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Cortical thickness and metabolite concentration in chronic stroke and the relationship with motor function

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Abstract

Introduction—Hemiparesis is one of the most prevalent chronic disabilities after stroke. Biochemical and structural magnetic resonance imaging approaches may be employed to study the neural substrates underpinning upper-extremity (UE) recovery after chronic stroke.

Objective—The purposes of this study were to 1) quantify anatomical and metabolic differences in the precentral gyrus, and 2) test the relationships between anatomical and metabolic differences, and hemiparetic arm function in individuals in the chronic stage of stroke recovery. Our hypotheses were: 1) the Stroke group would exhibit reduced precentral gyrus cortical thickness and lower concentrations of total N-acetylaspartate (tNAA) and glutamate+glutamine (Glx) in the ipsilesional motor cortex; and 2) that each of these measures would be associated with UE motor function after stroke.

Methods—Seventeen individuals with chronic (>6 months) subcortical ischemic stroke and eleven neurologically healthy controls were recruited. Single voxel proton magnetic resonance spectroscopy (¹H MRS) was performed to measure metabolite concentrations of tNAA and Glx in the precentral gyrus in both ipsilesional and contralesional hemispheres. Surface-based cortical morphometry was used to quantify precentral gyral thickness. Upper-extremity motor function was assessed using the Wolf Motor Function Test (WMFT).

Results—Results demonstrated significantly lower ipsilesional tNAA and Glx concentrations and precentral gyrus thickness in the Stroke group. Ipsilesional tNAA and Glx concentration and precentral gyrus thickness was significantly lower in the ipsilesional hemisphere in the Stroke group. Parametric correlation analyses revealed a significant positive relationship between

precentral gyrus thickness and tNAA concentration bilaterally. Multivariate regression analyses revealed that ipsilesional concentrations of tNAA and Glx predicted the largest amount of variance in WMFT scores. Cortical thickness measures alone did not predict a significant amount of variance in WMFT scores.

Conclusions—While stroke impairs both structure and biochemistry in the ipsilesional hemisphere our data suggest that tNAA has the strongest relationship with motor function.

Keywords

Stroke; Human; Metabolite; Motor Function; Cortical Thickness

1.0 Introduction

Hemiparesis after stroke is particularly common, with up to 70% of individuals experiencing mild to severe upper extremity (UE) dysfunction (Nakayama et al. 1994). In individuals with stroke, it has been suggested that the extent of structural damage to cortical areas likely underlies the potential for recovery (Schaechter et al. 2006). Therefore, assessing morphological differences within the motor cortex may provide valuable information of the neural events that underlie UE hemiparesis.

After stroke, morphological and structural changes are triggered spontaneously at the onset of infarction and may persist into the chronic phase post stroke (Dimyan and Cohen 2011). Spontaneous recovery of motor function appears to be related to lesion location (Shelton and Reding 2001), however there is a weak relationship between lesion location and UE functional recovery after stroke (Gauthier et al. 2009; Gauthier et al. 2014). Though the survival of peri-infarct tissue is an important component of recovery (Cramer et al. 2006), it is becoming clear that regions distant from the lesion are also important for recovery of motor function. For instance, after subcortical stroke, recovery of arm function has been linked with greater functional activity within cortical areas remote from the lesion (Weiller et al. 1993; Cramer et al. 1997; Cramer 2008). Further, functional imaging of individuals with chronic stroke shows that activation of the ipsilesional hemisphere is associated with improved motor outcome (Ward et al. 2003; Calautti et al. 2010) and structural integrity of cortical areas (Schaechter et al. 2006). It appears that morphological changes and the structural integrity of surviving cortical areas contribute to the overall magnitude and pattern of recovery of UE function in individuals with chronic stroke.

Metabolic changes in the cortex after stroke have previously been investigated using biological markers of membrane integrity and neuronal damage, and have been described in individuals with both acute and chronic stroke (Federico et al. 1998; Craciunas et al. 2013). One metabolite NAA, is considered to reflect neuronal structural and functional integrity (Demougeot et al. 2004). Magnetic resonance spectroscopic (MRS) studies of individuals in the acute stage post stroke have linked decreases in NAA concentration to poor functional recovery of the hemiparetic UE (Federico et al. 1998). NAA changes have also been observed in individuals with chronic stroke within ipsilesional normal appearing grey matter (Munoz Maniega et al. 2008) and have been associated with morphological changes, including neuronal death in stroke (Demougeot et al. 2004). In individuals with chronic

stroke, lower NAA concentrations have been reported within both ipsi- and contra-lesional primary motor cortices (Cirstea et al. 2011; Craciunas et al. 2013).

Another metabolite that has been investigated in individuals with chronic stroke is glutamate (and its readily available precursor glutamine, collectively referred to as Glx). In a study by Cirstea et al. (2011), ipsilesional concentrations of NAA and Glx in normal appearing grey matter were both positively correlated with arm motor impairment in individuals with chronic stroke.

While MRS has provided information about neuronal integrity and metabolism after stroke, it remains unclear how regional structural differences, including cortical thickness, may be associated with metabolic function after stroke. Increases in cortical thickness in the sensorimotor cortical areas have been reported in the contralesional hemisphere of individuals with sub-acute (Brodthmann et al. 2012) and chronic stroke (Schaechter et al. 2006). Voxel-based morphometric investigation in individuals with chronic subcortical stroke revealed grey matter atrophy in motor areas, which may be associated with hemiparetic arm impairment (Gauthier et al. 2012). In the current study, we performed metabolic and structural assessment of the primary motor cortex using ^1H magnetic resonance spectroscopy and cortical thickness measurement to investigate whether morphological differences are associated with UE motor performance.

