ORIGINAL ARTICLE

Discriminative Utility of Transcranial Magnetic Stimulation-Derived Markers of Cortical Excitability for Transient Ischemic Attack

Jodi D. Edwards, Jennifer K. Ferris, Fuqiang Gao, Kie Honjo, Lara A. Boyd

ABSTRACT: ***Background:*** Several guidelines currently recommend acute diffusion weighted imaging (DWI) for the detection of ischemia in transient ischemic attack (TIA). However, DWI hyperintensities resolve early and only 30%–50% with clinically defined TIA show acute DWI positivity. A recent meta-analysis reported an unexplained 7-fold variation in DWI positivity in TIA across studies, concluding that DWI does not provide a consistent basis for defining ischemia. Intracortical excitability, measured using transcranial magnetic stimulation (TMS), has previously been shown to be altered after TIA and associated with ABCD2 scores; however, whether altered cortical excitability is associated with clinical and DWI-based definitions of TIA remains unclear. ***Methods:*** Individuals with TIA symptoms ($N = 23$; mean age $= 61 \pm 12$) were prospectively recruited and underwent DWI and paired-pulse TMS. Multivariate linear regression was used to estimate associations between TMS-derived excitability thresholds, and clinical TIA diagnosis, and imaging-based evidence of cerebral ischemia (DWI positivity). Area under the curve (AUC) analyses was used to compare the discriminability of TMS-derived thresholds and clinical TIA diagnoses. ***Results:*** Thresholds for intracortical inhibition in the TIA-unaffected hemisphere were significantly associated with the clinical diagnosis of TIA. No associations between TMS-derived thresholds and DWI positivity were observed. TMS thresholds showed low-moderate discriminability and values differed by age (65+) and sex. ***Conclusions:*** In this small sample, TMS-derived markers of intracortical excitability were associated with clinical TIA diagnoses but not DWI positivity. Our results provide preliminary evidence for the potential discriminative utility of TMS for the diagnosis of TIA and highlight the need for future work in larger cohorts.

RÉSUMÉ : Utilité des marqueurs de l'excitabilité corticale dérivés de la stimulation magnétique transcrânienne dans des cas de patients victimes d'un accident ischémique transitoire. ***Contexte*** **:** Plusieurs lignes directrices recommandent à l'heure actuelle des IRM de diffusion pour détecter en phase aiguë des accidents ischémiques transitoires (AIT). Cependant, les hyper-signaux de cette technique d'imagerie médicale se résorbent rapidement et seulement 30 à 50 % des cas d'AIT bien définis sur le plan clinique satisfont en phase aiguë au seuil de positivité des IRM. À ce sujet, une méta-analyse récente a signalé une variation inexpliquée de 7 points du seuil de positivité des IRM de diffusion parmi différentes études, ce qui l'a amené à conclure que cette modalité diagnostique ne représente pas un outil fiable pour confirmer la présence d'un AIT. Dans le passé, on a déjà montré comment l'excitabilité intra-corticale, mesurée au moyen de la stimulation magnétique transcrânienne (SMT), pouvait être altérée à la suite d'un AIT et associée à des scores obtenus à l'échelle ABCD^2. Cela dit, la question de savoir si l'excitabilité corticale altérée peut être associée aux diagnostics cliniques et aux observations des IRM de diffusion quant aux AIT n'a toujours pas été tranchée. ***Méthodes*** **:** Des individus aux prises avec des symptômes d'AIT ($n = 23$; âge moyen $= 61 \pm 12$) ont été recrutés de manière prospective et ont subi une IRM de diffusion et une SMT par paire d'impulsions (*paired-pulse TMS*). Nous avons ensuite fait appel à la méthode de régression linéaire multivariée pour estimer les associations entre les seuils d'excitabilité corticale dérivés de la SMT, les diagnostics cliniques d'AIT et les preuves d'une ischémie cérébrale révélées par les seuils de positivité d'une IRM de diffusion. Nous avons aussi utilisé des analyses en fonction de l'aire sous la courbe (*under the curve analyses*) pour comparer la capacité de discrimination des seuils d'excitabilité corticale en comparaison avec les diagnostics cliniques d'AIT. ***Résultats*** **:** Les seuils d'inhibition intra-corticale dans l'hémisphère cérébral non-affecté par un AIT ont été associés de façon notable à un diagnostic clinique d'AIT. Qui plus est, aucune association entre les seuils d'excitabilité corticale dérivés de la SMT et les seuils de positivité d'une IRM de diffusion n'a été observée. Ces seuils dérivés de la SMT ont en outre montré une capacité de discrimination faible à modérée et des valeurs différant selon l'âge (65 +) et le sexe. ***Conclusions*** **:** Dans ce petit échantillon, les marqueurs de l'excitabilité intra-corticale dérivés de la SMT ont été associés à des diagnostics cliniques d'AIT mais pas aux seuils de positivité des IRM de diffusion. Ces résultats fournissent ainsi des preuves préliminaires de l'utilité potentielle discriminatoire de la SMT dans le diagnostic des AIT et soulignent la nécessité de travaux futurs menés avec des cohortes plus importantes.

