The relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+glutamine

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Running head: GABA, Glx and TMS in primary motor cortex

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Abstract

Transcranial magnetic stimulation (TMS) can provide an index of intracortical excitability/inhibition balance. However, the neurochemical substrate of these measures remains unclear. Pharmacological studies suggest the involvement of GABA\textsubscript{A} and GABA\textsubscript{B} receptors in TMS protocols aimed at measuring intracortical inhibition, but this link remains inferential. Proton magnetic resonance spectroscopy (\textsuperscript{1}H-MRS) permits measurement of GABA and glutamate + glutamine (Glx) concentrations in the human brain, and might help in the direct empirical assessment of the relationship between TMS inhibitory measures and neurotransmitter concentrations. In the present study, MRS-derived relative concentrations of GABA and Glx measured in the left M1 of healthy participants were correlated with TMS measures of intracortical inhibition. Glx levels were found to correlate positively with TMS-induced silent period duration whereas no correlation was found between GABA concentration and TMS measures. The present data demonstrate that specific TMS measures of intracortical inhibition are linked to shifts in cortical Glx, rather than GABA neurotransmitter levels. Glutamate might specifically interact with GABA\textsubscript{B} receptors, where higher levels of MRS-derived Glx concentrations seem to be linked to higher levels of receptor activity.

Key words: Magnetic resonance spectroscopy; Motor cortex; Cortical silent period; MEGA-PRESS
Introduction

Transcranial magnetic stimulation (TMS) is contributing significantly to our understanding of the pathophysiology of many neurological and psychiatric disorders (Chen et al. 2008). By using single and paired-pulse TMS over primary motor cortex (M1) it is possible to investigate physiological interactions between excitatory and inhibitory circuits (Hallett 2007). Furthermore, the combination of TMS protocols with the administration of central nervous system drugs permits indirect evaluation of the mechanism underlying these circuits (Teo et al. 2009) and potentially implicated receptors (Ziemann 2004). It has been suggested that short interval intracortical inhibition (SICI; Kujirai et al. 1993) induced by paired-pulse TMS protocols is mediated by gamma-aminobutyric acid A receptors (GABA_A). Indeed, the administration of benzodiazepine, a positive modulator of GABA_A, was found to enhance SICI (Ziemann et al. 1996a; Di Lazzaro et al. 2005). In parallel, pharmacological studies suggest that long interval intracortical inhibition (LICI) and the cortical silent period (CSP), which are TMS measures of long lasting intracortical inhibition, are increased by the administration of GABA_B receptor agonists tiagabine (LICI: McDonnell et al. 2006) and baclofen (CSP: Werhahn et al. 1999).

A better understanding of the effects of pharmacological agents on TMS measures of cortical excitability has also contributed to a better definition of the pathophysiology of numerous motor system disorders (Chen et al. 2008). For example, TMS studies have shown that both short- and long-interval intracortical inhibition was affected (Ziemann et al. 1997b; Mills, 2003) in patients with amyotrophic lateral sclerosis, a neurodegenerative disease selectively affecting motoneurons. In addition, abnormal intracortical inhibition was found in patients with Parkinson’s disease, where a shorter CSP (Cantello et al. 1991) and reduced SICI (Ridding et al. 1995) were observed. Other studies have suggested the presence of reduced intracortical

Recent studies have also demonstrated the presence of altered GABA$_B$ function in motor cortex inhibition in asymptomatic, concussed athletes (De Beaumont et al. 2007, 2012).

These studies suggest that TMS may present diagnostic utility in a variety of pathologies affecting primary motor cortex as well as providing a safe and rapid way of evaluating treatment response. However, TMS and pharmacological studies only allow an indirect measure of excitatory/inhibitory mechanisms and their implicated neurotransmitter systems. It is possible to directly and non-invasively evaluate the presence of alterations in brain neurochemistry by using proton magnetic resonance spectroscopy (1H-MRS). This technique allows in vivo detection and quantification of different neurometabolites, providing a sensitive and reliable assessment of neurochemical alterations (Ashwal et al. 2004; Holshouser et al. 2006). In addition to common neurometabolites (creatine (Cr) and phosphocreatine (PCr) ($tCr = Cr + PCr$), myo-inositol (mI), $N$-acetylaspartate + $N$-acetylaspartylglutamate (tNAA), glutamate (Glu) and glutamine (Gln) (Glx = Glu + Gln)), recent technological advances have allowed the detection and quantification of GABA neurotransmitter in the human brain (Mescher et al. 1998).