To our knowledge, no study has investigated how differences in cortical thickness relate to metabolic changes in individuals with chronic subcortical stroke. Total NAA (NAA and N-Acetylaspartylglutamate (NAAG)) and Glx were selected as metabolites of interest *a priori* because: 1) both are altered in individuals with chronic stroke, 2) the magnitude of change in these has been associated with the level of UE impairment (Cirstea et al. 2011; Cirstea et al. 2012), and 3) an observed decrease in cortical thickness may be explained by some form of neuronal cell degradation, which could be indexed using tNAA (Munoz Maniega et al. 2008).

The primary aim of this study was to characterize metabolic and morphometric properties of the precentral gyrus. In addition we considered how these properties related to UE motor impairment in individuals with chronic subcortical ischemic stroke. Our hypothesis was that individuals with stroke would exhibit reduced precentral gyrus cortical thickness and lower tNAA and Glx concentrations in the ipsilesional hemisphere. Further, we hypothesized that measures of ipsilesional cortical thickness, and tNAA and Glx concentrations, would be associated with UE motor function after stroke.

2.0 Materials and Methods

2.1 Participants

Seventeen individuals (12 male, 5 female; age 68 +/- 9.6 years) with subcortical ischemic stroke in the chronic phase (>6 months) of recovery, and 11 neurologically healthy controls (4 male, 7 female; age 60.4 +/- 6.0 years) were recruited for this study. The research ethics board at the University of British Columbia approved all aspects of this work and consent was obtained according to the Declaration of Helsinki. Individuals were excluded if they: 1)

were in the acute (0-3 months) or sub-acute (3-6 months) phase of recovery, 2) had contraindications to MRI, 3) had previous history of stroke, epilepsy, neurodegenerative disorder or head trauma, or 4) showed a visible lesion extending in to the precentral gyrus grey matter. Upon enrolment, each participant underwent neuroimaging assessment on a Philips Achieva 3.0T MRI scanner at the University of British Columbia, which was followed by functional assessment in the Brain Behaviour Lab.

2.2 Magnetic Resonance Imaging Acquisition

A high-resolution T₁-weighted scan (TR/TE: 7425/3.64ms, FOV=256×256mm, 160 sagittal slices, flip angle 6°, voxel size=1mm³) was performed on each enrolled participant. In addition, single voxel ¹H-MRS (PRESS, TR/TE=2000/35ms, sampling frequency: 2000Hz, data points=1024, signal averages=128) was obtained to measure absolute metabolite concentrations. A single 30mm × 22mm × 15mm voxel was centered over the hand area of the primary motor cortex in both ipsilesional and contralesional hemispheres. Projection based autoshimming was carried out. Unsuppressed water spectra were acquired to enable metabolite concentration estimations. Localization of hand representation for each individual and corresponding voxel placement was determined using known anatomical coordinates (Yousry et al. 1997) (Fig. 1).

2.3 Cortical Morphometry Analysis

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu>). The technical details of these procedures are described in prior publications (Dale et al. 1999; Fischl and Dale 2000). A number of steps for processing are required, and include: 1) motion correction and averaging (Reuter et al. 2010) of multiple volumetric T1 weighted images (when more than one is available), 2) removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al. 2004), 3) segmentation of the subcortical white matter and deep grey matter volumetric structures (Fischl et al. 2002; Fischl et al. 2004), 4) intensity normalization (Sled et al. 1998), 5) tessellation of the grey matter white matter boundary, and 6) automated topology correction (Fischl et al. 2001; Segonne et al. 2007) and surface deformation following intensity gradients. This final step is done to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale and Sereno 1993; Dale et al. 1999; Fischl and Dale 2000). MRI-derived measures of human cerebral cortical thickness have been shown to be highly reliable (Han et al. 2006), and have been described in a number of pathological conditions such as Huntington's disease (Rosas et al. 2002), schizophrenia (Kuperberg et al. 2003) and multiple sclerosis (Sailer et al. 2003). Recently the technique has been used to investigate regional differences in cortical thickness in sub-acute stroke (Brodthmann et al. 2012) and chronic stroke populations (Borich et al. 2015). We compared average cortical thickness in the precentral gyrus in both Stroke (ipsilesional/contralesional) and Control (non-dominant/dominant) groups.

2.4 Magnetic Resonance Spectroscopy Analysis

Metabolic measures were quantified using LCModel version 6.2-2B which provides automatic quantification of *in vivo* proton magnetic resonance spectra (Provencher 1993). Water scaling was used to estimate absolute metabolite concentrations using the reference area of the unsuppressed water signal along with the assumed water concentration of 35880mM within the largely grey matter voxel. Concentrations of tNAA and Glx were extracted as the primary metabolites of interest. Technical details can be found in Supplementary data.