Keywords: Cortical excitability, Transcranial magnetic stimulation, Transient ischemic attack

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Introduction

Transient ischemic attack (TIA) increases the risk of stroke[1]; this risk remains elevated for up to 5 years, even for clinically stable patients with TIA with no recurrent events in the early high-risk period.[2] TIA can be difficult to diagnose clinically and interobserver agreement of the involved territory among physicians is poor.[3] Clinical guidelines currently recommend the use of diffusion weighted imaging (DWI) in the investigation of patients with TIA and minor stroke to confirm cerebral ischemia and assess risk of recurrent ischemic events.[4] Recent multicenter registry data have shown that the presence of acute DWI lesions after minor stroke or TIA is predictive of recurrent stroke at 90 d, but not at 1 or 5 years.[5,6]

However, the detection of acute DWI positivity after TIA symptoms remains variable. A previous meta-analysis of 45 studies involving 9078 patients with TIA reported pooled estimates for DWI positivity of only 34.3%, reporting an unexplained 7-fold variation in positivity across studies.[7] Findings from a TIA registry of 4789 patients at 61 sites similarly reported evidence of acute brain infarction in only 33.4%,[5] suggesting that DWI provides inconsistent evidence of cerebral ischemia in those with suspected TIA. It is also well established that the hyperintensity of DWI lesions in patients with TIA or minor stroke decreases in intensity after 10 d and resolves early after the acute phase, reducing the diagnostic yield of DWI.[8] Further, prior reports have shown that up to 61% of patients with TIA delay presenting to medical care[9] and a FAST-based public education campaign did not improve delays or failure to seek attention in those with TIA or minor stroke.[10] These data indicate that for many individuals with suspected, particularly those with a delayed presentation, DWI may be an unreliable measure to confirm cerebral ischemia.

Previous work has demonstrated that intracortical excitability, measured using transcranial magnetic stimulation (TMS), is altered after TIA.[11-13] Specifically, with paired-pulse methods, several prior studies have shown that short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are asymmetric between the TIA-affected and TIA-unaffected primary motor cortices, independent of the presence of acute changes on structural imaging[12,13] and may persist for up to 14 d post-TIA symptom onset.[13] Further, hemispheric asymmetries in intracortical excitation are significantly correlated with the ABCD2 score[13] and show potential utility to discriminate TIA from migraine aura without headache.[14] Thus, similar to observations in subacute stroke populations,[15] TMS-derived markers of altered cortical excitability may show widespread alterations in both the TIA-affected and unaffected hemispheres after TIA and provide additional diagnostic information for the evaluation of TIA.

The objectives of the present study were to: (1) determine whether thresholds for intracortical excitability are associated with clinical TIA diagnoses and imaging-based evidence of cerebral ischemia in a prospective cohort of individuals presenting with symptoms of TIA and (2) to compare the diagnostic accuracy of TMS-derived thresholds of SICI and ICF to the clinical classification of TIA. The primary hypothesis was that thresholds of intracortical excitability would be associated with a clinical diagnosis of TIA and a secondary hypothesis was that they would have increased discriminative utility compared to the clinical TIA classification.