Similarly to TMS, MRS has provided a better understanding of the underlying biochemistry of different neuropathologies (Jissendi Tchofo and Balériaux 2009). For example, abnormal Glu concentration ratios characterize several brain pathologies, where a reduction of Glu/$tCr$ was found in Parkinson’s disease (Griffith et al. 2008), while abnormally elevated Glx concentrations were implicated in amyotrophic lateral sclerosis symptoms (Han and Ma 2010). Such neurometabolic alterations over regions of interest has also been shown in the acute concussion
phase, where injured athletes exhibit reduced NAA and Glu concentrations within the primary motor cortex (Henry et al. 2010).

Despite the parallel development of the TMS and MRS techniques, it remains unclear how the direct assessment of GABA and Glu concentrations corresponds to synaptic GABAergic and glutamatergic activity indirectly assessed by TMS. The nature of this link could help further understand what both techniques are specifically measuring. Stagg and collaborators (2011a) recently addressed this issue and reported no correlation between MRS-derived measures of GABA neurotransmitter levels and TMS measures of synaptic GABA_A (SICI; 2.5 ms) and GABA_B (LICI) receptor activity in M1. By contrast, a significant correlation between overall cortical excitability (input/output curve) and Glu levels was reported. Surprisingly, MRS-GABA levels were found to correlate positively with the slope of the input/output curve, whereby individuals with the greatest levels of M1 excitability (TMS) also showed the highest GABA concentration (MRS). These data suggest that MRS-derived GABA levels may not reflect specific synaptic activity, whereas MRS-derived Glu levels may relate to synaptic glutamatergic activity indirectly measured by the TMS input/output curve (Stagg and Nitsche 2011). The present study was conducted to provide further empirical insights into the presumed association between GABA concentration and TMS measures of intracortical inhibition, and to assess the link between GABA and the cortical silent period, a TMS inhibitory measure used in clinical and experimental settings.

Methods

Participants. The study group consisted of 24 right-handed participants (12 men and 12 women), from 20 to 38 (M = 24.7, SD = 4.1) years of age. The following exclusion criteria were used:
psychiatric or neurological history, traumatic brain injury or concussion, presence of a pacemaker, use of central nervous system-active medication, metal implanted in the skull, history of fainting, history of seizures or history of substance abuse. The study was approved by the local ethics committee, and all participants provided written informed consent prior to testing. Subjects received a financial compensation of $85 CAN for their participation. The experiment consisted of a single session of approximately 90 minutes, comprising 30 minutes of TMS immediately followed by a 50-minute session of MRS.

**TMS.** TMS was delivered through an 8 cm figure-of-eight coil connected to a MagPro stimulator (MagVenture, Farum, Denmark). The coil was positioned flat on the head of participants with an angle of 45° from the midline and with the handle pointing backwards. The induced current was biphasic with an anterior-posterior direction. The optimal site of stimulation was defined as the coil position from which TMS produced MEPs of maximum amplitude in the target muscle of the contralateral hand. The optimal site was then marked down on a cap placed over the head of the participant prior to TMS. Two self-adhesive electrodes were placed on the first dorsal interosseus (FDI) muscle to measure motor contraction. A ground electrode was positioned over the wrist. The EMG signal was filtered with a bandwidth of 20-1000 Hz and digitized at a sampling rate of 4 KHz using a Powerlab 4/30 system (ADInstruments, Colorado Springs, USA). MEPs were recorded using Scope v4.0 software (ADInstruments, Colorado Springs, USA) and stored offline for analysis. TMS pulses were delivered at a frequency of 0.1 to 0.2 Hz for all TMS protocols to avoid long lasting modulation of M1 excitability (Chen et al. 1997).

**Resting motor threshold:** The resting motor threshold (RMT) was initially determined for each subject. The RMT was defined as the minimum intensity used to elicit MEPs of 50 μV in 6 of 10
Paired pulse paradigms: The intensity of stimulation was first adjusted to produce MEPs of approximately 1 mV in amplitude. The protocol for short interval intracortical inhibition (SICI) was conducted in accordance with the method of Kujirai and colleagues (1993). A conditioning stimulus (CS) with an intensity of 70% of the MT was paired with a test stimulus (TS) of 1 mV using an interstimulus interval (ISI) of 3 ms. Ten MEPs were collected in addition to the TS alone. The protocol for long-term intracortical inhibition (LICI) was then performed by applying two pulses at an intensity adjusted to produce CS and TS amplitudes of approximately 1 mV peak-to-peak at an ISI of 100 ms.