2.5 Upper-extremity motor assessment

UE motor performance was assessed using the WMFT, which measures how rapidly individuals are able to perform a series of 15 functional tasks in the laboratory. A trained physiotherapist carried out all components of the assessment. Recently, Hodics et al. (2012) validated an approach that characterizes the WMFT by converting the time to complete each task into task rate data using the following equation:

$$\text{Task Rate} = 60(\text{s}) / \text{Performance Time}(\text{s})$$

This method of calculation has shown to be more sensitive in assessing the functional abilities of more severely affected individuals with stroke. Thus, participants in the current study were assessed using the standard 15-task WMFT; subsequently we calculated task-rate data (Hodics et al. (2012)).

2.6 Statistical Analysis

To examine differences in tNAA and Glx concentration and precentral gyrus thickness between group (Stroke, Control) multivariate analysis of variance (MANOVA) was conducted. Follow-up univariate analyses of variance (ANOVAs) for each dependent variable were conducted. Parametric correlation analysis using Pearson's *r* was conducted to examine the relationship between tNAA and Glx and precentral gyrus thickness in both hemispheres. Multiple linear regression analyses were performed to assess the amount of variance in UE motor performance (WMFT rate) explained by demographic information (age and post-stroke duration), metabolite concentration (tNAA and Glx), and cortical thickness. In the Stroke group, age and post stroke duration were entered first to account for post-stroke (Graham et al. 1993) and age related changes in metabolites (Angelie et al. 2001; Kaiser et al. 2005) and cerebral tissue (Resnick et al. 2003). Concentration of ipsilesional cerebral metabolites tNAA and Glx were the next predictors entered, based on previous reports suggesting their association with UE motor impairment (Cirstea et al. 2011; Cirstea et al. 2012). Ipsilesional cortical thickness was the final predictor entered into the model. When comparing between the Stroke and Control groups, data from the ipsilesional cortex in individuals with stroke were compared to data extracted from the non-dominant cortex in our Control group.

3.0 Results

3.1 Participants

Participant demographics from the Stroke group (Table 1) and the Control group (Table 2) are listed below. The location of each lesion was determined from T1-weighted MRI.

Anatomic and Metabolic Differences in Chronic Stroke—There was an overall main effect of Group across the measures ($F = 4.972$; $p = 0.004$). Concentrations of tNAA ($F = 6.47$; $p = 0.017$), Glx ($F = 10.37$; $p = 0.001$), and cortical thickness ($F = 6.12$; $p = 0.021$) were all significantly lower bilaterally in the Stroke group compared to the Control group. Within the Stroke group, significantly less ipsilesional tNAA concentration ($F = 4.14$; $p = 0.05$), Glx ($F = 11.72$; $p = 0.002$) and cortical thickness ($F = 6.37$; $p = 0.017$) was also observed compared to the contralesional hemisphere (Fig. 2). No significant difference between hemispheres was found in the Control group for any of the variables (Fig. 3).

3.2 Relationship Between Cortical Thickness and Metabolite Measures

A significant positive correlation was found between tNAA and precentral gyrus thickness in both ipsilesional ($r = 0.782$; $p < 0.001$) and contralesional ($r = 0.517$; $p = 0.033$) hemispheres of the Stroke group (Table 3, Fig. 4). No correlations between Glx concentration and precentral gyrus thickness was observed. No correlations were observed in the Control group.

3.3 Relationship between metabolite concentration, cortical thickness and upper extremity motor performance

Regression analysis results are summarized in Table 4 and Fig. 5. In the Stroke group, after adjusting for age and post-stroke duration, ipsilesional metabolite concentrations (tNAA and Glx) accounted for 53% of the total variance of hemiparetic UE WMFT score ($R^2 = 0.535$, $p = 0.043$). tNAA concentration explained a larger amount of variance in WMFT motor performance than Glx. Adding ipsilesional precentral gyrus cortical thickness to the model did not explain an additional amount of unique variance in WMFT score, and the overall model was not significant (R^2 change = 0.005, $p = 0.088$).

4.0 Discussion

We observed thinner cortex in the hand area of the precentral gyrus, as well as lower tNAA and Glx concentration in individuals with stroke, particularly in the ipsilesional hemisphere. Lower bilateral tNAA concentration was associated with a less cortical thickness bilaterally in the Stroke group. Our results suggest that ipsilesional precentral gyrus thickness and tNAA concentration were associated with UE motor performance.

4.1 Metabolite Concentrations

To our knowledge, this is the first study to report significantly lower Glx concentration in the precentral gyrus of individuals in the chronic stage post-stroke. We also observed a lower concentration of the cerebral metabolite tNAA, which is consistent with previous findings in individuals with stroke (Cirstea et al. 2011; Craciunas et al. 2013). Because NAA and

NAAG are believed to exist almost exclusively in intact neurons, a possible explanation for our finding of abnormal Glx and tNAA concentrations includes neuronal death (Pereira et al. 1999). Neuronal death following ischemic stroke is often attributed to improper homeostatic balance of glutamate. The release of glutamate following ischemia results in a cascade of cellular events such as intracellular calcium increase and mitochondrial dysfunction that ultimately leads to cellular death (Hazell 2007). Acutely after stroke, glutamate concentration increases for approximately 6 hours after the onset of infarction (Davalos et al. 1997); this may cause permanent damage. Because lower ipsilesional tNAA and Glx was accompanied by a thinner precentral gyrus, neuronal death may, in part, explain our results. Supporting this possibility, age-related brain shrinkage has been associated with decreased NAA and Glx concentration in the motor cortex (Kaiser et al. 2005). Similarly, in the current study we observed a positive correlation between tNAA concentration and precentral gyrus thickness.