Methods

Study Design

Individuals presenting with symptoms of TIA ($N = 23$; mean age = 61 ± 12) were prospectively recruited from a tertiary care Stroke Prevention Clinic at the Vancouver General Hospital within 60 d of symptom onset (mean = 19 d; range = 7–57). Inclusion criteria were: TIA with unilateral motor or somatosensory symptoms and resolution of symptoms within 24 h. Exclusion criteria were: contraindications to TMS, including prior history of stroke, seizures, or epilepsy and family history of epilepsy, and contraindications to MRI. All participants underwent sessions of multimodal magnetic resonance imaging (MRI), including DWI, and single and paired-pulse TMS at baseline. The University of British Columbia research ethics board approved all aspects of the study protocol, and informed consent was obtained for each participant in accordance with the Declaration of Helsinki.

Study Variables

The study exposures were the clinical classification of TIA (i.e., TIA versus TIA-mimic), confirmed by the evaluating stroke neurologist, and imaging-based evidence of cerebral ischemia, indexed by DWI lesion status (i.e., positivity or negativity) on the baseline imaging examination, as rated by two independent neuroradiologists. The primary outcome was TMS-derived thresholds for short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in the TIA-affected and TIA-unaffected hemispheres.

Magnetic Resonance Imaging (MRI) Acquisition

MR acquisition was conducted at the University of British Columbia MRI Research Centre on a Philips Achieva 3.0T whole body MRI scanner (Philips Healthcare, Best, The Netherlands), using an eight-channel sensitivity encoding head coil and parallel imaging. All participants received a three-dimensional T1-weighted MPRAGE scan (TR = 7.722 ms, TE = 3.58, flip angle $\theta = 8°$, SENSE factor= 2, FOV = 256 × 170 × 200 mm, 1 mm3 isotropic voxels) and diffusion MRI using a single-shot spin echo DwiSE sequence (TR = 7465 ms, TE = 60 ms, FOV = 212 × 1312 mm, 60 slices, voxel dimensions = 2.2 × 2.2 × 2.2 mm^3).

DWI Lesion Identification

DWI scans were evaluated and rated for lesion positivity by two independent neuroradiologists (FG, KH) at Sunnybrook Health Sciences Centre in Toronto. Kappa statistics were performed to evaluate interrater reliability for lesion identification.[16] Discrepancies in lesion ratings were subsequently resolved via consensus meeting among members of the study team prior to analyses.

Transcranial Magnetic Stimulation (TMS)

Cortical motor excitability was assessed with single and paired-pulse TMS, delivered through a figure-of-eight coil connected to two Magstim 200[2] stimulators (Magstim Co., Wales, UK). Motor-evoked potentials (MEPs) were recorded using surface electromyography (EMG) placed over bilateral abductor pollicis brevis (APB). EMG data were collected using LabChart 7.0 software, in conjunction with a Powerlab EMG acquisition/

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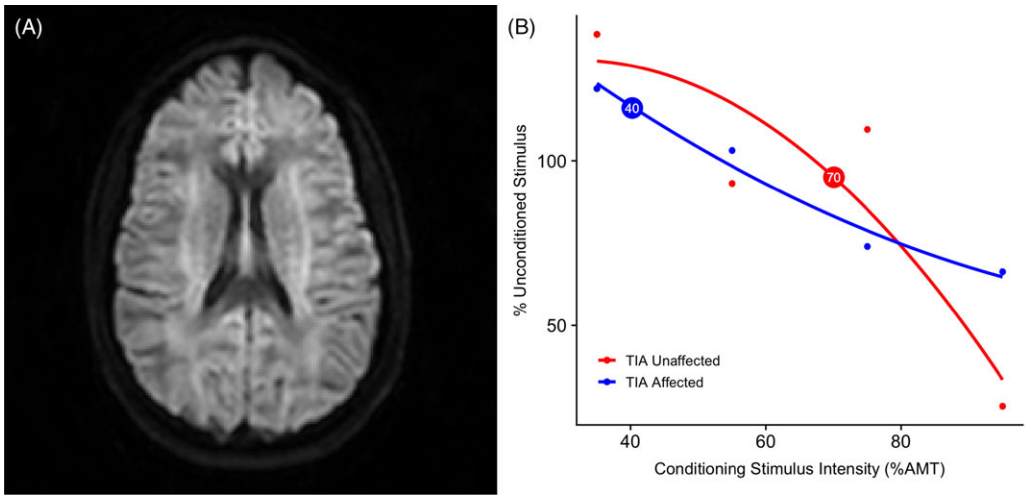

