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Treatment of dysphasia with rTMS and language therapy after childhood stroke: Multimodal imaging of plastic change



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ABSTRACT

Expressive dysphasia accompanies left inferior frontal gyrus (IFG/Broca) injury. Recovery may relate to interhemispheric balance with homologous, contralesional IFG but is unexplored in children. We evaluated effects of inhibitory rTMS to contralesional IFG combined with intensive speech therapy (SLT). A 15 year-old, right-handed male incurred a left middle cerebral artery stroke. After 30 months, severe non-fluent dysphasia impacted quality of life. Language networks, neuronal metabolism and white matter pathways were explored using MRI. Language function was measured longitudinally. An intensive SLT program was combined with contralesional inhibitory rTMS of right *pars triangularis*. Procedures were well tolerated. Language function improved persisting to four months. Post-treatment fMRI demonstrated increased left perilesional IFG activations and connectivity at rest. Bilateral changes in inositol and glutamate metabolism were observed. Contralesional, inhibitory rTMS appears safe in childhood stroke-induced dysphasia. We observed clinically significant improvements after SLT coupled with rTMS. Advanced neuroimaging can evaluate intervention-induced plasticity.

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1. Introduction

Childhood stroke often causes disability that lasts a lifetime (Kirton & deVeber, 2015). Symptomatic language disorders are poorly studied but affect 20–30% of survivors (Geranmayeh, Brownsett, & Wise, 2014; Wade, Hewer, David, & Enderby, 1986), a rate comparable to adult stroke (Engelter et al., 2006; Pedersen, Vinter, & Olsen, 2004). Stroke-induced expressive dysphasia accompanies left inferior frontal gyrus (IFG or Broca's area) injury, featuring non-fluent speech and word finding difficulties (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013) with

challenges across academic, social, and daily functioning (Gomes, Rinehart, Greenham, & Anderson, 2014; Westmacott, Askalan, MacGregor, Anderson, & Deveber, 2010). Our use of the term dysphasia in this case refers to acquired dysphasia, the partial loss of the ability to communicate through speech as a result of injury to the brain (aphasia).

Spontaneous functional language recovery after stroke often plateaus within a year (Robey, 1998) but can improve with speech language therapy [SLT; (Bhogal, Teasell, Foley, & Speechley, 2003; Bhogal, Teasell, & Speechley, 2003; Cherney, Patterson, Raymer, Frymark, & Schooling, 2008; Robey, 1998)]. Mechanisms of poststroke plasticity and reorganization, and how they determine function, are complex (Torres, Drebing, & Hamilton, 2013). Similar to motor recovery models, relative over-activity of contralesional, homotopic language areas may occur after stroke (Heiss & Thiel,

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2006; Rosen et al., 2000). The resulting imbalance between interhemispheric connectivity with excessive inhibition from non-lesioned to lesioned hemisphere (caused by the lesion) may underlie chronic dysphasia (Geranmayeh, Brownsett, & Wise, 2014; Heiss & Thiel, 2006; Naeser et al., 2012; Rosen et al., 2000). Recovery and therapy effects in stroke dysphasia may relate to the reduction of interhemispheric imbalance between lesioned and homologous, contralesional IFG and recently this has been identified as a promising rehabilitation target (Heiss & Thiel, 2006).

Neuromodulation with non-invasive brain stimulation may modulate cortical targets to enhance stroke recovery through alterations of cortical excitability. Demonstrations that transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) may enhance SLT efficacy in dysphasia are increasingly reported (Mylius, Zouari, Ayache, Farhat, & Lefaucheur, 2012; Naeser et al., 2012; Torres et al., 2013; Zumbansen & Thiel, 2014). Repetitive TMS (rTMS) also shows promise as a well-tolerated emerging treatment for adult stroke dysphasia. Indeed, lasting improvements in language function have been demonstrated after rTMS alone (Barwood et al., 2011a, 2011b; Hamilton et al., 2010; Naeser et al., 2005, 2011) and when paired with SLT (Martin et al., 2009; Naeser et al., 2012; Thiel et al., 2013).

Modulating inter-hemispheric balance by inhibiting right contralesional IFG (right *pars triangularis* [PTr], Brodmann's area 45) with rTMS may improve adult stroke dysphasia (Barwood et al., 2011a, 2011b; Hamilton et al., 2010; Naeser et al., 2011). Excitatory TMS or tDCS over left IFG may also improve stroke-induced dysphasia (Cotelli et al., 2011; Szaflarski et al., 2011) when paired with SLT that persists for many weeks (Vestito, Rosellini, Mantero, & Bandini, 2014). Enhancing perilesional language-related brain areas appears to be more effective than recruiting non languagespecialized structures in the right hemisphere (Naeser et al., 2012; Postman-Caucheteux et al., 2010; Saur et al., 2008; Winhuisen et al., 2007) although this question is far from answered and continues to be explored (Anglade, Thiel, & Ansaldo, 2014; Richter, Miltner, & Straube, 2008; Turkeltaub et al., 2012).