4.2 Cortical Thickness

Precentral gyrus thickness was also significantly lower in the Stroke group compared to the Control group, and ipsilesional thickness in the Stroke group was significantly associated with UE motor performance. These results are consistent with previous reports suggesting that bilateral diffuse tissue loss may occur in individuals with chronic stroke (Kraemer et al. 2004; Gauthier et al. 2012). Further, decreases in grey matter density in non-infarcted motor regions in individuals with chronic stroke correlates with WMFT of UE motor function (Gauthier et al. 2012). Interestingly, these results differ from previous reports of increased contralesional sensorimotor cortical thickness in individuals with chronic stroke (Schaechter et al. 2006), and greater contralesional paracentral and superior frontal cortical thickness in individuals with sub-acute stroke (Brodthmann et al. 2012). It is possible that these differences could be explained by compensatory mechanisms within the contralesional hemisphere, such as structural plasticity within cortical regions in response to brain injury. Functional reorganization of contralesional motor cortical areas has been described previously in animal models of stroke undergoing rehabilitation training (Nudo et al. 1996), and has been linked with improved hand function. There is evidence to suggest that contralesional compensatory changes are dependent upon increased use of the less-impaired limb (Nudo et al. 2001). This idea is supported by previous work that demonstrated a relationship between grey matter changes and arm motor impairment in chronic stroke patients undergoing specific rehabilitation programs (Gauthier et al. 2008). Indeed, individuals engaged in Constraint-Induced Movement Therapy (CIMT), a rehabilitation therapy that combines restraint of the non-hemiparetic limb with intensive use of the hemiparetic limb, show significant increases in grey matter in sensory and motor areas both contralateral and ipsilateral to the hemiparetic arm (Gauthier et al. 2008). Unfortunately, it is common in stroke survivors for daily use of the hemiparetic arm to be severely limited (Rand and Eng 2015), therefore, it is possible that non-use of the hemiparetic arm might explain the observed differences in ipsilesional precentral gyrus thickness.

4.3 Upper extremity motor assessment

In our regression analyses, age and time post stroke alone were not significantly associated with UE motor performance. When these variables were combined with tNAA and Glx

concentration the model was able to explain a significant amount of variance in hemiparetic UE motor function. tNAA explained the greatest amount of variance in motor function as shown by WMFT scores. These results suggest that tNAA concentration, a marker for neuronal integrity, in spared ipsilesional motor cortical areas may contribute to UE motor function in individuals in the chronic stage post-stroke. These data support previous work noting decreased grey matter structural density in individuals with chronic stroke, suggesting that grey matter atrophy may contribute to arm motor function (Gauthier et al. 2012). The addition of precentral gyrus thickness to our model only resulted in a small increase in R^2 , but the overall model lost significance, suggesting that the two measures (tNAA concentration and cortical thickness) may be redundant.

Contrary to our hypothesis, we observed no association between Glx and UE motor function. Our original hypothesis that ipsilesional Glx concentrations would be associated with UE motor performance was based on: 1) reported intracortical excitability differences after stroke (Tarkka et al. 2008; Carmichael 2012), and 2) past findings showing that Glx concentration in motor areas correlated with arm motor impairment in individuals with chronic stroke (Cirstea et al. 2011). Further, Glx concentration in the motor cortex has been correlated with global motor cortical excitability (assessed by transcranial magnetic stimulation) (Stagg et al. 2011), which was a predictor of motor recovery after stroke (Jung et al. 2012). Further investigation of the relationship between glutamate and glutamine concentration and motor function in individuals after stroke will be required to resolve these issues.

4.4 Limitations

There were limitations to this study. First, our sample size was small, however previous studies using magnetic resonance spectroscopy (Cirstea et al. 2012; Craciunas et al. 2013) and other imaging approaches (Pavakis et al. 1999; Mang et al. 2015) in individuals with chronic stroke have had comparable sample sizes. Our design was cross-sectional and our findings could be used to provide preliminary evidence that may inform future longitudinal or interventional studies. Larger longitudinal studies should be performed in order to: 1) further examine relationships between lesion volume and location; 2) understand how these measures may be associated with real world arm function after stroke; and 3) determine how physical rehabilitation may be related to metabolites or cortical thickness in chronic stroke.

The mean age of the Stroke group was greater than that of the neurologically healthy Control group. Because normal aging is associated with cerebral tissue loss (Resnick et al. 2003) and changes in NAA and glutamate concentration (Angelie et al. 2001; Kaiser et al. 2005), it is possible that the group differences observed in these measures can be explained by age differences. Yet the age difference between the groups in our current study was relatively small (Stroke group age 68 +/- 9.7 years; Control group age 60.4 +/- 6.0 years). There was also an unequal distribution of men and women between the Stroke group (12 male, 5 female) and the Control group (4 male, 7 female). This is important to note because some evidence suggests women have poorer functional outcome after ischemic stroke than men (Gibson 2013). While it is possible this gender imbalance in our sample affected the results, a study published from the Registry of the Canada Stroke Network found that

women had only slightly worse functional status at 6 months post stroke, and that there were no striking sex differences in stroke severity, 6-month mortality or quality of life (Kapral et al. 2005). Additionally, pre-stroke hemisphere dominance information was not collected, however, we compared data from the ipsilesional cortex in individuals with stroke to data extracted from the non-dominant cortex in our Control group.