Figure 1: *MR Imaging and TMS data from a representative subject with clinically diagnosed TIA at 14 d postsymptom onset. (A-B) DWI (A) and FLAIR (B) sequences rated DWI negative for acute ischemia by study neuroradiologists. (C) TMS-derived metrics of short-interval intracortical inhibition (SICI) show differences in the threshold for inhibition in the TIA-affected and TIA-unaffected hemispheres. Plots are median amplitudes of motor-evoked potentials (MEPs) in the abductor pollicis brevis (APB) muscle at tested conditioning stimulus (%CS) intensities. Thresholds for SICI are indexed by the red circle, with the numerical value representing %CS intensity at threshold. Higher thresholds indicate reduced intracortical inhibition (i.e., as shown in the TIA-unaffected hemisphere in Panel C), because a greater intensity of TMS stimulation is required to evoke an inhibitory cortical response.*

amplification system (AD Instruments, Colorado Springs, USA). EMG signals were sampled at 2000 Hz, amplified ×1000, and band-pass filtered at 10–1000 Hz. Data were recorded from 100 ms prior to 350 ms after TMS delivery.

Single TMS pulses were delivered to localize the 'hotspot' that reliably elicited MEPs in the contralateral APB. Brainsight™ neuronavigation software (Rogue Research Inc., Montreal, Canada) was used to stereotaxically register the TMS coil with individual T1-weighted MR images and target stimulation over the hotspot. Resting motor threshold was identified as the lowest stimulator output intensity to elicit an MEP of 50 μV in 5 out of 10 trials. Active motor threshold (AMT) was the lowest intensity to elicit a MEP of 200 μV in 5 out of 10 trials, while the participant actively engaged APB isometrically at 20% of their maximum voluntary contraction, measured using a handgrip dynamometer (AD Instruments, Colorado Springs, USA). Force output during voluntary contraction was digitized and presented on a screen in front of the participant for visual feedback.

Paired Pulse TMS Protocol

Paired pulse TMS data were acquired according to a modified recruitment curve protocol.[17] A subthreshold conditioning stimulus (CS) was followed by a suprathreshold test stimulus (TS), set to the output intensity required to consistently evoke an MEP of 1000 μV in the relaxed APB. Mean TS MEP amplitudes are summarized in Supplementary Table 1. Interstimulus intervals (ISI) were set to 12 ms to induce ICF and 2 ms for SICI. Recruitment curves for ICF and SICI were generated by holding TS and ISI constant, while varying the CS intensity in 20% increments from 35% to 95%, and 110%, 125% and 140% of AMT for ICF and from 35% to 95% of AMT for SICI. Eight trials at each CS intensity, plus 8 pulses of unconditioned stimuli, were delivered randomly for a total of 64 pulses for ICF and 40 pulses for SICI. The order of paired pulse delivery was counterbalanced across participants for hemisphere and ISI. Both SICI and ICF were collected in one hemisphere before switching to the second hemisphere. The order of data collection (TIA-affected and unaffected Hemispheres, ICF and SICI) was pseudo-randomized across participants.

Thresholds for SICI and ICF

Thresholds for ICF and SICI were derived using methods previously described.[17] Briefly, peak-to-peak MEP amplitudes for each hemisphere and ISI were calculated and trials exceeding two standard deviations of the mean amplitude were excluded. MEP amplitude was plotted as a function of %CS intensity, and a quadratic regression function was fit to these data to derive the minimum CS intensity at which MEP amplitude exceeded variability at 0% CS (baseline variability plus/minus one standard error of the estimate). This method has previously been shown to have greater reliability than paired-pulse methods based on averaged responses from a single conditioning stimulus intensity.[18] These values represent the threshold required to elicit inhibition (SICI) or facilitation (ICF) in each participant (Figure 1).

