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Case Report Open Access

Positive Effect of Impairment-Oriented Training on N-Acetylaspartate Levels of Ipsilesional Motor Cortex in Subcortical Stroke: A Case Study

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Abstract

Background and Purpose: We investigated the effects of an intensive impairment-oriented training on neuronal state (assessed by proton MR spectroscopy, 1H-MRS) of the spared motor and premotor cortices in the injured (ipsilesional) hemisphere and clinical impairment in a patient with chronic subcortical stroke.

Methods: One survivor of a single ischemic stroke located outside of the motor and premotor cortices (assessed on T1-weighted MRI) was studied at six months after stroke. We used functional MRI-guided 1H-MRS to quantify the levels of N-acetylaspartate (NAA - a putative neuronal marker) in the hand representation within ipsilesional primary motor cortex (M1), dorsal premotor cortex (dPM) and supplementary motor area (SMA), and Fugl-Meyer (normal=66 points) test to assess the arm motor impairment immediately before and after a motor training paradigm. Training comprised intensive variable practice (1080 repetitions over 12 day-period) of a reach-to-grasp task with the impaired hand while focusing the learner's attention on an altered movement component, i.e., decreased elbow extension.

Results: At baseline, the patient was severely impaired (Fugl-Meyer score=25 points) and exhibited lower level of NAA in all areas (M1, 9.2 mM vs. 11.6 ± 2.0 mM in healthy controls; dPM, 8.9 mM vs. 12.2 ± 1.9 mM; SMA, 7.4 mM vs. 11.0 ± 2.3 mM). After training, the patient improved clinically (by 6 points) and displayed higher levels of NAA across all areas (by 0.6-3.3 mM).

Conclusions: Our data demonstrated that the radiologically normal-appearing ipsilesional motor and premotor areas have the resources to boost behavioral output in response to an intervention. We hope that these data will act as a starting point for further research to test the potential of 1H-MRS measures to provide a biomarker of neuroplasticity in response to restorative therapies in chronic stroke.

Keywords: Chronic subcortical stroke; N-acetylaspartate; Ipsilesional motor cortex; Impairment-oriented training; Arm motor recovery

Introduction

In addition to being the third leading cause of death in Western countries, stroke contributes significantly to the incidence of physical disabilities and handicaps [1,2]. Up to 88% of stroke survivors show an initial upper extremity sensory-motor dysfunction. Despite advances in acute medical treatments, such impairments persist in 55 to 75% of patients three to six months later [3]. Given the higher prevalence of stroke in the elderly, the burden of stroke is likely to increase as our population ages. People at younger ages are also suffering from this debilitating disease. This is an issue of considerable impact; therefore, it is imperative to develop innovative, neurobiologically founded, restorative stroke therapies. An essential approach for this is to better understand the mechanisms underlying brain changes after stroke. For instance, little is known about the longitudinal changes in the neuronal state of spared motor system over the course of a therapy and their functional relevance. An evidence-based approach that applies the quantitative methods (i.e., neuronal biomarker levels) and concepts of motor control and learning might provide insight into the neural correlates of recovery in these patients. Such understanding might also provide the basis for future attempts at augmentation, for example, through modulation of neural state, i.e., non-invasive brain stimulation [4].

This study addresses this issue by investigating the changes in levels of a neuronal biomarker (N-acetylaspartate, NAA [5]) within the hand/arm representation in the spared motor areas in the injured (ipsilesional) hemisphere (by using functional MRI-guided proton magnetic resonance spectroscopy - 1H-MRS) in a patient with chronic severe hemiparesis that underwent an intensive motor training focused on arm dysfunctions (so-called impairment-oriented training). 1H-MRS provides a non-invasive means to measure levels of certain metabolites associated with a specific cell type or system in living persons [6]. Although several metabolites can been quantified [7], we focused on one metabolite, NAA, found exclusively in neurons and their processes [8] and considered a putative marker of their integrity