For H^1 MRS data collection, we used a technique known as single voxel spectroscopy (SVS), which obtains a signal from a single volume of interest. An alternative technique to SVS, known as chemical shift imaging (CSI) obtains a chemical signal simultaneously from multiple voxels in brain regions of interest. A limitation with SVS is that our voxel size ($30 \times 22 \times 15$ mm) extended beyond the hand area of the primary motor cortex, and therefore captured data from the cortex and underlying white matter. We selected SVS because it is the preferred method for obtaining consistent, high quality *in vivo* spectra (Drost et al. 2002). Further, the integrity of white matter tracts underlying the motor cortex is associated with motor output in chronic stroke (Schulz et al. 2015), and is therefore relevant to the overall objectives of the study.

Last our MRS acquisition did not include saturation bands for suppression of lipid signal from sub-cutaneous regions outside the brain. Since the voxel placement was relatively close to sub-cutaneous regions outside the brain, saturations bands might have reduced contributions to the spectrum from lipids near the voxel. A small number (2-3) of both control and stroke subject spectra included lipid peaks, which overlapped slightly with the NAA spectral peak. However, in all cases the lipid peak was very well fit by LCModel and the NAA fits had Cramer-Rao lower bounds of 3% or less.

5.0 Conclusions

These findings suggest a relationship between arm motor function, metabolite concentrations and cortical thickness. Taken together our results advance knowledge regarding the interactions amongst these factors, and suggest biochemical differences may be important markers of post-stroke motor dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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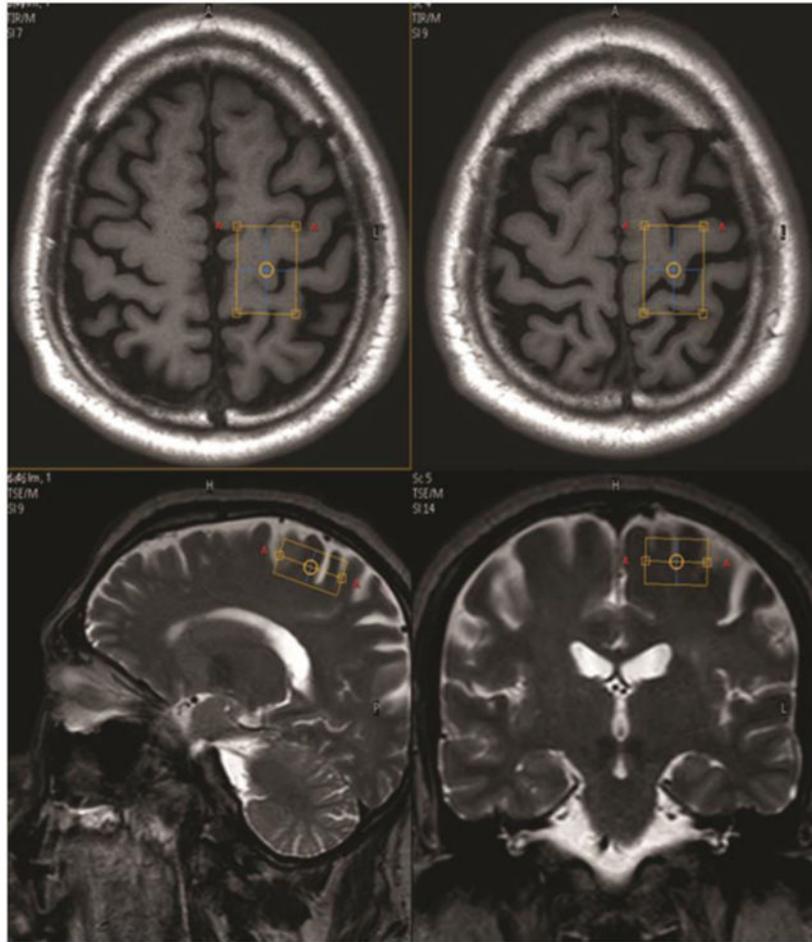


Fig. 1. Orientation of the voxel for MRS. A single $30 \times 22 \times 15$ mm voxel was centered over the hand area of the primary motor cortex in both ipsilesional and contralesional hemispheres.