CSP: To induce a CSP, single pulse TMS with an intensity of 120% and 130% of RMT was performed while participants maintained a voluntary isometric muscle contraction of the right FDI at approximately 20% of maximal strength. Ten MEPs were collected for both intensities.

Analysis of TMS data. For SICI, ratios of CS-TS on TS alone were computed. For LICI, ratios of the CS on the TS were computed. The length of the CSP was manually evaluated by an investigator blind to MRS data and defined as the beginning of EMG activity suppression until the resumption of sustained electromyographic activity. The two different intensities of stimulation for CSP (120% and 130%) were computed as a single variable (csp average) for analysis. Incomplete acquisition of TMS data led to the exclusion of one participant.

MR acquisition. Magnetic resonance (MR) acquisitions were performed using the 3T whole-body system (MAGNETOM Trio, a TIM systems, Siemens, Erlangen, Germany) at the “Unité de
Neuroimagerie Fonctionnelle, Centre de recherche de l’Institut universitaire de gériatrie de Montréal”. Radiofrequency transmission was performed with the built-in body coil, and signal was received with at 12-channel receive-only head coil. The prescription of M1 voxel and detection of potential structural abnormalities were performed using anatomical images of the brain obtained with a T1-weighted MPRAGE sequence (TR = 2300 ms; TE = 2.91 ms; FA: 9°; FOV = 256 x 256 mm²; 256 x 256 matrix; 160 axial slices of 1 mm; acquisition time: 9 min 50 s).

The voxel of interest (27 x 24 x 32 mm³) was positioned over the left hand area of the primary motor cortex using two accepted anatomical landmarks (Yousry et al. 1997; Figure 1). MRS data were acquired using a MEGA-PRESS sequence (Mescher et al. 1996, 1998) with double-banded pulses used to simultaneously suppress water signal and edit the $\gamma$–CH$_2$ resonance of GABA at 3 ppm. Additional water suppression using variable power with optimized relaxation delays (VAPOR) and outer volume suppression (OVS) techniques (Tkac et al. 1999) was optimized for the human 3T system and incorporated prior to MEGA-PRESS. The final spectra were obtained by subtracting the signals from alternate scans with the selective double-banded pulse applied at 4.7 ppm and 7.5 ppm (‘EDIT OFF’) and the selective double-banded pulse applied at 1.9 ppm and 4.7 ppm (‘EDIT ON’) (Figure 2). MEGA-PRESS data were acquired in four interleaved blocks of 32 (‘EDIT OFF’, ‘EDIT ON’) scans each with frequency drift correction between blocks. FIDs were stored separately in memory for individual frequency and phase correction using the tCr signal at 3.03 ppm, as well as correction for residual eddy-current using unsuppressed water signal obtained from the same voxel.