[5]. The specific role of NAA in central nervous system is open to some conjecture but hypotheses include the following: myelin synthesis, neuronal energetics, neuronal osmoregulation, and axonal-glial signaling. Studies of certain neurological conditions, i.e., brain ischemia, traumatic brain injury, multiple sclerosis, Alzheimer disease, have identified lower levels of NAA likely indicating neuronal death and/or neuronal metabolic down-regulation. For example, in the acute phase of experimental ischemic injury [9], lower NAA in the infarct core parallels the reduction of neuronal number and cell size, nuclear pyknosis and infiltration of polymorphonuclear and mononuclear cells. A similar decrease in NAA levels was found in the ischemic core in patients and the outcome predictions based upon the residual NAA in the infarct core have proved accurate [10,11]. More importantly, our recent 1H-MRS studies established a relationship between NAA levels in spared motor areas and behaviorally-relevant neurophysiological brain changes in chronic subcortical stroke [12-14]. Specifically, we found lower levels of NAA, putatively reflecting neuronal metabolic depression [15], in the paretic hand area representation in the ipsilesional motor and premotor areas. It is likely that these measures capture body alterations of neurons whose axons are “injured” at the subcortical level. Indeed, morphological [16] and biochemical [17,18] cell body changes, shifting from a "transmitting" state to a "degenerative/regenerative" state, have been reported after axonal injury and may cause neuronal metabolic depression. These changes are also characterized by decrease in synthesis of neurotransmission related-proteins and in increase in proteins associated with growth and damage [19,20]. Neuronal metabolic depression may also be due to diaschisis, the distant neurophysiological changes due to a direct inhibitory effect of injury [21-23]. Notably, lower levels of NAA in these areas were associated with larger extent of motor-related activation and poorer clinical outcomes [12-14]. In sum, these findings suggest that the neuronal state in spared motor areas is likely to impact the functional role of the ipsilesional hemisphere on movement and subsequently motor impairment. However, no studies have examined the dynamics of the remote neuronal state under certain circumstances, i.e., motor intervention, and their relationships to motor recovery. Therefore, the purpose of this case study was to determine the effects of an impairment-oriented training on the NAA levels in the spared ipsilesional motor and premotor areas. We predicted that the levels of NAA would increase after training and this increase would parallel the improvement in clinical measures of motor impairment.

Case Report

Patient’s description

The patient was a 59 years old male who suffered a right-hemisphere ischemic stroke 144 months before study’s participation. Before stroke, the patient was a homebuilder for 35 years. The personal medical history included chronic hypertension and type II diabetes with no other neurological, psychiatric, or cardiovascular diseases. The patient was a smoker for 45 years before stroke, but quit smoking afterwards. According to the standard body mass index measures, the patient was obese (having a score of 36.4; obese ≥ 30). Taken together, this patient presented four major risk factors to develop an ischemic stroke: i) hypertension [24], ii) cigarette smoking [25]; note that co-existence of the first two factors, hypertension and cigarette smoking, significantly increases the risk of stroke [26,27], iii) obesity [28-31], and iv) diabetes [32]. The current medication status included Quinapril for high blood pressure and Metformin and Glipizide for diabetes.

Imaging and clinical assessments

The patient underwent magnetic resonance imaging (MRI, including structural and functional MRI (fMRI) and 1H-MRS, at 3Tesla Siemens Allegra), and clinical assessments within 24 hours prior and after a motor training period of four weeks.

A structural MRI (whole-brain 3D T1-weighted image, repetition time (TR)=2300 milliseconds (ms), echo time (TE)=3 ms, field of view (FOV)=240 millimeter (mm), matrix size=256 × 256, slice thickness=1 mm, 208 slices, 0 skip, resolution=1 × 1 mm^2) was used to identify the location of the stroke (Figure 1). As shown in Figure 1, the patient suffered an ischemic stroke in the right middle cerebral artery territory, including corona radiata and striato- capsular territory. We also calculated the lesion volume by manually tracing the lesion on slice-by-slice basis in the axial view (MedINRIA, Medical Image Navigation and Research Toll by INRIA, Cedex, France; http://www.sop.inria.fr/asclepios/software/Medinria) and then quantifying the volume (MIPAV, http://mipav.cit.nih.gov/). The lesion volume in this patient was 1451.9 mm^3.

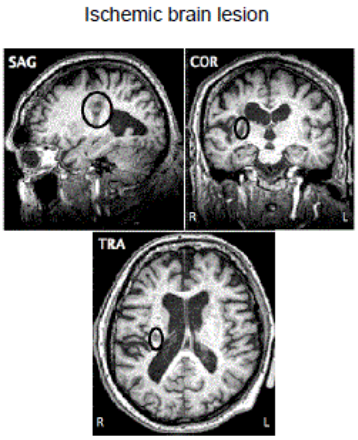

Figure 1: T1-weighted image showing ischemic lesion located in the right-hemisphere striato-capsular territory of middle cerebral artery (marked with black circle); SAG indicates sagittal view, COR, coronal view, TRA, transversal view; L, left, R, right.