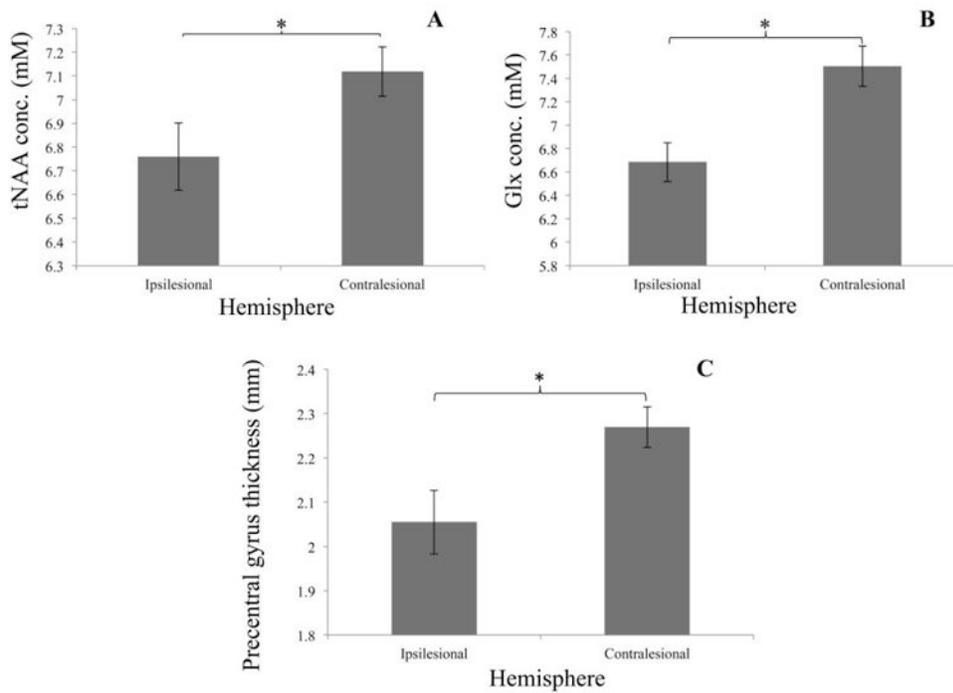


Fig. 2. Mean values for metabolite concentrations and cortical thickness measurement from the Stroke group. A) tNAA and B) Glx both exhibited significantly lower concentration in the ipsilesional hemisphere. C) Ipsilesional precentral gyrus thickness was also significantly lower in the ipsilesional hemisphere. Standard error bars are depicted. Significance ($p < 0.05$) is indicated with a star (*).

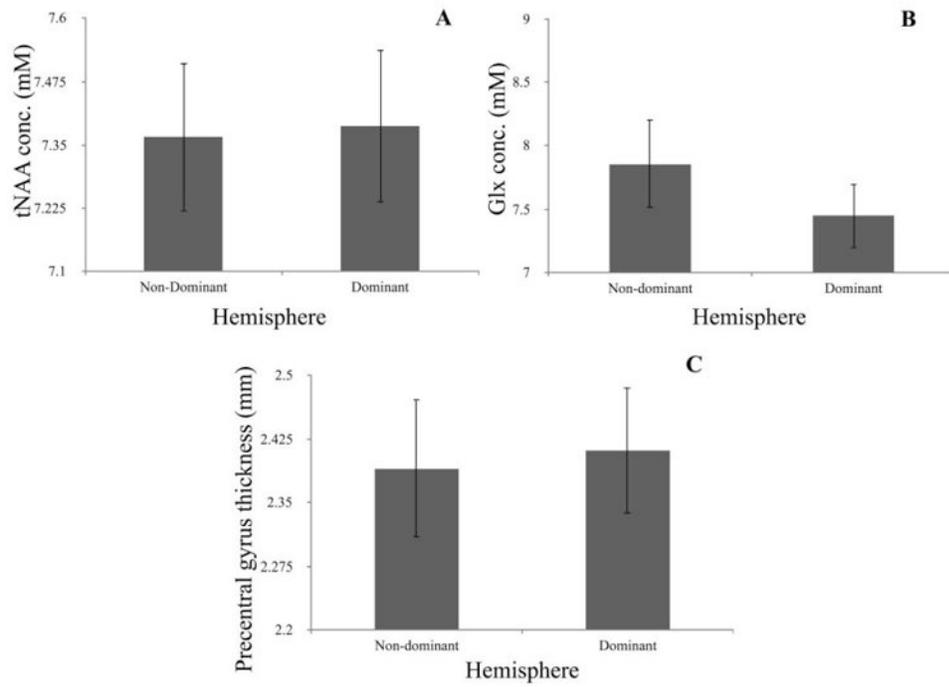


Fig. 3. Mean values for metabolite concentrations and cortical thickness measurements in the Control group. No significant hemispheric differences were observed for any of the measures. Standard error bars are depicted.