Neuroimaging can explore baseline and intervention-induced change in language networks (Meinzer, Harnish, Conway, & Crosson, 2011). Examples include examining cortical language areas using task-related functional MRI (fMRI), network connectivity using resting state MRI (rsMRI), neuronal metabolism with magnetic resonance spectroscopy (MRS) and white matter (WM) structure using diffusion tensor imaging (DTI). Such approaches have greatly advanced understanding and therapeutic opportunities in adult stroke (Geranmayeh et al., 2014). Using multimodal imaging leverages the relative strengths of each modality and gives a more comprehensive picture regarding brain function (Crinion, Holland, Copland, Thompson, & Hillis, 2013; Meinzer et al., 2011) and possible inter-hemispheric shifts after intervention (Kiran, Meier, Kapse, & Glynn, 2015).

Task-based functional MRI identifies patterns of blood oxygen level dependent (BOLD) response activation in brain areas currently recruited during a task. The importance of activation level and extent in left IFG of adult patients appears to correlate significantly with language function (Fridriksson, Baker, & Moser, 2009; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Saur et al., 2006). Tasks used in fMRI language studies vary widely and include picture naming, rhyming, and category exemplar generation (Meinzer et al., 2008). In the current study we used overt picture naming and investigated changes in fMRI activation patterns with changes in picture naming abilities (Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010).

Task-free resting state fMRI (rsMRI) calculates the temporal synchronicity of BOLD activations to infer connectivity thereby characterizing networks without an overt task (Biswal, Yetkin, Haughton, & Hyde, 1995). Regions of interest for both fMRI techniques included bilateral IFG (including *pars triangularis* [*pTr*] and *pars opercularis* [*pOp*]), middle frontal gyrus (MFG), middle temporal gyrus (MTG) and superior temporal gyrus (STG) as they have been implicated in previous aphasia rehabilitation studies (Kiran et al., 2015; Turkeltaub, Messing, Norise, & Hamilton, 2011; van Hees et al., 2014).

White matter tractography using diffusion weighted images allows for reconstruction of white matter tracts of interest and calculation of the microstructure of those tracts (Beaulieu, 2002). Tracts such as the arcuate fasciculus (AF)/superior longitudinal fasciculus (SLF) and others appear central to language function (Saur et al., 2008; Smits, Jiskoot, & Papma, 2014). Past studies have demonstrated that degree of damage to arcuate and uncinate fascicles is predictive of non-fluent speech production in aphasia (Fridriksson et al., 2013). Here we use tractography to examine microstructure of language tracts pre and post-intervention, including AF/SLT and inferior longitudinal fasciculus (ILF) (Saur et al., 2008).

Proton MR spectroscopy (MRS) quantifies metabolite concentrations within a region of interest. MRS can provide information on neuronal integrity (N-acetyl-aspartate [NAA]), energy metabolism (creatine), cell membrane integrity (choline), and glial cells (*myo*-Inositol) among others (Dani & Warach, 2014). MRS has not been used extensively in childhood stroke although there is some evidence that spectroscopy markers are predictive of neurologic outcomes in children with central nervous system injury (Holshouser et al., 1997).

We also collected additional data on the safety and tolerability of rTMS in our patient to add to the emerging literature that TMS is safe in a pediatric sample (Krishnan, Santos, Peterson, & Ehinger, 2015; Lefaucheur et al., 2014; Rajapakse & Kirton, 2013). This was monitored closely with twice daily measurements of language function and repeated tolerability measures intended to assess any discomfort.

Overall, multimodal neuroimaging applications in childhood stroke have been limited and never employed in combination to explore baseline neurophysiology and therapeutic brain stimulation in stroke-induced dysphasia. The aim of this study was to examine brain plasticity after rTMS and intensive language therapy. As such, our study provided brain stimulation and intensive SLT to an adolescent with post-stroke dysphasia, using multimodal neuroimaging to define endogenous reorganization and therapy-induced change. We hypothesized that SLT combined with contralesional, IFG inhibitory rTMS would result in improved language function with favourable tolerability while shifting language networks toward perilesional areas.

2. Methods

2.1. Subject

A 15 year old, right-handed English-speaking male with excellent athletic and academic performance (including studying German) incurred a proximal M1 left middle cerebral artery (MCA) arterial ischemic stroke secondary to focal cerebral arteriopathy. Large areas of damage included left temporal, frontal and parietal lobes and basal ganglia. Frontal damage included the inferior frontal gyrus but areas of anterior, medial left frontal lobe were spared (Fig. 1). He required emergency decompressive hemicraniectomy. He was non-verbal for 1 month with relative sparing of receptive language. At 30 months post injury (17 years of age), moderatesevere, non-fluent dysphasia (see detailed descriptions below) affected his quality of life. Additional deficits included right homonymous hemianopsia and severe right hemiparesis. Prior to participation, verbal assent and written parental consent were obtained in accordance with the Conjoint Health Research Ethics Board, University of Calgary.



Fig. 1. Lesion location and extent. A. Six axial slices from a pre-treatment T1-weighted MRI at 15 mm intervals illustrating the location and extent of the left MCA stroke-. B. Reconstructed brain volume. Slices are in radiological convention (right is left).

2.2. Intervention

A two week (10 week-days), daily treatment program included rTMS paired with a customized SLT program based on individualized rehabilitation goals. Each day began with inhibitory rTMS over right inferior frontal gyrus (IFG) *pars triangularis*. Anatomical localization was confirmed by three independent expert assessments using original imaging and 3D reconstructions to confirm IFG targeting.