Analysis of MRS data. Both ‘EDIT OFF’ and difference spectra were analyzed using LCModel 6.2-1A (Provencher 1993, 2001), which calculated the best fit of the experimental spectrum as a linear combination of model spectra. The basis set for ‘EDIT OFF’ spectra was simulated using
home-written software based on density matrix formalism (Henry et al. 2010) in MATLAB, using known chemical shifts and $J$ couplings (Govindaraju et al. 2000). The simulated spectra of the following 20 brain metabolites were included in the basis set: alanine (Ala), ascorbate (Asc), aspartate (Asp), Cr, GABA, glucose (Glc), Glu, Gln, glycerophosphorylcholine (GPC), glycine (Gly), glutathione (GSH), lactate (Lac), myo inositol (mI), NAA, N-acetylaspartylglutamate (NAAG), PCr, phosphorylcholine (PCho), phosphorylethanolamine (PE), scyllo-inositol (sI), and taurine (Tau). Default simulations of lipids and macromolecular resonance were allowed during the LCModel fitting that was performed over the spectral range from 0.2 to 4.0 ppm. The basis set for difference spectra included an experimentally measured metabolite-nulled macromolecular spectrum from the occipital region (average from 11 subjects) and the experimentally measured spectra from 100 mM phantoms of NAA, GABA, Glu and Gln at 37°C and with pH adjusted to 7.2. The LCModel fitting was performed over the spectral range from 0.5 to 4.0 ppm, restricting modeling of the baseline by the use of the minimal number of spline knots allowed by the program. No baseline correction, zero-filling, or apodization functions were applied to the in vivo data prior to LCModel analysis. Visual inspection of the spectra led to exclusion of two subjects because of contamination from subscapular lipid signal. All remaining Cramér-Rao lower bounds (CRLB) were > 40% for GABA, Glx, tNAA and tCr. Linewidth of water spectra were all < 10 Hz, but two were larger than 2*SD over the mean and were excluded from further analysis. The scaling factor for the simulated and measured basis sets was calculated using the group average of tNAA measured from ‘EDIT OFF’ spectra and the group average tNAA from difference spectra. This scaling factor allowed for the fitted values to be on the same scale. Measures of GABA, Glx, and tNAA were extracted from difference spectra, whereas tNAA and tCr were extracted from ‘EDIT OFF’ spectra. The metabolites of interest, GABA and Glx, were expressed as ratios to tCr.
Statistical Analysis. T-tests were computed to verify the efficacy of TMS inhibitory protocols. Pearson correlations were also computed to look at the relationship between intracortical inhibition/facilitation protocols and metabolite concentration ratios. A $p$ value of $< 0.05$ was considered significant.

Results

Average GABA/tCr and Glx/tCr values across participants were $0.06 \pm 0.01$ and $1.05 \pm 0.11$, respectively. Cramér-Rao lower bound from LCModel analysis was $24.05 \pm 4.48$ for GABA and $3.37 \pm 0.50$ for Glx. Paired-sample $t$-tests were first conducted to verify the inhibitory effects of the TMS protocols. SICI ($t_{(18)} = 6.56, p = 0.0001$) and LICI ($t_{(18)} = 2.88, p = 0.01$) induced a significant inhibition of the TS. Correlations between MRS and TMS variables were then computed. Two-tailed Pearson correlations between TMS parameters and metabolite ratios are shown in Figure 3 and 4. Because both CSP conditions (120-130%) were highly correlated ($r = 0.88, p < 0.0001$), they were calculated as a compound measure to reduce the number of comparisons. No significant correlation was found between GABA/tCr ratio and SICI ($r = 0.26, p = 0.30$; Figure 3a), LICI ($r = 0.31, p = 0.20$; Figure 3b), or CSP ($r = 0.20, p = 0.41$; Figure 3c). There was no significant correlation between SICI and Glx/tCr ($r = 0.35, p = 0.14$; Figure 4a) or LICI and Glx/tCr ($r = 0.12, p = 0.62$; Figure 4b). However, a significant positive correlation was found between Glx/tCr ratio and CSP duration ($r = 0.57, p = 0.03$, Bonferroni-corrected; Figure 4c), which remained significant when corrected for GABA ($r = 0.57; p = 0.04$, Bonferroni-corrected). Multiple regression analysis was performed to evaluate the contribution of TMS inhibitory measures (SICI, LICI, CSP) to Glx/tCr concentration values. The regression
model was significant ($r^2 = 0.44$, $p = 0.03$) with CSP duration being the only significant predictor ($\beta = 0.54$, $p = 0.14$). Multiple regression analysis with GABA/tCr and the TMS inhibitory measures was not significant ($r^2 = 0.21$; $p = 0.31$). The correlation between GABA/tCr and Glx/tCr ratios was also computed and revealed a significant positive correlation ($r = 0.58$, $p = 0.01$; Figure 5). Finally, none of the TMS measures were correlated with one another (SICI vs LICI: $r = -0.13$, $p = 0.61$; SICI vs CSP: $r = 0.06$, $p = 0.80$; LICI vs CSP: $r = 0.07$, $p = 0.77$).

Discussion

This study was conducted to investigate the relationship between TMS measures of intracortical inhibition and levels of GABA and Glx in human primary motor cortex. We report two major findings: 1) MRS-derived GABA did not reflect GABAA or GABAB synaptic activity measured by TMS; 2) A positive correlation was found between GABAB synaptic activity (CSP) and MRS-derived Glx.