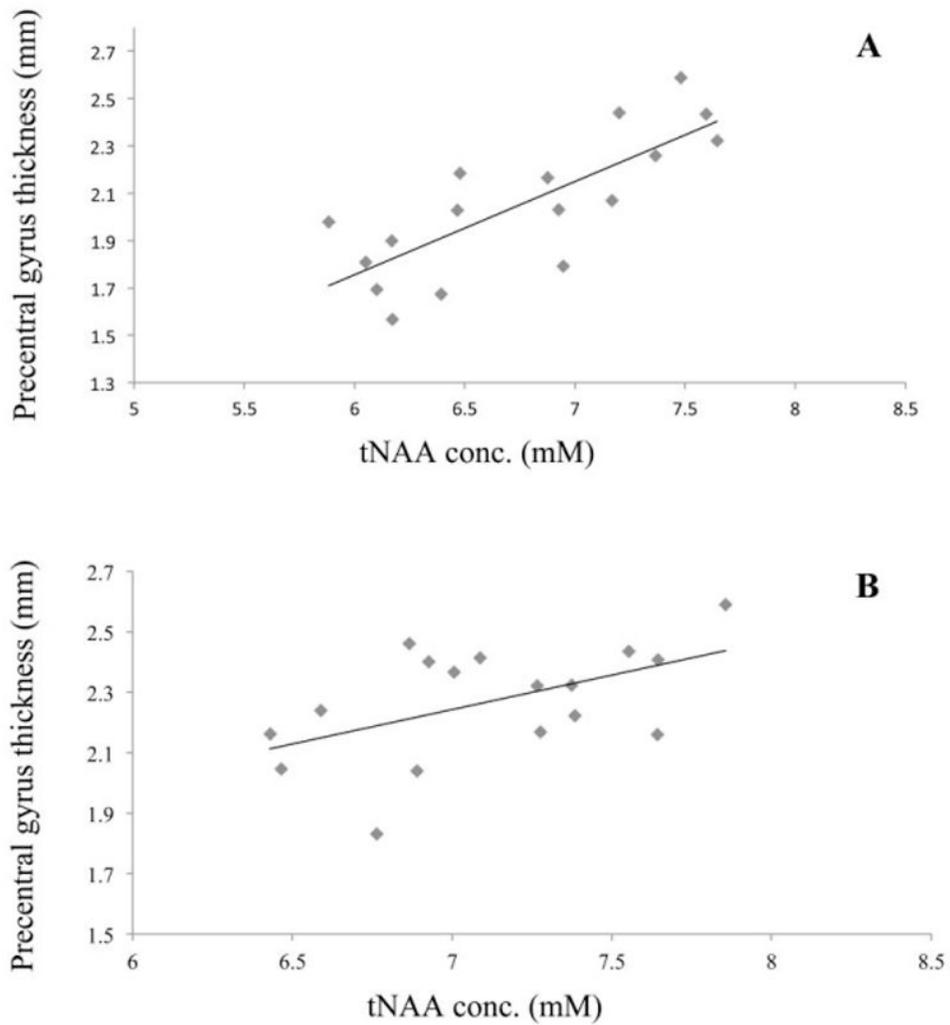


Fig. 4. Scatterplot depicting the bivariate relationship between precentral gyrus thickness and tNAA concentration. Parametric correlation analysis using Pearson's r showed a significant positive correlation between precentral gyrus thickness and tNAA concentration in A) ipsilesional and B) contralesional hemispheres.

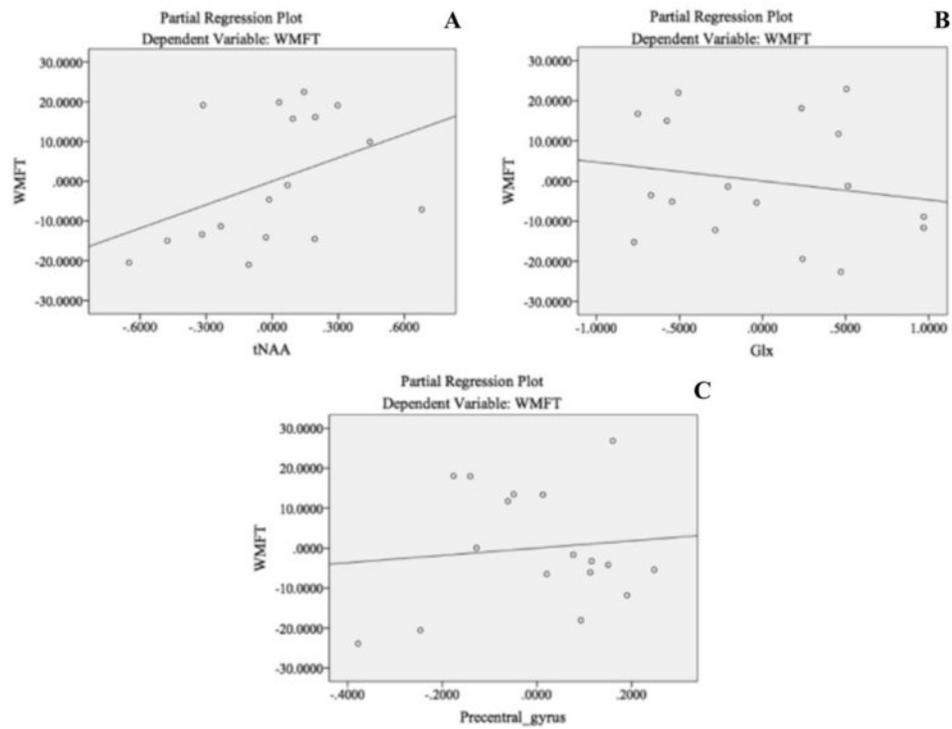


Fig. 5. Partial residual plots illustrating the relationship between WMFT score of the hemiparetic UE and ipsilesional: A) tNAA concentration after accounting for age and post-stroke duration B) Glx concentration after accounting for tNAA concentration, age and post-stroke duration and C) precentral gyrus thickness after accounting for tNAA concentration, Glx concentration, age and post-stroke duration.