A Magstim 70 mm Airfilm coil attached to a Magstim superrapid 2 rTMS machine (Cardiff, UK) was placed over this target using real-time neuronavigation (Brainsight2; Rogue Research, Montréal). Rest motor threshold (RMT) of right primary motor cortex (M1) was determined before the first session by standard methods (Frye, Rotenberg, Ousley, & Pascual-Leone, 2008; Rajapakse & Kirton, 2013).

Inhibitory rTMS was applied to the right IFG at 1 Hz with an intensity of 120% RMT. The patient sat comfortably while the fixated, navigated coil stimulated for 20 min (1200 stimulations) during which he received part of his daily SLT. A pediatric TMS safety and tolerability measure was administered on days 1, 5, 6 and 10 (Garvey, Kaczynski, Becker, & Bartko, 2001). This measure requires the child to report any side effects (e.g., headaches, tingling) and to rank their current TMS experience among seven common childhood experiences (e.g., long car ride, going to the dentist).

SLT focused on word retrieval using principles from the Word Finding Intervention Program (German, 2005; Lazzari & Peters, 1980, 2009) and lasted approximately two hours. Ageappropriate activities were aligned with his interests. These included improving communication over the phone (e.g., making plans with friends, ordering pizza), socializing, and talking while gaming online. Phone technology using a speech to text application allowed him to generate novel messages. Familiar games (e.g., Uno) were utilized to increase response speed when interacting. Complexity of required responses was increased to expand vocabulary. Preferred phrases were generated for use when gaming with friends and visual cues were provided to assist retrieval. The patient received daily homework to complete in the evenings (30 min). During the rest of each day, he participated in the group activity sections of a peer-supported pediatric stroke motor rehabilitation program with nine other children and continued interacting verbally with others.

2.3. Language assessments

Language function was assessed using the Boston Diagnostic Aphasia Examination, Third Edition (BDAE-Short-3; Goodglass, Kaplan, & Barresi, 2001) at three time points: baseline (3 days before intervention), follow-up (1 week after intervention) and 4 months. The therapist who performed BDAE testing and scoring was blinded to rTMS and SLT treatments and was told that the patient was attending the rehabilitation camp for motor therapy, not for speech and language therapy. In addition, the examiner was unaware of the content of the speech therapy since it was performed by a different therapist and was also blinded to whether this patient received sham or active rTMS. Percentile scores on each BDAE-3 sub-test (calculated based on a population of individuals with aphasia) characterized dysphasia and tracked change over time. Subtests included overall language fluency, including length of phrases, speech prosody (i.e., melodic line), and grammatical form of retrieved phrases. Ability to form speech sounds (i.e., articulatory agility), answer simple questions (i.e., responsive naming) and name simple pictures (i.e., Boston Naming Test) were also assessed.

Daily picture naming (PN) accuracy and latency were assessed using subsets of 260 Snodgrass images standardized on name agreement, image agreement, familiarity and visual complexity (Snodgrass & Vanderwart, 1980). Pictures were presented for 3 s and the subject was asked to name each item out loud with no feedback provided. PN was assessed at baseline, twice daily (before and after rTMS/speech therapy), and at 1 week and 4 month follow-up sessions. Pre-treatment testing consisted of 65 novel pictures from which 12 "challenge" pictures (incorrect or unnamed) were repeated each day. Daily PN consisted of 12 novel and the 12 "challenge" pictures. PN sessions were videotaped and percent performance was calculated. PN latency was the duration (in seconds) between image onset and patient response for correct responses.

2.4. Imaging

Images were acquired at the same time of day, 3 days pre- and 7 days post-intervention at the Alberta Children's Hospital Diagnostic Imaging Suite using a 3.0 T GE Discovery MR750w MRI scanner (GE Healthcare, Waukesha, WI) with an MR Instruments 32-channel head coil. High-resolution anatomical T1-weighted fast spoiled gradient echo (FSPGR BRAVO) images were acquired in the axial plane [166 slices, no skip; voxel size = 1.0 mm isotropic; repetition time (TR) = 8.5 ms; echo time (TE) = 3.2 ms; flip angle = 11°; field of view (FOV) = 256; matrix = 256 × 256].

2.4.1. Task functional MRI

Task fMRI acquisition used 137 T2-weighted whole brain echo planar volumes (EPI; 36 interleaved contiguous slices; voxel size = 3.6 mm isotropic; TR = 2000 ms; TE = 30 ms; flip angle = 60° ; matrix = 64×64). Five volumes (10 s) were discarded at the beginning of each functional run to attain magnetic field equilibrium.

Language activation patterns were localized using a picture naming fMRI task. Pictures of common objects from the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III; Wechsler, 2002) with matched familiarity were presented immediately to the left of fixation (accommodating for right homonymous hemianopsia) in a block design (eight pictures, mean stimulus size = 2.8° visual angle, duration = 4 s, total 32 s) and the patient named them aloud. Rest blocks were passive viewing of a fixation cross for 24 s. Five blocks of rest and 4 blocks of task required approximately 4 min.