We used blood oxygen level-dependent fMRI (BOLD, TR=2000 ms, TE=50 ms, FOV=240 mm, matrix=64 × 64, slice thickness=5 mm, 25 slices, 0 skip, resolution=5 × 5 mm^2, 100 time points) to functionally localize the hand representation in ipsilesional motor and premotor areas. Two alternating conditions were repeated: movement condition (20 seconds), where the participant was visually-cued to perform a handgrip with the impaired hand; and rest condition (20 seconds), where the participants were motionless. During scanning, a target pressure was set at 25% of maximal voluntary contraction (MVC) for each participant. Prior to scanning, participants generated MVC on three five-second trials; the highest peak pressure produced was used as the MVC. The pre-training MVC value was also used after training. The target pressure was indicated by a vertical bar on the screen placed in front of the participant (LabVIEW 7.1, National Instruments, and Texas). The handgrip rate was indicated visually by a green circle displayed on the screen for 2 seconds at every 4 seconds (a red circle was provided with the same rate during the rest condition). The green

circle indicated to the participant to perform a single brief handgrip until the column representing applied pressure reached the vertical bar displayed on the screen, at which point the grip could be released. Prior to scanning, the participant was trained to confirm the absence of associated or mirror movements (by observation and palpation) and to ensure that the participant is able to control the force output (given the initial motor impairment, see below).

BOLD data were analyzed using the scanner analysis software to guide the 1H-MRS image slab positioning. Specifically, three consecutive slices corresponding to the activated motor hand areas were used to select the corresponding coincident T1-weighted image upon which the 1H- MRS imaging slab was centered (Figure 2A).

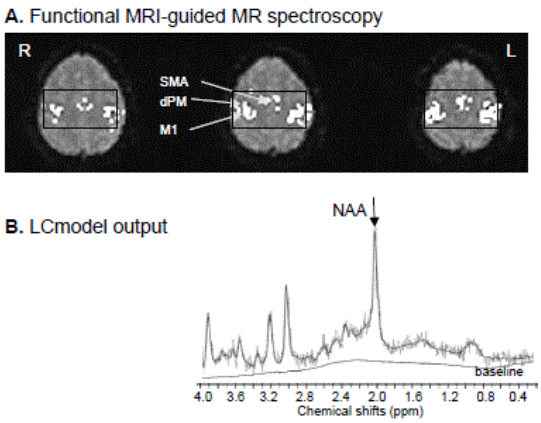

Figure 2: (A) 1H-MRS image slab (black box) was positioned according to the maximal motor- related activation. BOLD signal was analyzed on-line and three consecutive slices (each of 5 mm thickness) in order to place the 1H-MRS image slab (15 mm thickness). As expected, the motor activation in a severely impaired patient was bilateral22; M1: primary motor cortex; dPM: Dorsal Premotor Cortex; SMA: Supplementary Motor Area; L: left; R; Right. (B) An example of LCModel output, including N-acetylaspartate (NAA) peak, emanating from dominant grey matter in the primary motor cortex; ppm, parts per million.

An axial 1H-MRS imaging slab was selected in the frontal (and parietal) lobe, including motor and premotor areas [33]. MRSI was acquired using a point-resolved spectroscopy sequence (PRESS, TE=30 ms, T=1500 ms, FOV=160 mm, matrix=16 × 16, slice thickness=15 mm, resolution=5 × 5 mm^2). Scalp lipid artifact was minimized with outer voxel suppression bands. Automated and manual shimming yielded an optimal full-width at half maximum of <20 Hz of the water signal from the entire excitation volume. NAA concentrations were calculated using LCModel [34] (Figure 2B), using corrections based on the transmitter gain to account for variations in coil loading across subjects. After zero-filling the spectroscopic data in the spatial dimensions (32 × 32 matrix), NAA concentrations were calculated for each spectroscopic voxel. The T1-weighted images were also segmented (SPM5, Welcome Department of Cognitive Neurology, London, UK). As previously shown [12-14], we overlaid the LCModel output on the segmented T1-weighted images (Matlab v7.1) to display NAA concentrations from LCModel and grey matter percentage from SPM in each voxel. Then, we selected three spectroscopic voxels corresponding to the hand representation in three core areas of motor-execution network [35]: primary motor cortex (M1), dorsal premotor cortex (dPM), and supplementary motor area (SMA) (http://neuro.imm.dtu.dk/services/jerne/ninf/voi.html). The selection of these areas was based on their major contribution to the recovery of motor function after stroke, particularly in severely affected patients [36-40]. Each voxel contained more than 75% grey matter, yielded a signal-to-noise ratio more than 10, and had Cramer-Rao bounds lower than 20% for NAA. NAA concentrations were grey matter-corrected by normalizing the LCModel output as follows: c=cLCModel *(1/gray matter), where c is final NAA concentration, cLCModel is NAA concentration from LCModel, and grey matter is the percentage of grey matter in the spectroscopic voxel. Finally, the corrected NAA concentrations for all voxels were averaged to provide a mean NAA concentration per each area. Concentrations were expressed in millimoles (mM) per kilogram wet weight by converting the institutional unit in mM with a calibration factor obtained by matching the mean NAA concentration in our healthy control group (described previously [14]) to the mean concentration of NAA reported in healthy brain [41-43].