The lack of correlation between GABA synaptic activity and MRS-derived GABA levels replicates previous results reported by Stagg and collaborators (2011a), where no relationship between TMS-derived GABAA (SICI) and GABAB (LICI) synaptic activity and MRS-GABA concentration was found. We can hypothesize that a major difference in the specificity of the two methods can be responsible for this result. Indeed, studies have shown that TMS protocols reflect specific activity of GABAA or GABAB receptors (Reis et al. 2008), whereas MRS mostly reflects extracellular and intracellular GABA concentrations (Maddock and Buonocore 2012). GABA is found in two major pools in the human brain (Stagg et al. 2011b; Maddock and Buonocore 2012), a large cytoplasmic pool (primarily produced by glutamate) and a small vesicular one (primarily found in pre-synaptic boutons). The ability of MRS to detect vesicular GABA, which plays an
important role in inhibitory synaptic neurotransmission, remains unknown (Maddock and Buonocore 2012).

Unlike GABA levels that do not seem to correspond to synaptic inhibitory activity, a counterintuitive relationship between the CSP, thought to provide a measure of GABA_{B} synaptic activity (Ziemann 2004), and Glx/tCr was found in M1. Glx (Glu+Gln) signal mostly comes from Glu, which like GABA, is present in multiple pools. Glu is present in all cell types with the largest pool in glutamatergic neurons and smaller pools in GABAergic neurons and astroglia (Danbolt 2001). It plays a central role in Glu-Gln neurotransmitter cycle. Gln is synthesized from Glu by Gln synthethase in the astroglia and it is broken down to Glu by phosphate-activated glutaminase in neurons (Danbolt 2001). The exact mechanism underlying the relationship between GABA_{B} synaptic activity and Glx remain unknown. However, animal studies suggest a close relationship between pre-synaptic GABA_{B} and glutamatergic neurons (Chalifoux and Carter 2011), where GABA_{B} agonist Baclofen has a significant effect on excitatory rather than inhibitory transmission in the visual system (Luo et al. 2011).

A similar phenomenon was reported previously, where MRS-GABA levels were found to correlate positively with the slope of the TMS input/output curve (Stagg et al. 2011a), which indexes global corticospinal excitability. Moreover, Stagg and collaborators (2011a) also found a relationship between MRS-glutamate levels and TMS input/output curve. Authors suggest that this relationship could reflect the fact that greater pre-synaptic glutamate stores is linked to higher levels of glutamate (Stagg et al. 2011a). Moreover, pharmacological studies suggest that TMS measures of intracortical facilitation indirectly involve several neurotransmitters including glutamate (Reis et al. 2006) and GABA (Ziemann et al. 1996b), which could explain why the
input/output curve is linked to both MRS-levels of GABA and glutamate in their study. Although intracortical facilitation was not measured in the present study, combining results from both studies gives a better picture of the relationship between GABA, glutamate and TMS measures of inhibiton/excitation. Indeed, both results suggest the existence of a close relationship between GABA and glutamate within primary motor cortex, a notion that is compounded by the fact that GABA and Glx/tCr levels measured by spectroscopy correlate strongly. As such, an increase in the concentration of glutamate was associated with parallel increases in GABA concentration levels and GABA$_B$ synaptic activity. A different measure of GABA$_B$ activity (LICI) and a measure of GABA$_A$ activity failed to correlate with Glx/tCr levels in the same region. This confirms data from a previous report (Stagg et al. 2011a) and is not surprising in light of the fact that the three TMS inhibitory measures failed to correlate between them.