Task-based functional analyses used Statistical Parametric Mapping (SPM version 12b [5763], Wellcome Trust Centre for Neuroimaging, UCL, London, UK) running within Matlab (Mac i64 version R2014a, Mathworks, Natick, MA). Slice timing correction, realignment, and co-registration were performed, and head motion parameters were estimated. Co-registered images were segmented using standard SPM tissue probability maps. Images were normalised into Montreal Neurological Institute (MNI) space using the standard 152-average template and smoothed with an 8 mm³

full-width at half-maximum (FWHM) Gaussian kernel. Head motion and other outliers were corrected using the Artifact Repair Toolbox (Mazaika, Hoeft, Glover, & Reiss, 2007) by identifying volumes with global mean activation greater than $z = \pm 3$, exceeding 1 mm of movement or exceeding 0.025 rad of rotation. Identified volumes were de-weighted in the general linear regression model (GLM). No volumes had head motion greater than ±1.5 mm and no more than 10% of volumes from a given sequence were deweighted. Whole-brain voxel-wise statistical calculations were completed using the GLM to calculate the task related hemodynamic response function. Data were high-pass filtered (1/128 s) and nuisance variables were included as covariates. Pre/post intervention functional activation analyses utilized paired *t*-test contrasts (Family wise error corrected [FWE] significance threshold p = 0.05) and resulting activation maps were created using MRIcron (Rorden, Karnath, & Bonilha, 2007).

2.4.2. Resting state fMRI

Resting state images were acquired using 150 T2-weighted whole brain EPI volumes (parameters as above). The subject was told to fixate on a centrally presented cross while thinking of nothing in particular. Resting state functional analyses were performed through SPM using the Functional Connectivity Toolbox (CONN; Whitfield-Gabrieli & Nieto-Castanon, 2012). In addition to the pre-processing described above, rsMRI data went through a temporal pre-processing step where time courses of activations were extracted for the GM, CSF and WM. The CSF and WM time courses and head motion were regressed out of the GLM model. Subsequent seed-to-voxel and ROI-to-ROI analyses for the whole brain were performed using six seeds of interest selected via a Brodmann area (BA) atlas [left and right IFG (pars triangularis), right IFG (pars opercularis), right superior temporal gyrus (STG), right middle temporal gyrus (MTG) and left inferior prefrontal gyrus]. Seeds in the left superior or middle temporal gyri or IFG (pars opercularis, BA44) could not be placed due to damage. For seed-to-voxel, regressions identified brain regions with activations that significantly covaried with one of the six seed regions. Peak activation clusters of sufficient volume ($k \ge 100$ voxels) were identified using xiView (http://www.alivelearn.net/xjview). For ROI-to-ROI, Pearson correlations were performed among each of the six ROIs to examine connectivity.

2.4.3. Diffusion imaging

Diffusion weighted images (DWI) were acquired in the axial plane for 60 contiguous slices. Thirty-two diffusion gradient directions were sampled (b = 0, 750 s/mm², voxels = 2.2 mm³ isotropic, duration = 6 min, TR = 11.5 s, TE = 70 ms, FOV = 220 mm, matrix = 256 \times 256). Images were corrected for eddy current distortions and simple head motion using FMRIB's Diffusion Toolbox (FDT; Behrens et al., 2003) part of FSL (FMRIB Software Library; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). Volumes were registered to the first b0 volume using affine registration.

Diffusion tensor and fractional anisotropy (FA) maps were calculated using MRTrix (Tournier, Calamante, & Connelly, 2012; Tournier, Calamante, Gadian, & Connelly, 2004). Tracts of interest were extracted by manually outlining multiple inclusion regions of interest (ROIs) at anatomically guided locations on the FA map. Inclusion ROIs were combined using a logical "AND" rule requiring all streamlines project through both regions using probabilistic tractography (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Streamlines passing through an exclusion region were discarded. A minimum FA threshold of ≥ 0.2 was required for voxel inclusion.

Dorsal language pathways (Saur et al., 2008): To isolate the right arcuate fasciculus/superior longitudinal fasciculus (SLF), an inclusion

region (Fig. 2A) was delineated on a coronal slice using a triangular-shaped ROI at the dorsal portion of the SLF (Mori et al., 2002, 2008). A second axial inclusion ROI was outlined around the triangular-shaped region lateral to the splenium of the corpus callosum where the SLF projects into the temporal lobe (Smits, Jiskoot, & Papma, 2014). An exclusion plane excluded streamlines projecting toward midline.

Ventral language pathways (Makris et al., 2013; Saur et al., 2008): To isolate the middle/inferior longitudinal fascicules (Md/ ILF), an inclusion region (Fig. 2C) was delineated on the coronal slice just posterior to fMRI language task activations in the left anterior IFG and on a corresponding area on the right side (Makris et al., 2013; Saur et al., 2008). A second coronal inclusion region was demarcated just lateral to the posterior limb of the internal capsule.

Whole brain maps of FA, apparent diffusion coefficient (ADC), axial diffusivity [AD = λ_1 the principal eigenvalue] and radial diffusivity [RD = ($\lambda_2 + \lambda_3$)/2, the average of the other two eigenvalues] were calculated. Binary masks generated from WM tractography sampled tensor parameter maps and provided indices of WM microstructure.

