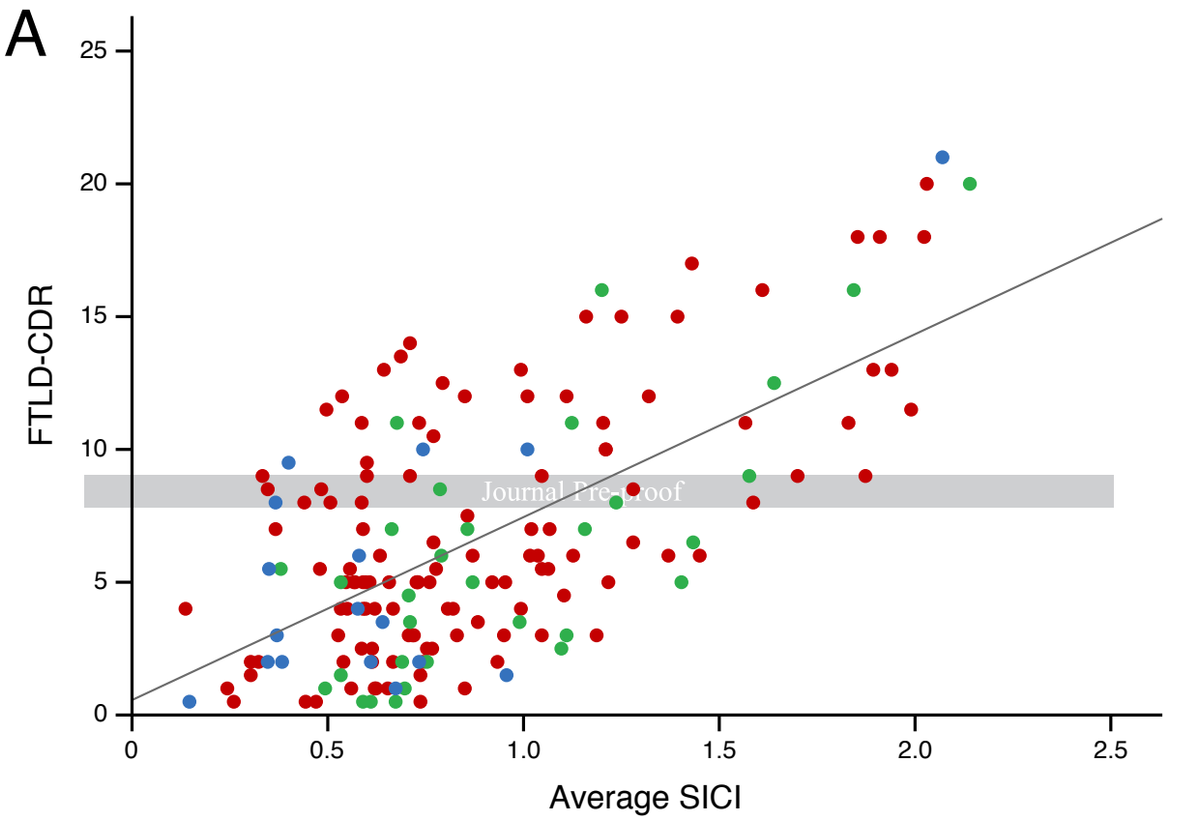
Figure 2. Significant associations between neurophysiological and functional measures.