Our data thus show that GABA$_A$- and GABA$_B$-related synaptic activity measured with TMS interact differently with glutamate as measured with MRS. Physiological studies suggest that GABAergic neurons exerts rapid synaptic inhibition via anion permeable GABA$_A$ receptors (Isaacson and Scanziani 2011), while GABA$_B$ receptors are responsible for slow inhibition via the opening of K+ channels (Lüscher et al. 1997). Although we should be cautious in translating these results to our findings, it could be hypothesized that, knowing this physiological discrepancy in their mechanism of action, GABA$_A$ activity would rapidly decrease in response to an increase of glutamate, while GABA$_B$ activity would exert a fine tuning on the balance between excitatory and inhibitory mechanisms by slowly increasing its activity in response to enhanced excitability of the neuron.
At the same time, the present data highlight the fact that LICI and CSP are likely to tap into different mechanisms underlying GABA$_B$-related inhibition in motor cortex. Indeed, it has been shown that the early part of CSP relies on spinal inhibition (Inghilleri et al. 1993), whereas LICI appears to be linked exclusively to cortical inhibition (Werhahn et al. 1999). Moreover, Ziemann and collaborators (1996a) have shown that GABA$_B$-agonist Baclofen can enhance LICI, but has no impact on the CSP duration. Finally, as mentioned earlier, the CSP and LICI measures of inhibition did not correlate in the present study. It should also be noted that there exists a possibility that the TMS measures, which were taken before MR acquisition, may have altered glutamate and GABA concentration in M1. This appears unlikely since a low frequency of stimulation was used (between 0.1 and 0.2 Hz), which has been shown not to modify cortical excitability (Chen et al. 1997). Furthermore, a limited number of TMS pulses were applied to M1, as only MT, LICI, CSP and SICI were evaluated, with 10 pulses for each condition. Finally, between the end of TMS and the start of MRS acquisition, approximately 30 minutes elapsed due to participant preparation and anatomical MRI acquisition.

**Conclusion**

Our data show that the amount of intracortical inhibition assessed by TMS does not reflect global levels of GABA neurotransmitters in the primary motor cortex. Instead, the cortical silent period, a TMS-measure of intracortical inhibition, appears to be linked to cortical glutamate levels. Further research is needed to fully understand the mechanisms of action underlying these complex interactions. In addition, these results suggest that cautious, complementary interpretations should be given to research data assessing the GABAergic system with MRS or TMS. Greater emphasis should be given to the fact that both techniques can only provide reliable information about specific aspects of GABAergic inhibition. This is particularly relevant in the
study of patient populations when a mechanistic explanation of disease is needed.
Acknowledgements

The authors would like to thank Edward J. Auerbach, Ph.D. (Center for Magnetic Resonance Research, University of Minnesota) for implementing MEGA-PRESS sequence on Siemens, and Romain Valabregue, Ph.D. (Centre de NeuroImagerie de Recherche, Paris, France) and Brice Tiret, Ing (Unité de neuroimagerie fonctionnelle, Montréal) for developing processing tools.

Grants

This work was supported by grants from the Canadian Institutes of Health Research and the Fonds de Recherche en Santé du Québec to HT. ST was supported by a Vanier Canada Graduate scholarship of the Canadian Institutes of Health Research. APL was supported in part by the Harvard Clinical and Translational Science Center (Harvard Catalyst; NCRR-NIH UL1 RR025758). MM acknowledges the support from Biotechnology Research Center (BTRC) grant P41 RR008079 and P41 EB015894 (NIBIB), and NCC P30 NS057091. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Conflict of interest disclosures

Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Allied Mind, Neosync, and Novavision, and is an inventor on patents and patent applications related to noninvasive brain stimulation and real-time integration of TMS with EEG and fMRI.
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Figure captions

Figure 1. Position of the voxel of interest (27 x 24 x 32 mm³) over the left hand area of the primary motor cortex in (A) sagittal, (B) axial (C) and coronal slices.

Figure 2. Representative ‘EDIT OFF’, ‘EDIT ON’, and difference (‘DIFF’) spectra. tCr was obtained from ‘EDIT OFF’ spectrum, Glx, and GABA from difference spectrum, and tNAA from both. ‘EDIT OFF’ and ‘EDIT ON’ spectra are the average of 128 scans each.

Figure 3. Correlation between TMS and MRS-GABA/tCr measures. Relationship between GABA-MRS levels and (A) SICI, (B) LICI, (C) CSP.

Figure 4. Correlation between TMS and MRS-Glx/tCr measures. Relationship between Glx-MRS levels and (A) SICI, (B) LICI, (C) CSP.

Figure 5. Correlation between Glx/tCr and GABA/tCr MRS levels.
A

**SICI (% inhibition)**

\[ r = 0.35 \]
\[ p = 0.14 \]

B

**LICI (% inhibition)**

\[ r = 0.12 \]
\[ p = 0.62 \]

C

**CSP duration (msec)**

\[ r = 0.57 \]
\[ p = 0.01 \]
GABA/tCr vs. Glx/tCr

- $r = 0.58$
- $p = 0.01$