2.4.4. MR spectroscopy

MRS data were acquired using a standard point-resolved single voxel spectroscopy (PRESS) sequence (TR = 2000 ms, TE = 30 ms, 128 averages). ROIs were defined using two 4 cc voxels $(20 \times 20 \times 10 \text{ mm})$ placed on axial T1 slices (Fig. 4A) with location determined by BOLD activations during the fMRI picture naming task (above). Voxel 1 was in right IFG and corresponded to the rTMS site. Voxel 2 was anterior to the lesion on the left. ¹H MRS spectra were generated and analyzed using LCModel (Provencher, 2001). Absolute concentrations (institutional units, i.u.) of glutamate (Glu), glutamate/glutamine (Glx), N-acetyl-

aspartate/N-acetyl-aspartylglutamate (NAA + NAAG), choline compounds (glycerophosphocholine/phosphocholine; GPC + PCh), and inositol (Ins) were measured. Percent change ($\%\Delta$) of metabolite concentrations between pre and post intervention scans assessed possible treatment effects [$\%\Delta$ = ((post-pre)/pre) * 100]. A percent change exceeding previously determined test-retest variability (Geurts et al., 2004) was considered a significant change. Only metabolites with Cramér-Rao bounds <10% were analyzed.

2.5. Statistical analyses

The Statistical Package for the Social Sciences (IBM SPSS Version 19 for Windows, Chicago, USA) was used to perform Pearson's correlations on picture naming (for both novel and repeated word lists) and latency scores as a function of treatment session. Statistical significance threshold was set to p < 0.05. This statistical analysis was performed to quantify changes in latency and improved performance in picture naming over the course of the intervention period and four months post-intervention. As discussed in Thompson (2006), the presence of "response generalization", i.e., changes in untrained language behaviour for the novel word list, may indicate an improvement in function. Of note, materials used for testing of daily picture naming abilities, fMRI task picture naming, BDAE testing and speech language therapy were completely independent with no overlap of stimuli.

3. Results

3.1. Tolerability

rTMS treatment was well tolerated. Facial twitching on the first day was significantly uncomfortable but the patient wished to continue and tolerance improved. He ranked the rTMS experience as 6



Fig. 2. Region of interest placement and resulting reconstructed language white matter tracts. A. Right arcuate fasciculus/superior longitudinal fasciculus (SLF) was selected using inclusion ROIs on coronal and axial slices (green). A sagittal limit plane (red) excluded streamlines that projected toward midline. B. Reconstructed SLF. C. Middle/ Inferior longitudinal fascicules (Md/ILF) were selected using inclusion ROIs (green) on coronal slices, one placed just posterior to LPtr, the other just lateral to the CST. A sagittal ROI positioned just left of midline slice (red) was used to exclude streamlines projecting medially. D. Reconstructed Md/LILF. Tract colours represent planes of projection: blue: superior-inferior, green: anterior-posterior, red: right-left.

on a scale of 1–8 common childhood experiences where "play a game" was rated the most pleasant (1) and "throw up" was most unpleasant (8). No adverse events such as headaches, neck pain or unpleasant tingling were reported.

3.2. Language function

Picture naming accuracy significantly improved for both novel (r = 0.54, p < 0.01) and repeated "challenge" images (r = 0.53, p < 0.05) as a function of treatment sessions (Fig. 3A). Naming latency decreased over treatment sessions indicating significantly faster correct responses for repeated images (r = -0.60, p < 0.01, Fig. 3B) but not novel images (r = -0.26, p = 0.26). Over treatment sessions, more naming attempts were made (r = 0.55, p < 0.01). The higher number of naming attempts may have increased naming latency in later sessions.

Post-treatment BDAE-3 performance showed improved fluency and articulation scores (Fig. 3C & Table 1). Phrase length showed a marked change, improving from the 20th percentile at baseline to the 100th percentile. Naming ability showed improvements at one-week post intervention (a 10 percentile-point increase) but this did not persist to 4 months (Fig. 3D).

Qualitative improvements in language function were also observed. The subject demonstrated increased confidence in speaking, spontaneously initiating an interaction with another camp participant to share his camp scrapbook. Using practiced vocabulary and a script he had prepared, he successfully ordered pizza over the phone at the end of treatment.

3.3. Task fMRI: Language activations

BOLD response patterns during the pre- and post-treatment picture naming task are illustrated in Fig. 5. Significant activations were seen in primary and supplementary motor cortex, visual cortex, right IFG and left perilesional frontal areas. A similar pattern was seen for post-treatment activations.

A comparison between pre- and post-intervention activations demonstrated significantly increased left perilesional frontal activations (p < 0.01) post-treatment. There were no significant changes to language activation patterns in right IFG PTr (corresponding to the site of rTMS).



Fig. 3. Post-treatment language outcomes. A. Picture naming accuracy. B. Picture naming latency. C. BDAE fluency. D. BDAE Articulation and naming. Shaded central areas denote rTMS and SLT treatment. Baseline testing was done three days before treatment started (day -3), follow-up sessions were on days 18 (1 week) and 164 (4 months) after treatment commenced. Linear trend lines in panels A & B do not include 4-month follow-up session.

Table 1

Performance on the Boston Diagnostic Aphasia Examination (BDAE-3).