Statistical Analyses

Descriptive statistics were generated to characterize the study cohort for demographic and clinical variables (SPSS 20.0; IBM Corp., Armonk, N.Y., USA) (Table 1). For the primary analysis, multivariate linear regression was used to estimate associations between the clinical diagnosis of TIA and DWI positivity and thresholds for SICI and ICF in the TIA-affected and TIA-unaffected hemispheres, adjusting for age, sex, and time since symptom onset, using a backward elimination fit selection. Final models were evaluated for overall significance, and the significance of the addition of each predictor variable into the model was assessed by adjusted R2 values.

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Table 1: Demographic and clinical characteristics of individuals presenting with symptoms of TIA ($N = 23$), overall and by clinical TIA diagnosis and imaging-based confirmation of cerebral ischemia; *p*-value for between-group comparisons

	Overall cohort *N* (%)	Clinical TIA positive *N* (%)	Clinical TIA negative *N* (%)	*p*-value	DWI Positive *N* (%)	DWI Negative *N* (%)	*p*-value
Age (Mean, SD)	61 (12)	62 (14)	61 (10)	0.84	61 (12)	62 (13)	0.93
Sex							
Male	15 (65.2)	9 (39.2)	6 (26.0)		3 (13.0)	12 (52.2)	
Female	8 (34.8)	4 (17.4)	4 (17.4)	0.49	0 (0.0)	8 (34.7)	0.26
Clinical diagnosis							
TIA positive	7 (30.4)				4 (17.4)	0 (0.0)	
TIA negative	16 (69.6)				9 (39.2)	10 (43.5)	0.10
Imaging diagnosis							
DWI positive	3 (13.0)	4 (17.4)	0 (0.0)				
DWI negative	20 (87.0)	9 (39.2)	10 (43.5)	0.10			
Affected hemisphere							
LH	13 (56.5)	9 (39.2)	4 (17.4)		3 (13.0)	10 (43.5)	
RH	10 (43.5)	4 (17.4)	6 (26.0)	0.16	1 (4.3)	9 (39.2)	0.40
Time since symptom onset (days; mean, SD)	19.6(11.4)	20 (12.9)	18 (9.7)	0.71	20 (11.0)	19 (11.8)	0.87

DWI = diffusion-weighted imaging; TIA = transient ischemic attack; SD = standard deviation; LH = left hemisphere; RH = right hemisphere; ABCD2 = clinical score including parameters of age, blood pressure, clinical features of TIA, duration of TIA, presence of diabetes.

Secondary analyses were performed to assess the diagnostic utility of TMS-derived thresholds for SICI and ICF using a receiver operating characteristic (ROC) approach, with the clinical diagnosis of TIA by the evaluating stroke neurologist set as the classification variable (i.e., gold standard) (MedCalc 18.6; Broekstraat, Mariakerke, Belgium). Area under the curve (AUC) values for TMS-derived SICI and ICF thresholds in the TIA-affected and TIA-unaffected hemispheres were calculated, with values less than 0.7, between 0.7 and 0.9, or greater than 0.9 representing low, moderate, and high diagnostic accuracies, respectively. Due to the small sample size, AUC values were only calculated for TMS thresholds and not for the DWI-based confirmation of cerebral ischemia. In an additional exploratory analysis, AUCs for each test were compared both within the overall cohort and separately for clinical subgroups of interest, including women vs. men, age <65 vs. 65+ and time since symptom onset <7 d vs. 7+ days; p-values less than 0.05 were considered statistically significant.

