Is "metabolic connectivity" across spared non-primary motor areas altered in stroke?

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Introduction

After unilateral stroke, proton magnetic resonance spectroscopy (^{1}H-MRS) studies commonly report low N-acetylaspartate (NAA), a marker of neuronal integrity, in ipsilesional radiologically normal-appearing (spared) dorsal premotor cortex (PMd). Although other ^{1}H-MRS-visible metabolites, e.g., *myo*-inositol (mI), a putative glial marker, glutamate-glutamine or Glx, reflective of neuronal-glial neurotransmission system, might be informative, as recently reported in primary motor cortex (Cirstea et al., 2011), no such studies have been reported on PMd or SMA. In the current work, our first goal was to quantify regional concentrations of these metabolites in spared PMd and SMA in chronic subcortical stroke. Based on previous evidence of correlations in primary motor cortices (Cirstea et al., 2011), and the anatomic and functional connectivity between PMd and SMA, our second goal was to identify whether correlations among metabolites or "metabolic connectivity" between non-primary motor areas was altered after stroke.

Methods

We used fMRI-guided PRESS at 3 Tesla (TE=30ms, TR=1500ms, matrix=16x16cm^2, FOV=160mm^2, slice=15mm) in 20 chronic survivors (6-106 months after stroke) of mild-to-severe subcortical ischemic stroke (confirmed on T2-weighted MRI). We used LCModel to quantify N-acetylaspartate, *myo*-inositol, and glutamate/glutamine in spared dorsal premotor cortex (PMd) and supplementary motor area (SMA) in both ipsi- and contralesional hemispheres. Metabolite concentrations corrected for voxel brain tissue fraction were compared with those in 16 age- and sex-matched healthy controls. Since most strokes were left-sided, we compared ipsilesional metabolites in patients with left-sided metabolites in controls. We used Pearson correlation to examine metabolite relationships between PMd and SMA within each hemisphere (intra-hemispheric) and between hemispheres within each region (inter-hemispheric). Then, to assess the overall correlations of each correlation matrix (3x3 metabolites), we carried out canonical correlation analyses and compared intra- and inter-hemispheric canonical correlations between groups using non-parametric bootstrapping.

Results

Metabolite concentrations. We found generally lower NAA and higher mI in non-primary motor areas. Not surprisingly, the magnitude of effects was greater in the ipsilesional hemisphere: NAA was lower by 8.4% (p=0.09) in PMd and 14.4% (p=0.02) in SMA; mI was higher by 14.8% (p=0.04) in PMd but only by 1.5% (p=0.77) in SMA. Ipsi and contralesional Glx concentrations were not significantly different.

Metabolite correlations. The pattern and magnitude of individual metabolite correlations was similar in each of left and right hemispheres in controls. In contrast, certain correlations between individual metabolites were significantly lower in stroke compared to control, particularly those involving metabolites in the contralesional PMd and SMA (see Table).

Overall, inter-hemispheric metabolite correlations (canonical analysis) were generally lower in stroke compared with controls, especially in SMA (r_c, 0.68±0.12 vs. 0.94±0.03, *p=0.04*).

Table. Pearson correlation coefficients between PMd and SMA

	Control Right hemisphere			**Stroke** Contralesional hemisphere		
	SMA			**SMA**		
PMd	NAA	mI	Glx	NAA	mI	Glx
NAA	0.77	0.32	0.43	-0.01	0.07	0.25
mI	0.43	0.53	0.40	-0.46	0.11	-0.16
Glx	0.60	0.35	0.34	-0.25	-0.10	0.06

Conclusions

Our findings of low NAA and high mI in spared ipsilesional non-primary motor areas suggest that diaschisis is possibly involved. Although diaschisis has been reported several weeks to months post-stroke, our data suggest that metabolite alterations might persist considerably longer, i.e., up to nine years post-injury. Our finding of lower (weaker) correlations between metabolites among non-primary motor areas after stroke suggests an alteration of neuron-glial interactions and consequently perturbed neuronal function. However, although many aspects of this coupling remain to be elucidated, these findings may provide new insights into brain connectivity.

Reference. Cirstea et al. *Stroke*. 2011;42:1004-1009.