Domain	Baseline	1 week	4 months
Subtest	Percentile (raw score)		
Overall severity	40 (1)	40 (1)	40 (1)
Fluency Phrase length (rating scale) Melodic line (rating scale) Grammatical form (rating scale)	20 (4) 0 (1) 0 (1)	100 (7) 10 (2) 20 (3)	100 (7) 20 (3) 30 (4)
Conversation/expository speech Simple social responses	100 (7)	100 (7)	100 (7)
Auditory comprehension Basic word discrimination Commands Complex ideation material	60 (15) 30 (7) 30 (3)	100 (16) 30 (7) 30 (3)	100 (16) 30 (7) 50 (4)
Articulation Articulatory agility	40 (4)	50 (5)	70 (6)
Recitation Automatized sequences	20 (2)	100 (4)	20 (2)
Repetition Words Sentences	60 (4) 30 (0)	60 (4) 30 (0)	60 (4) 30 (0)
Naming Responsive naming Boston naming test Special categories	50 (7) 70 (10) 30 (10)	60 (8) 80 (12) 100 (12)	40 (6) 70 (10) 25 (9)
Paraphasia Rating from speech profile Phonemic Verbal Neologistic Multi-word	40 (4) 40 (2) 25 (5) 100 (0) 100 (0)	50 (5) 100 (0) 40 (3) 100 (0) 100 (0)	0 (1) 40 (2) 60 (2) 30 (1) 100 (0)
Reading Matching cases and scripts Number matching Picture-word-matching Oral word reading Oral sentence reading Oral sentence comprehension Sentence/paragraph comprehension	100 (4) 100 (4) 100 (4) 20 (6) 30 (0) 100 (3) 100 (4)	100 (4) 100 (4) 100 (4) 40 (12) 30 (0) 20 (1) 100 (4)	100 (4) 100 (4) 100 (4) 20 (6) 30 (0) 100 (3) 70 (3)
Writing Form Letter choice Motor facility Primer words Regular phonics Common irregular words Written picture naming Narrative writing	10 (8) 10 (15) 30 (9) 30 (3) 30 (0) 20 (0) 30 (1) 0 (0)	15 (9) 10 (14) 35 (10) 30 (3) 30 (0) 20 (0) 30 (1) 0 (0)	15 (9) 5 (13) 30 (9) 20 (2) 50 (1) 20 (0) 30 (1) 0 (0)

Table note: Scores are percentiles from the BDAE-3 calculated using normative scores from a group of patients with aphasia. Raw scores on each subtest are provided in brackets.

3.4. Resting state MRI: Connectivity

For seed-to-voxel analyses, activity in seeded areas at rest was found to be synchronous with activity in other areas typically associated with language and executive functions.

Activity in the left perilesional seed appeared synchronous with other areas in the left frontal lobe (middle/inferior frontal gyrus) and homologous areas on the right as well as right temporal (superior and middle temporal gyri) and parietal areas. This pattern of connectivity is consistent with language, executive function, and working memory networks (Geranmayeh et al., 2014). Posttreatment activations were more extensive than pre-treatment with significant overlap.

To separate the relative contributions of language, executive, and working memory networks, seeds were placed in right IFG *pars triangularis* and *opercularis*, areas of interest if language functions A comparison between pre/post treatment correlations resulting from ROI-to-ROI analyses (Fig. 6) indicated that both seeded areas had increased connectivity with other frontal areas (e.g., left inferior prefrontal gyrus, right *pars opercularis*, right *pars triangularis*) after treatment. Correlations between seeds and selected temporal areas showed little change or small decreases posttreatment.

3.5. DTI: White matter microstructure

Dorsal (AF) and ventral (Md/ILF) language pathways were successfully mapped in the right hemisphere (Fig. 2B). Only the ventral pathway could be tracked in the left hemisphere due to extensive damage (Fig. 2D). The anterior portion of the ventral language pathway in the left perilesional area corresponded well with the location of functional activation in task-related fMRI and resting state MRI connectivity analyses. Changes in tract FA and diffusivity values following intervention averaged ±5–8% with no clear differences.

3.6. MRS: Neuronal metabolism

Cramér-Rao bounds ranged between 3% and 9% for all metabolites indicating good fit for the estimated model. At the site of rTMS in right IFG, choline compound concentrations decreased following intervention (Δ GPC + PCh = -13.2%) and glutamate increased (Δ Glu = +15.5%). In left anterior perilesional areas corresponding to task fMRI activations, a large increase was observed in inositol (Δ Ins = +28.9%) as well as a decrease in glutamate (Δ Glu = -15.0%). These differences were larger than anticipated for repeated measures variability (Geurts et al., 2004).

4. Discussion

We present evidence from a single subject demonstrating improvements in expressive language function after intensive SLT and rTMS therapy. Multimodal imaging results indicate increased task-related activations in perilesional IFG with no concomitant activation changes in contralesional areas corresponding to the site of rTMS. Resting state analysis showed increased connectivity for perilesional left IFG with other language and frontal areas. An increase in the metabolite inositol was found in perilesional areas and no changes were seen in white matter microstructure after intervention. Our case suggests that contralesional, inhibitory rTMS paired with intensive SLT is a potentially feasible rehabilitation strategy for adolescents with stroke-induced dysphasia. Given the increased connectivity, activation and neuronal metabolism in left perilesional areas, our results appear to be consistent with an increase in function in the left hemisphere (Barwood et al., 2011a, 2011b; Hamilton et al., 2010; Naeser et al., 2011). Advanced, multimodal neuroimaging may provide novel insights to endogenous and interventional plasticity in childhood stroke (Kiran et al., 2013; Meinzer et al., 2011).