Results

The cohort was comprised of 23 individuals presenting with unilateral motor or somatosensory TIA symptoms (mean age = 61 ± 12). Within the cohort, 13 (56.5%) were clinically diagnosed as TIA by the evaluating stroke neurologist and 10 (43.5%) were not clinically confirmed as TIA. Kappa statistics showed poor agreement among neuroradiologist raters for DWI positivity (Kappa = 0.01, SE = 0.08), consistent with prior evidence of a lower diagnostic yield when DWI is delayed in relation to symptom onset.[8] Discrepancies were resolved via consensus yielding 3 individuals (13.0%) with evidence of DWI positivity. Demographic and clinical characteristics of the study cohort are presented in Table 1. Chi-square, Fisher exact, and *t*-test comparisons showed no significant differences between those with a clinical TIA diagnosis or those that showed imaging-based evidence of cerebral ischemia on demographic or clinical variables ($p > .05$).

In the primary analysis, multivariate linear regression showed a significant association between the clinical classification of TIA and *increased* thresholds for SICI (i.e., reduced inhibition) in the TIA-unaffected hemisphere, after adjusting for age, sex, and time since symptom onset (days) ($p = 0.04$; Table 2). However, no significant associations between DWI positivity and thresholds for cortical excitability were observed in this cohort (all $p > 0.05$) (Table 2).

Secondary analyses to estimate AUC values from the ROC indicated that, for the overall cohort, thresholds for SICI and ICF showed low to moderate ability to discriminate TIA. Thresholds for SICI in the TIA-unaffected hemisphere showed the highest level of discriminability (0.70) and thresholds for ICF in the TIA-affected hemisphere had the lowest level of discriminability (0.57) (Table 3). Further an exploratory analysis of discriminability by age, sex and time since symptoms onset revealed that the performance of all diagnostic tests was higher in individuals over the age of 65, with AUC values for SICI thresholds in both the TIA-affected and TIA-unaffected hemispheres increasing to moderate-high levels (0.86) (Table 3). There also appeared to be differences in performance by sex, with women showing the highest TIA discriminability for thresholds for ICF in the TIA- affected hemisphere (0.75) and men showing the highest

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Table 2. Associations between clinical and imaging classifications of TIA and thresholds for intracortical inhibition and facilitation in TIA-affected and TIA-unaffected cortical hemispheres; multivariate linear regression[†]

	Clinical TIA diagnosis				DWI positivity		
Outcome	**Mean (SD)**	**Standardized B**	**Adjusted *R*-Square**	***p*-value**	**Standardized *β***	**Adjusted *R*-square**	***p*-value**
Intracortical inhibition							
TIA-affected	52.6 (17.1)	−0.27	−0.12	0.37	−0.38	0.02	0.21
TIA-unaffected	60.4 (19.2)	−0.50	−0.23	**0.04**	−0.09	0.39	0.65
Intracortical facilitation							
TIA-affected	86.0 (27.1)	−0.19	−0.05	0.49	−0.08	−0.14	0.77
TIA-unaffected	71.1 (29.7)	−0.05	0.12	0.85	−0.02	−0.19	0.95

TIA=transient ischemic attack; DWI=diffusion-weighted imaging.
[†]Adjusted for age, sex, time since symptom onset (days)

Table 3. Receiver operating characteristic (ROC) analyses comparing clinical TIA diagnoses (gold standard) to the classification of TIA using thresholds for SICI and ICF in TIA-affected and TIA-unaffected hemispheres; AUC values, standard errors and 95% confidence intervals