Table 1

Stroke participant demographics

Participant number	Age	Gender	Time post stroke	Stroke hemisphere	Ipsilesional tNAA conc. (mM)	Contralateral tNAA conc. (mM)	Ipsilesional Glx conc. (mM)	Contralateral Glx conc. (mM)	Ipsilesional precentral gyrus thickness (mm)	Contralateral precentral gyrus thickness (mm)	WMFT rate score (paretic arm)	WMFT rate score (non-paretic arm)
S01	73	M	142	L	7.645	7.642	7.247	7.24	2.321	2.159	57.6	76.4
S02	71	F	83	L	6.927	6.464	7.424	8.099	2.031	2.045	52.0	64.2
S03	85	M	35	R	6.875	6.429	6.318	6.198	2.166	2.162	34.0	40.7
S05	63	M	41	R	6.946	7.385	6.783	8.436	1.791	2.222	10.3	65.8
S07	50	F	37	L	7.597	7.856	5.365	7.422	2.435	2.589	58.2	61.5
S08	56	F	27	R	7.365	7.266	6.682	6.523	2.259	2.32	38.4	71.4
S12	76	M	81	L	7.168	6.89	6.489	6.978	2.07	2.039	64.1	63.6
S14	71	M	20	R	7.482	7.554	6.399	7.756	2.588	2.435	42.7	61.6
S15	65	M	67	R	6.393	6.764	6.101	7.445	1.674	1.832	44.4	52.4
S21	82	M	12	R	6.101	6.588	6.989	7.093	1.694	2.24	46.4	52.9
S22	61	M	91	L	6.169	7.088	6.794	8.096	1.898	2.413	11.3	75.9
S23	69	M	15	R	6.478	7.005	7.092	6.42	2.185	2.367	53.0	62.8
S27	57	M	94	L	6.467	6.927	7.715	8.472	2.028	2.401	9.2	47.5
S28	79	M	18	L	7.202	7.374	7.845	7.274	2.441	2.324	45.0	54.9
S30	69	F	50	R	6.171	7.277	6.827	8.366	1.567	2.168	0.42	40.3
S31	58	M	25	L	5.883	6.865	5.821	7.773	1.979	2.46	3.48	44.2
S34	65	F	21	L	6.05	7.644	5.74	7.961	1.808	2.406	12.3	44.4

Table 2

Control participant demographics

Participant number	Age	Gender	Dominant hemisphere	Non Dominant tNAA conc. (mM)	Dominant tNAA conc. (mM)	Non Dominant Glx conc. (mM)	Dominant Glx conc. (mM)	Non Dominant precentral gyrus thickness (mm)	Dominant precentral gyrus thickness (mm)
HC01	55	F	R	6.631	6.844	6.97	5.974	2.571	2.647
HC02	54	F	L	7.686	7.447	8.674	7.713	2.702	2.749
HC03	68	M	L	7.289	7.736	8.561	8.623	2.132	2.16
HC04	66	F	L	7.633	7.48	6.348	6.196	1.818	2.323
HC05	64	M	L	7.439	7.662	9.492	6.908	2.615	2.214
HC06	51	F	L	7.685	7.478	7.995	7.638	2.403	2.433
HC07	53	F	L	7.428	7.421	6.768	7.428	2.527	2.627
HC08	64	F	L	7.133	6.599	6.136	7.742	2.269	2.298
HC09	64	M	L	7.165	7.792	9.387	8.62	2.708	2.76
HC10	64	M	L	6.632	6.63	8.022	7.368	2.288	2.046
HC11	61	F	L	8.301	8.169	8.076	7.737	2.262	2.272

Table 3
Results from bivariate correlation analysis in Stroke group

		tNAA	Glx	Precentral gyrus thickness
tNAA	Pearson Correlation	1	0.092	0.782
	Sig. (2-tailed)	-	0.725	0.000*
	N	17	17	17
Glx	Pearson Correlation	0.092	1	0.063
	Sig. (2-tailed)	0.725	-	0.809
	N	17	17	17
Precentral gyrus thickness	Pearson Correlation	0.782	0.063	1
	Sig. (2-tailed)	0.000*	0.809	-
	N	17	17	17

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Table 4
Regression modeling of predictors of upper-extremity Wolf Motor Function Test score in stroke participants

<i>Ipsilesional Hemisphere</i>	Predictors	R ²	R ² Change	F statistic	Significance	β Age (sig)	β Post Stroke Duration (sig)	β NAA (sig)	β Glx (sig)	β Cortical thickness (sig)
Model										
1	Age, PSD	0.131	0.131	1.051	0.375	0.348 (0.186)	0.125 (0.625)	-	-	-
2	Age, PSD, NAA, Glx	0.535	0.404	3.445	0.043	0.369 (0.113)	0.040 (0.857)	0.640 (0.008)	-0.137 (0.556)	-
3	Age, PSD, NAA, Glx, Cortical thickness	0.540	0.005	2.580	0.088	0.380 (0.121)	0.072 (0.772)	0.536 (0.165)	-0.150 (0.542)	0.125 (0.731)
<i>Contralateral Hemisphere</i>	Predictors	R ²	R ² Change	F statistic	Significance	β Age (sig)	β Post Stroke Duration (sig)	β NAA (sig)	β Glx (sig)	β Cortical thickness (sig)
Model										
1	Age, PSD	0.195	0.195	1.698	0.219	-0.152 (0.536)	0.405 (0.114)	-	-	-
2	Age, PSD, NAA, Glx	0.371	0.176	1.767	0.200	-0.163 (0.557)	0.515 (0.052)	0.312 (0.243)	-0.376 (0.173)	-
3	Age, PSD, NAA, Glx, Cortical thickness	0.371	0.000	1.298	0.333	-0.154 (0.625)	0.526 (0.089)	0.302 (0.322)	-0.377 (0.193)	0.027 (0.938)