An experienced physical therapist administrated two valid and highly reliable scales to assess upper extremity impairment: Fugl-Meyer (FM) [44,45] and Composite Spasticity Index (CSI) [46] before and after training. The FM scale is a reliable clinical and research tool to assess both the severity of impairment and responsiveness to therapeutic interventions [47,48]. Briefly, FM assesses muscle tone, range of motion, tendon reflexes and proximal and distal voluntary movements. A maximum score of 66 corresponds to normal arm function. The CSI provides a clinical measure of spasticity and assesses biceps tendon jerks, resistance to passive stretch, and wrist clonus for scores ranging from 4 (normal tone) to 16 (severe spasticity). Grip strength was also evaluated with a Jamar dynamometer (Asimow Engineering Co, Los Angeles, California).

Impairment-oriented training

Based on our prior motor learning studies in stroke [49,50], before training, we measured the active range of elbow extension of our patient during a reach-to grasp task [51]. As expected, we found that our patient exhibited significantly lower elbow extension (15.2°) compared to a healthy control group (described previously [14]) who executed the same task (57.9 5.2°). Then, we focused the attention of the participant on this specific impairment decreased elbow extensionduring practice.

Practice: The patient was seated in front of a table (Figure 3). At the initial position, the patient had the impaired arm rested on the table. An object was placed within a comfortable range for grasping (about 90% arm's length vertically oriented [52] (Figure 3), on a platform located in front of the patient. Because variable practice facilitates learning, retention, and generalization better than constant practice [53], we introduced a variable component during training: three different sizes (sizes corresponding to usual objects' sizes, such as cane, cup, jar) and three different weights (50, 100, 150 grams) of the object were presented in a randomized order in front of the subject. Then, the patient was instructed to perform a reach-to-grasp task for the presented object with the whole hand, and then move the object to the initial position of the arm at a comfortable self-selected speed. This task was selected based on its high ecological relevance. The patient had no arm or trunk restrictions during practice and pauses were provided at each 20 trials.

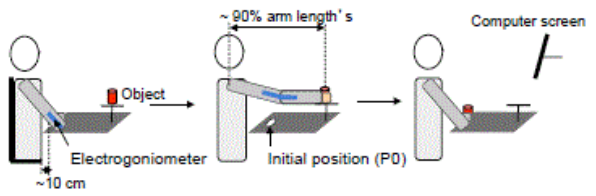

Figure 3: During training, the patient was seated in front on a table and practiced a reach-to-grasp task with the impaired arm for 90 times per day, 3 days per week, 4 weeks consecutively (n=1080 repetitions). During practice, his attention was directed towards the impaired active range of elbow extension. The patient had no arm or trunk restrictions during practice.

Intensity/repetition: The training consisted of 12 sessions over a period of four consecutive weeks (90 times per day, 3 days per week, 4 weeks, a total of 1080 movement repetitions). Feedback: During training, the patient received visual feedback about the active range of elbow extension by using an electrogoniometer (Exos, Inc., Woburn, MA, USA) placed on the lateral epicondyle - knowledge of performance. Elbow extension movement was displayed on a computer screen placed in front of the patient after the end of the task. Mean elbow extension from a healthy group executing the same task was presented as a target goal on the same screen. To minimize dependency on feedback, the feedback was provided with a decreasing frequency (faded frequency) throughout the practice session (for the first 30 trials, the feedback was given following every single trial, for the second 30 trials, every 2nd trial and for the last 30 trials, every 5 trials).

Results

The patient was severely impaired and exhibited lower levels of NAA in the ipsilesional motor and premotor areas prior training

The baseline clinical evaluation of our patient revealed severely impaired motor abilities (FM, 25 out of 66), moderate spasticity (CSI, 8 out of 16), and severely reduced grip strength in the affected UE (1.5 pounds per square inch (psi) or 4.4% of the non-affected hand grip strength 34 psi).