We observed clinically significant changes in expressive language function. These included overall fluency, phrase length, and articulation of speech sounds accompanied by new found confidence in speaking that improved activities of daily living. Many improvements persisted to the four-month follow-up though treatment sessions lasted just two weeks. Lasting effects after such



Fig. 4. Pre-treatment MRS voxel placement and resulting spectra from LPTr. A. Two MRS voxels were placed, one on right IFG/PTr and one on left anterior perilesional IFG corresponding to fMRI language activation patterns. B. Resulting spectra illustrate concentrations (in i.u.) of Glu, NAA and PCr for pre-treatment.



Fig. 5. fMRI activation maps. A. Pre-treatment and B. post-treatment activation maps illustrating BOLD response during a picture naming task shows activity in motor, supplementary motor (M1, SMA), visual areas (V1) and IFG/MFG in both right and left hemispheres.

"intensive bursts" of therapy are increasingly described in adult stroke rehabilitation, most notably for constraint therapy and, to a lesser degree, for brain stimulation (Wolf et al., 2008). As our patient was in the chronic phase post-stroke (~3 years), the likelihood of spontaneous recovery was reduced (Robey, 1998) although establishing a stable baseline pre-intervention would have been advantageous. The relatively young age of our patient (17 years) may also have allowed for more plasticity of language function compared to older patients. During adolescence, specialization of the left hemisphere for language appears to occur as evidenced by increased lateralization of function until the mid 20s (Holland et al., 2007; Szaflarski, Holland, Schmithorst, & Byars, 2006). Previous evidence indicates greater cortical plasticity with earlier stroke (Szaflarski et al., 2014). While only a single case, our results are consistent with adult stroke and emerging studies in the developing brain that suggest non-invasive neuromodulation may provide clinically significant benefits many years following injury.

We provide important new safety and tolerability data for neuromodulatory rTMS in a pediatric condition. Therapeutic non-invasive brain stimulation trials are increasingly described in children (Krishnan et al., 2015; Lefaucheur et al., 2014). In pediatric stroke, only small childhood stroke (n = 10; Kirton et al., 2008) and more recent perinatal stroke (n = 19; Gillick et al., 2014) trials have been published, both with favourable safety and tolerability. Despite significant facial twitching, our subject's tolerability scores were favourable and he completed the intervention with no decrease in language function. In adult dysphasia, safety data is more substantial (Geranmayeh et al., 2014). However, careful mapping of contralesional IFG targets has been emphasized by studies demonstrating worsening of language function with inhibitory stimulation of neighbouring regions (Naeser et al., 2011). The improvements we observed in our subject, while far from definitive of efficacy, at least suggest that such a negative effect was very unlikely. We suggest that accurate targeting, including multiinvestigator identification of anatomical targets, incorporation of task fMRI for mapping, and neuronavigated rTMS systems for consistent coil placement, could be useful options to consider for future studies.

We chose validated language measures targeting the subject's primary clinical deficits but additional complex language assessments are available. The BDAE-3 is effective in measuring specific language domains and accurately reflects functioning on specific subtests. However it may be less sensitive to subtle changes in overall global language performance, especially in individuals with



Fig. 6. An illustration of rsMRI ROI-to-ROI connectivity analyses. Values represent Fisher-transformed Pearson correlation coefficients between the seed (green) and five regions of interest (red). Some ROIs in the left hemisphere (outlined in grey) represent brain regions that could not be seeded due to extensive injury. A & B. Pre- (A) and post-treatment (B) connectivity with a seed in left perilesional *pars triangularis*. C & D. Pre- (C) and post-treatment (D) connectivity with a seed in right *pars triangularis*. Post-treatment correlations suggest increased connectivity of seeded areas with perilesional frontal areas (denoted with *). Correlations between seeds and right temporal areas indicated no change or small decreases in connectivity. PTr – *pars triangularis*, POp – *pars opercularis*, MTG – middle temporal gyrus, STG – superior temporal gyrus, IpFG – inferior prefrontal gyrus.

severe impairments. We supplemented these quantitative measures with qualitative observations to best capture other potential changes in overall language function. Outcome measures have varied across adult stroke dysphasia brain stimulation studies (Geranmayeh et al., 2014), further limiting comparability across them and to our study.

We demonstrate preliminary feasibility of using multimodal, complementary neuroimaging to model and understand brain changes at baseline and accompanying intervention in childhood stroke. Our single-case, open-label design makes it challenging to determine the relative contributions of SLT, brain stimulation, subject variability, and placebo effects to the clinical and imaging changes observed. However, a substantial opportunity was afforded to examine multiple modalities, networks, structures, and functions in depth in a heavily disabled but highly motivated young person. We attempted to optimize our imaging methods using rigorous artefact repair, head motion correction algorithms, and multiple comparison family-wise corrections for thresholding activations. We could only measure these imaging outcomes once, so how they changed beyond 1 week in accordance with clinical function is unknown but would be very informative to include in future studies.