Variable	**AUC**	**SE**	**95% CI**	**AUC**	**SE**	**95% CI**
Overall Cohort						
ICF TIA-affected hemisphere				0.57	0.13	0.35 - 0.77
ICF TIA-unaffected hemisphere				0.64	0.12	0.41 - 0.83
SICI TIA-affected hemisphere				0.65	0.13	0.43 - 0.84
SICI TIA-unaffected hemisphere				0.70	0.13	0.48 - 0.87
Clinical Subgroups		***Women***				***Men***
ICF TIA-affected hemisphere	0.75	0.20	0.35 - 0.97	0.69	0.15	0.40 - 0.89
ICF TIA-unaffected hemisphere	0.63	0.25	0.25 - 0.92	0.65	0.15	0.37 - 0.87
SICI TIA-affected hemisphere	0.56	0.27	0.20 - 0.81	0.70	0.16	0.42 - 0.91
SICI TIA-unaffected hemisphere	0.63	0.25	0.25 - 0.92	0.76	0.16	0.48 - 0.94
		Age <65				***Age 65+***
ICF TIA-affected hemisphere	0.58	0.26	0.19 - 0.91	0.57	0.43	0.22 - 0.87
ICF TIA-unaffected hemisphere	0.58	0.27	0.19 - 0.91	0.79	0.17	0.41 - 0.97
SICI TIA-affected hemisphere	0.50	0.29	0.14 - 0.86	0.86	0.17	0.48 to 0.99
SICI TIA-unaffected hemisphere	0.67	0.33	0.25 - 0.95	0.86	0.17	0.48 to 0.99
	Time since Symptom onset ≤ 7 d			Time since Symptom onset ≥ 8 d		
ICF TIA-affected hemisphere				0.61	0.13	0.38 - 0.81
ICF TIA-unaffected hemisphere				0.61	0.13	0.38 - 0.81
SICI TIA-affected hemisphere				0.65	0.13	0.42 - 0.84
SICI TIA-unaffected hemisphere				0.69	0.14	0.46 - 0.87

TIA = transient ischemic attack; ICF = intracortical facilitation; SICI = short-interval intracortical inhibition.

discriminability for thresholds for SICI in the TIA-unaffected hemisphere (0.76), although the sample size for these analyses was very low. While there was insufficient test data acquired within 7 d after symptom onset to perform an ROC analysis, the performance of all diagnostic tests at 8+ days after symptom onset was low-moderate.

Discussion

In this study, we evaluated associations between TMS-derived thresholds for intracortical excitability, clinical TIA diagnosis, and DWI positivity. We also compared the discriminative performance of excitability thresholds to the clinical classification of

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TIA. Although limited by the small sample size, we found a significant association between the clinical classification of TIA (i.e., TIA versus TIA-mimic) and increases in the threshold for motor cortical inhibition (i.e., reduced inhibition) in the TIA-unaffected hemisphere. No relationships between DWI lesion status and TMS-derived thresholds after TIA were observed. Findings also demonstrated that TMS-derived thresholds of intracortical excitability show low-moderate discriminative ability compared to the clinical classification of TIA. Although these findings require investigation in a larger cohort, they suggest that TMS-derived markers of altered cortical excitability may have potential discriminative utility for the classification of TIA.

The finding that *increased* thresholds for SICI (i.e., reduced inhibition) in the TIA-*unaffected* hemisphere were associated with the clinical diagnosis of TIA is consistent with previous paired-pulse TMS studies demonstrating disrupted intracortical excitability *contralesionally* poststroke.[15,19-21] In subacute stroke patients with upper extremity impairment, inhibitory effects of the conditioning stimulus have been shown to be abnormally reduced in contralesional M1 at higher stimulation intensities, indicating an overall shift toward excitatory activity post-stroke,[15,19] which may reflect early reorganizational processes in the contralesional hemisphere and support early functional recovery.[20,21] The present findings indicate that these processes may begin at even the earliest stage of ischemic injury and are associated with clinical features of transient ischemia with unilateral sensorimotor symptoms. While our findings are also consistent with prior reports of alterations in intracortical excitability after TIA,[11-13] there were also notable differences. Unlike the present study, Koerner et al.[12] demonstrated reduced SICI in the *affected* hemisphere in patients with TIA. However, the focus of that study was on patients with very short TIA duration, symptoms <60 min, which may account for differences in the extent of intracortical changes distal to the involved territory, as observed in the present study. Taken together, these data suggest that TMS-derived markers of cortical excitability may have a role in confirming the clinical classification of TIA. Yet a number of questions remain and further research is required to: (1) determine the extent of intracortical and transcallosal alterations in patients with TIA and (2) delineate potential differences among subtypes of patients with TIA of different etiologies and symptom duration.