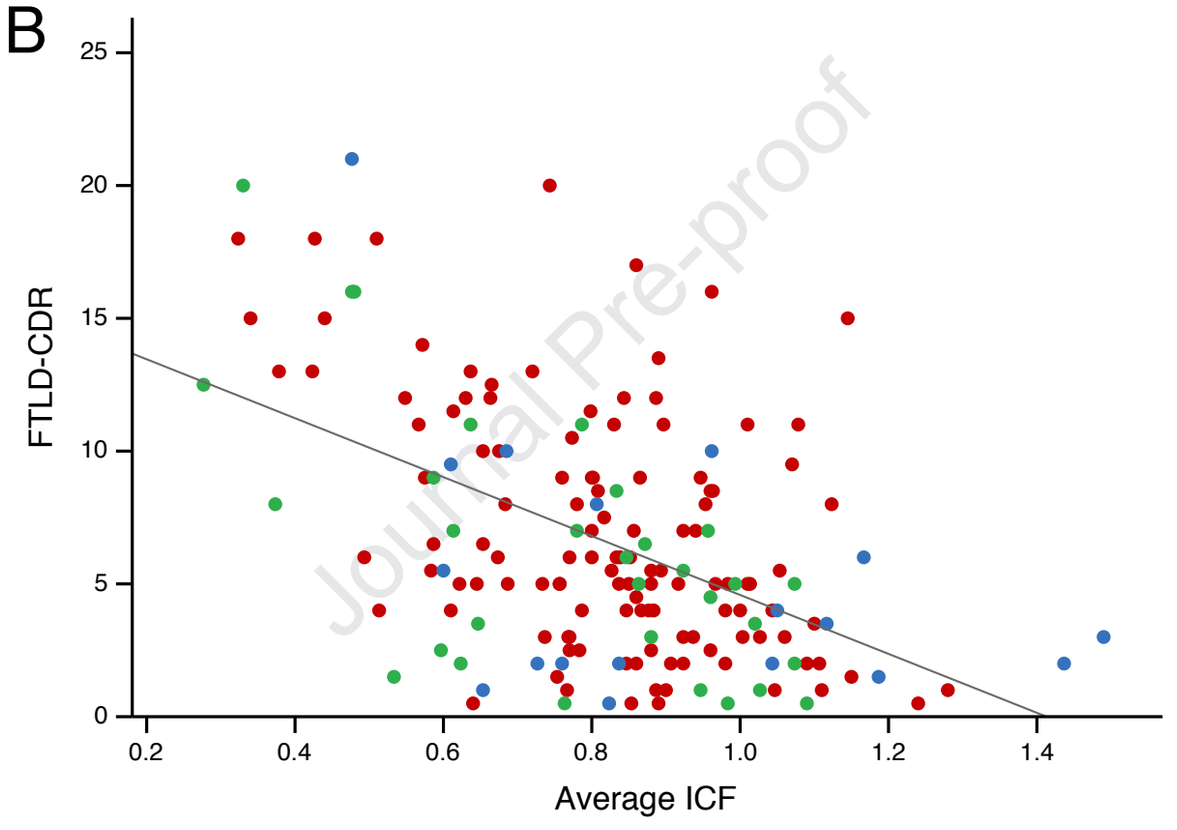
Legend. Association between FTLD-CDR and (A) average SICI (ISI 1, 2, 3 ms), (B) average ICF (ISI 7, 10, 15 ms) and (C) average LICI (ISI 50, 100, 150 ms).
SICI = short-interval intracortical inhibition; ICF = intracortical facilitation; LICI = long-interval intracortical inhibition; FTLD-CDR = frontotemporal lobar degeneration-modified clinical rating scale sum of boxes.

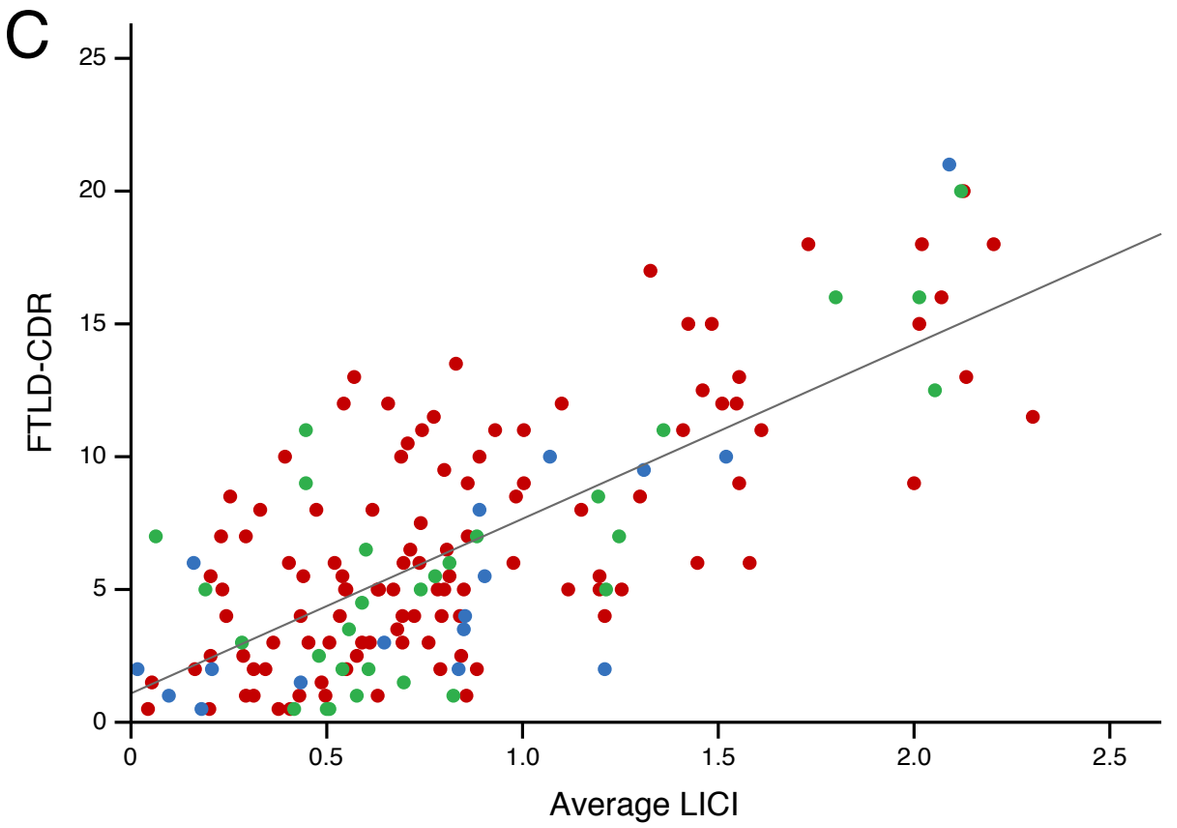
Figure 3. Predicted values of ΔFTLD-CDR scores at 12 months according to baseline SICI.