It is important to point out that while this study was not designed to be an efficacy study, single subject case controlled studies are still informative regarding aphasia treatment (Kiran et al., 2013; Thompson, 2006). The gold standard in treatment efficacy is an ABAB design in which treatment (B) is interleaved with no treatment (A) to illustrate efficacy (Thompson, 2006). The current study is more akin to the ABA design in which treatment was provided and then withdrawn. Clinical language function was systematically investigated by repeated measurements of dependent variables (i.e., picture naming was tested twice each day with trained and untrained stimuli), and response generalization to untrained tasks was monitored (i.e., naming of novel pictures, daily communication skills). Further investigations would benefit from more extensive establishment of baseline prior to intervention and the incorporation of an ABAB design (Kiran et al., 2013; Thompson, 2006). Ideally, a randomized controlled trial (RCT) including sham TMS and establishment of multiple pre-intervention baselines would be better able to assess the relative contributions of each intervention both independently and together.

Our connectivity analysis suggested that combined SLT and rTMS may alter neural network plasticity and re-order function within perilesional areas. The increased activation patterns observed post-treatment in left perilesional language areas is consistent with this and previous adult stroke dysphasia studies (Bhogal, Teasell, & Speechley, 2003; Bhogal et al., 2003; Cherney,

Patterson, Raymer, Frymark, & Schooling, 2008; Holland, Fromm, DeRuyter, & Stein, 1996; Naeser et al., 2012; Robey, 1998; Saur et al., 2006; Torres et al., 2013; Zumbansen & Thiel, 2014). Resting state networks showed increased connectivity for left perilesional areas as evidenced by increased ROI-to-ROI correlations posttreatment and more extensive areas of activation in seed-tovoxel analyses. It is possible that enhanced connectivity at rest in the lesioned hemisphere is evidence of a realignment of language networks back to a more balanced network that existed preinjury. Studies have shown that the degree of such intrinsic connectivity correlates with language function in dysphasic stroke patients (Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; van Hees et al., 2014; Zhu et al., 2014). Distinguishing language from domain-general executive functional networks in dysphasia is challenging (Geranmayeh et al., 2014). Our picture naming task was effortful for the patient with significant decision-making. attentional, and executive functions in addition to lexical components. Changes in complementary imaging modalities may be helpful in making such difficult distinctions.

Functionally relevant white matter tracts were definable except where obliterated by the stroke lesion. Convincing changes following intervention were not appreciable for FA or other diffusion variables. We did not anticipate this modality would be the most sensitive to intervention-induced changes. However, previous adult stroke dysphasia studies have suggested diffusion variables in these pathways can change in association with intervention (Schlaug, Marchina, & Norton, 2009). Longer term follow-up may also be needed to detect structural changes in WM. However, tractography may also provide important confirmation of other functional imaging. For example, we were able to isolate the ventral language Md/ILF pathway in the injured left hemisphere which appeared to be intact and corresponded well to the activation patterns in the anterior portion of left perilesional areas. Homologous language pathways also appeared to be intact in the right hemisphere. More specific fMRI language tasks might be able to probe different functional pathways relevant to these pathways (Kümmerer et al., 2013; Saur et al., 2008).

Interrogation of altered regional brain metabolism with MRS has not been described in childhood stroke. Large post-treatment increases in inositol concentrations in the left perilesional areas were intriguing given concurrent functional activation changes during language tasks and at rest in the same areas. The meaning of inositol changes on MRS is not well understood. Some suggest elevations are a marker of glial activation associated with neuronal injury or inflammation (Cloak, Chang, & Ernst, 2004; Ernst, Chang, & Arnold, 2003) while others suggest associations with cellular growth and proliferation through the phosphoinositide pathway (Moore, 1998). While purely speculative, one possibility is that increased inositol relates to recruitment of perilesional areas. MRS may have additional utility in assessing interventioninduced brain change (e.g. γ -Aminobutyric acid, GABA; Yang et al., 2014) and likely represents an under-utilized tool in the study of developmental plasticity. Our current MR protocol did not include the capacity for resolving GABA but this would be advantageous for future studies to address the role of such inhibitory neurotransmitters.

All of the above rests on the premise of altered interhemispheric balance following stroke. Such models are quite well established for motor function but more recent studies suggest this may only apply to certain subpopulations, such as those with subcortical strokes and less than severe hemiparesis. In fact, more complex and variable models including both inter- and intra-hemispheric reorganization and connectivity are being established (Pino et al., 2014). The question of the relative roles of the right and left hemispheres in aphasia rehabilitation is far from answered at this point and continues to be investigated (Anglade, Thiel, & Ansaldo, 2014;

Meinzer et al., 2011; Turkeltaub et al., 2012). Our single case cannot add substantially to these models that remain to be defined in childhood stroke. However, careful therapeutic trials employing multimodal advanced imaging to better understand mechanisms such as ours seem an essential component to further advancing childhood stroke rehabilitation.

In conclusion, we successfully employed contralesional, inhibitory rTMS in an adolescent with stroke-induced dysphasia. Intensive therapy coupled with rTMS can generate clinically significant naming improvements. SLT and rTMS-induced changes in language function in perilesional language areas may underlie these effects.

Conflict of Interest

None of the authors has any conflicts of interest to declare.

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