The relationship between the clinical characteristics of TIA and DWI positivity is still controversial. While some studies have reported that DWI provides information useful to confirm the clinical diagnosis or vascular territory after TIA[22] and that baseline DWI volume is predictive of new lesions at 7 d in those with TIA or minor stroke,[23] others have shown no association between DWI positivity and symptom duration or ABCD2 score[24] and report similar long-term stroke risks among DWI-positive and DWI- negative patients with TIA.[25] A recent meta-analysis evaluating rates of DWI positivity reported a pooled prevalence of 33.4%, with a 7-fold DWI-positive variation across studies and indicated that available evidence does not account for why 2/3 of patients with TIA with specialist confirmed TIA have negative DWI findings.[7] Evidence for low interrater agreement for DWI lesion status and the lack of relationship between TMS-derived excitability thresholds and DWI positivity in the present study provides further evidence for the variability in DWI signal changes after TIA. Our findings suggest that alterations in cortical excitability can be measured in the absence of focal abnormalities on DWI in patients with TIA and merit further exploration to determine the utility for the classification of TIA.

In addition to an observed association with the clinical diagnosis of TIA, the threshold for SICI in the TIA-unaffected hemisphere showed the strongest discriminability for the classification of TIA in the overall cohort, with AUC values higher than that of the other TMS-derived excitability thresholds. Importantly, the discriminative performance of all excitability thresholds increased substantially for patients with TIA over the age of 65, with inhibitory thresholds showing high discriminability for this subgroup. Further, differential discriminative effects emerged for women vs. men, with thresholds for ICF performing highest among women and inhibitory thresholds showing the highest discriminability for men. These data provide preliminary evidence that TMS-derived excitability thresholds show potential utility for the classification of TIA and also support the potential need for individualized protocols based on patient factors including sex and age at TIA onset. However, given the small sample sizes for these subgroup analyses, our findings should be interpreted as exploratory and require confirmation in a larger cohort in future research.

Strengths of the current study included the prospective collection of TMS and DWI measures in patients with clinical features of TIA, which reduced the potential for selection bias in this cohort. The use of neuro-navigation to target M1 for stimulation reduced the potential for measurement error in TMS acquisition. The current study had several limitations. The sample size was limited and thus, findings regarding the discriminative utility of thresholds for cortical excitability require replication in a larger cohort. The prevalence of DWI positive cases was markedly lower in the present cohort (13.0%) than in previous studies (pooled estimates: 33%), potentially limiting our power to detect relationships among TMS-derived thresholds for cortical excitability and DWI positivity. It is also possible that for some participants, DWI positive lesions resolved by the time of MRI and TMS collection. Yet this finding illustrates the potential utility of using paired pulse TMS in this population; changes to intracortical excitability may persist for a longer time period than transient ischemic signal on DWI imaging. TMS data are known to be variable between and within subjects. To address this limitation, we employed a threshold-based measure of paired-pulse intracortical excitability, fitting a quadratic curve to TMS-evoked responses across a range of stimulation intensities. This method is more time-consuming to collect than paired-pulse measures based on averaging trials across a single CS intensity; however, threshold-based measures have higher reliability than paired-pulse estimates at a single conditioning stimulus intensity.[18] Finally, as comprehensive data on vascular comorbidities were not available for all participants, we did not adjust for comorbid conditions in our multivariate models.

Conclusion

Although DWI is recommended acutely to confirm cerebral ischemia in individuals with suspected TIA, the rapid resolution of DWI hyperintensities and high degree of variability for DWI positivity in clinically defined TIA suggests DWI is an unreliable

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measure of ischemia. Thus, new measures for the detection of cerebral ischemia are required that show increased reliability across longer durations post TIA. In the current study, TMS-derived markers of cortical excitability were associated with clinical TIA diagnosis but not DWI positivity in a cohort of patients with TIA up to 2 months post TIA event. Our findings provide preliminary evidence for the potential utility of TMS-based measures in a small prospective TIA cohort and illustrate the need for future investigations in larger cohorts.

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Disclosures

The authors have no conflicts of interest to report.

Statement of Authorship

JDE and LAB were responsible for the design of the study, all data analyses, and interpretation and manuscript preparation and editing. JDE was also responsible for all data acquisition. JKF was responsible for data analysis and interpretation and manuscript editing. FG and KH were responsible for interpretation of the MRI imaging data and manuscript review and editing.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.62.

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