Relative to healthy controls (described previously [14]), the patient exhibited lower NAA in all three areas at baseline (M1, 9.2 mM vs. 11.6 2.0 mM in controls; dPM, 8.9 mM vs. 12.2 1.9 mM; SMA, 7.4 mM vs. 11.0 2.3 mM). Lower NAA levels likely indicate neuronal metabolic down-regulation in these areas [12-14].

The patient improved functionally and exhibited higher levels of NAA in the ipsilesional motor and premotor areas with training

The patient exhibited reduction in arm motor impairment (6-point increase on the FM score) and increase in grip strength (3.5 psi or 9.5% of the non-affected hand grip strength=37 psi), but no change in spasticity level (CSI, 8 out of 16) (Table 1). Because in patients with severe impairment a change greater than 10% on the baseline FM score (which will be 2.5 points in our case) is considered clinically meaningful improvement [47], a 6-point increase reported here clearly signifies a clinically meaningful improvement. As expected, due to our type of training, the patient also showed an increase in the active range of elbow extension (from 15.2° to 27.3°).

The levels of NAA increased in all three motor areas with training (with a range between 0.6 to 3.3 mM, Table 1). This is an exciting result and suggests possible plastic structural changes in these areas induced by training. Outcomes	Prior training	After training
M1	9.2	9.8
dPM	8.9	9.6
SMA	7.4	10.7
FM (points)	25	31
Spasticity (points)	8	8
Grip strength (% of the non-affected hand)	4.4	9.5

Table 1: Training-related changes in cortical levels of NAA and clinical scores. NAA: N-acetylaspartate; M1: Primary Motor Cortex; dPM: Dorsal Premotor Cortex; SMA: Supplementary Motor Area; mM: Millimoles; FM: Fugl-Meyer tests (normal=66); CSI: Composite Spasticity Index (normal=4).

Discussion

The main finding here is that the levels of NAA in the ipsilesional motor and premotor areas increase during a therapy targeting upper extremity and parallel the arm motor improvement. This is the first demonstration that remote neuronal state could be altered with a therapy and these alterations may be associated with therapy-related behavioral gains in a chronic stroke survivor.

As stated above, this patient exhibited baseline lower NAA levels in the ipsilesional motor and premotor areas, presumably reflecting neuronal metabolic depression [12-14]. This is in line with previous reports demonstrating metabolic cell body changes after axonal injury at the subcortical level [16] and/or metabolic abnormalities associated to diaschisis in these areas [54]. We speculate that the increase in NAA levels with training suggests that the metabolically depressed neurons retain the ability to underlie structural plastic changes with training. Examples of such changes are synaptic plasticity [55] and/or structural changes in axons, dendrites, spines and synapses [56], which are likely to yield an increase in the levels of NAA [57,58]. For instance, such changes would enable these neurons to i) recruit adjacent neurons with intact axons which potentially have muscle projections similar to that of metabolically depressed neurons, and/or ii) facilitate the activation of multiple novel muscle synergies that are required for motor skill acquisition. This would explain the motor improvement observed with training. Note also that NAA levels increased in both motor and premotor areas. This is an expected result since the premotor areas are likely to paly a major role in restoring motor function after damage to motor neurons or their axons, particularly in patients with severe disabilities [22].

Further, our data revealed the potential of this patient to significantly improve the arm motor function even after 12 years after stroke onset with this training paradigm. Although the attention of the participant was directed to a specific impairment (i.e., decreased elbow extension motion), we observed an overall improvement in clinical scores. We explain this by a possible generalization of the improved elbow control to movements evaluated by FM [59]. Note that the magnitude of FM changes (+6 points) was somehow higher to those reported by previous studies using similar motor training and clinical outcome measures (change 4.2 points [60]; +3.6 points [50]). This difference could be explained by clinical severity at baseline, in our case severely impaired patient, but who retain the ability to improve, compared to patients with different levels of clinical severity, from less severe to mild hemiparesis, studied in above- mentioned studies. In addition to FM improvement, this patient also improved handgrip strength and subjectively noticed improvements in activities of daily living with training. Certainly, clinical changes were important, but these subjectively described changes are worth emphasizing as they indicate the potential of this training paradigm to generalize to other behaviors that are of high ecological relevance.

Although this is a case study, we hope that these data act as a starting point for further research to test the potential of 1H-MRS measures to provide a means of assessing plastic changes in intact motor cortex and possibly a biomarker of neuroplasticity in response to therapeutic interventions. Further research and understanding in this area will undoubtedly have major implications for rehabilitation of the patients with chronic stroke. In addition, these findings suggest that a treatment approach could be successful even in very chronic stage of stroke when specific feedback that orients the learner's attention to missing/altered movement components is providing during repetitive practice.

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