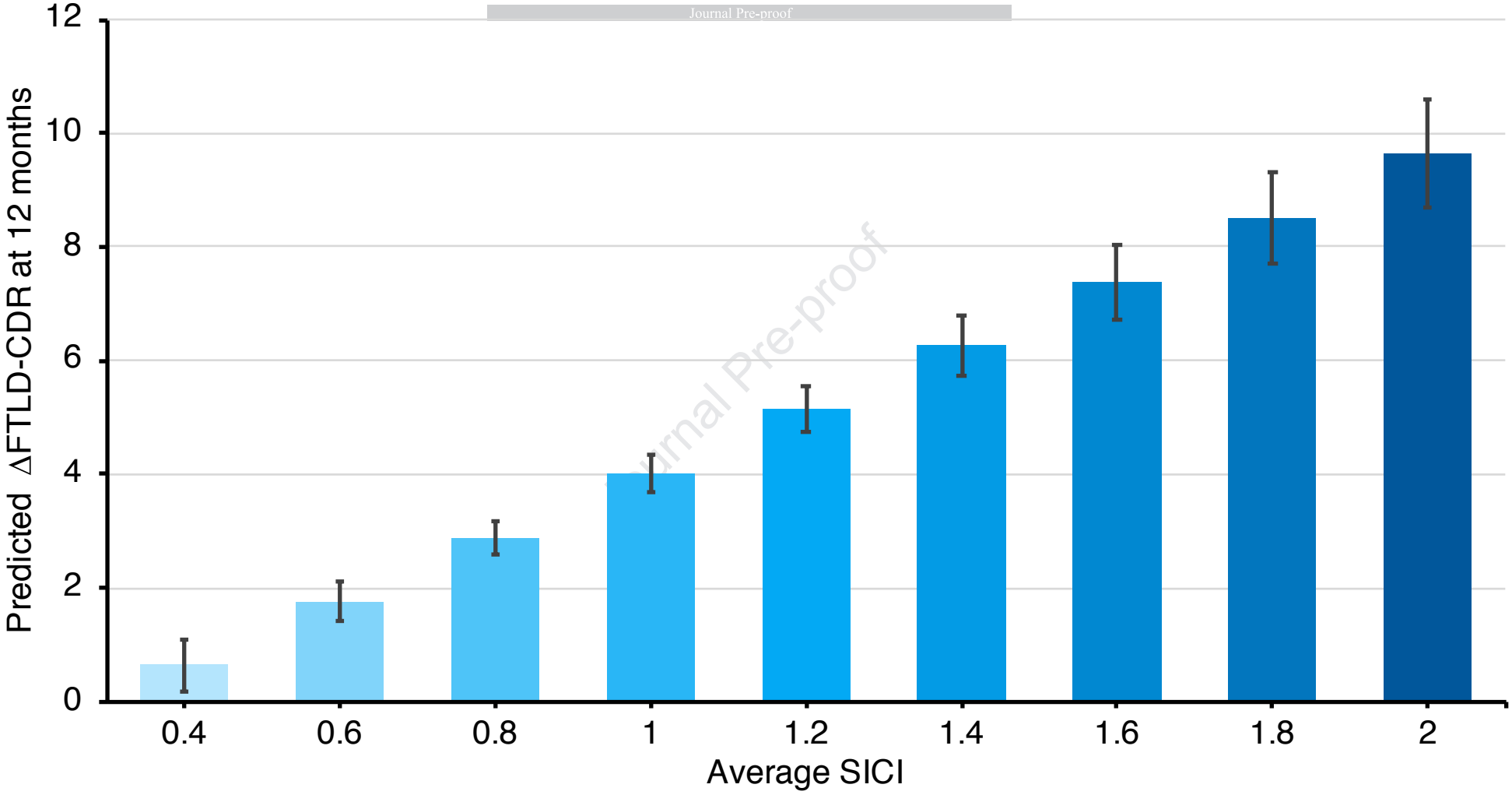
Legend. Average baseline SICI (ISI 1, 2, 3 ms) and 95% confidence intervals; SICI = short-interval intracortical inhibition; FTLD-CDR = frontotemporal lobar degeneration-modified clinical rating scale sum of boxes.











Highlights

• Intracortical connectivity was assessed with TMS in frontotemporal dementia.

• TMS measures correlated with disease severity.

• TMS measures were significant predictors of functional decline at 12 months.