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Multimodal Adaptations to Expiratory Musculature-Targeted Resistance Training: A Preliminary Study in Healthy Young Adults

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ABSTRACT

Purpose: Exercise-induced adaptations, including neuroplasticity, are well studied for physical exercise that targets skeletal muscles. However, little is known about the neuroplastic potential of targeted speech and swallowing exercises. The current study aimed to gather preliminary data on molecular and functional changes associated with the neuroplastic effects of 4-week expiratory musculature-targeted resistance training in healthy young adults.
Method: Five healthy young adult men aged between 19 and 35 years, *M* (*SD*) = 28.8 (2.68) years, underwent 4 weeks of expiratory muscle strength training (EMST). We measured changes in maximum expiratory pressure (MEP), serum brain-derived neurotrophic factor (BDNF), and insulin-like growth factor 1 (IGF-1) levels at baseline and posttraining conditions. Furthermore, functional and structural magnetic resonance images were obtained to investigate the neuroplastic effects of EMST. We analyzed the effects of training using a linear mixed model for each outcome, with fixed effects for baseline and posttraining.
Results: MEP and serum BDNF levels significantly increased posttraining. However, this effect was not observed for IGF-1. A significant increase in functional activation in eight regions was also observed posttraining. However, we did not observe significant changes in the white matter microstructure.
Conclusions: Preliminary data from our study suggest targeted resistance training of expiratory muscles results in molecular and neuroplastic adaptations similar to exercise that targets skeletal muscles. Additionally, these results suggest that EMST could be a potential intervention to modulate (or prime) neurotrophic signaling pathways linked to functional strength gains and neuroplasticity.

Exercise-based therapies (regimes) have long been used to remediate various speech and swallowing disorders (Stathopoulos & Felson-Duchan, 2006). Borrowing from the physical exercise framework, these regimens are designed to deliver either an endurance (aerobic) stimulus or a resistance (strengthening) stimulus. An endurance stimulus aims to improve overall functional stamina and cardiovascular health by delivering repetitive low-intensity load over an extended period. A resistance training stimulus aims to improve the target muscle's strength, that is, its ability to generate maximum force. This is achieved by subjecting the target muscle to a high resistance load within a short-duration session. Resistance training that targets skeletal muscles increases strength by inducing adaptations at musculoskeletal and neural levels. At the periphery, the primary morphological adaptation that leads to increased strength includes an increase in the cross-sectional area of the whole muscle and individual muscle fibers (Folland & Williams, 2007). Increased motor unit recruitment, increased firing rates, and improved motor unit synchronization have been reported to occur

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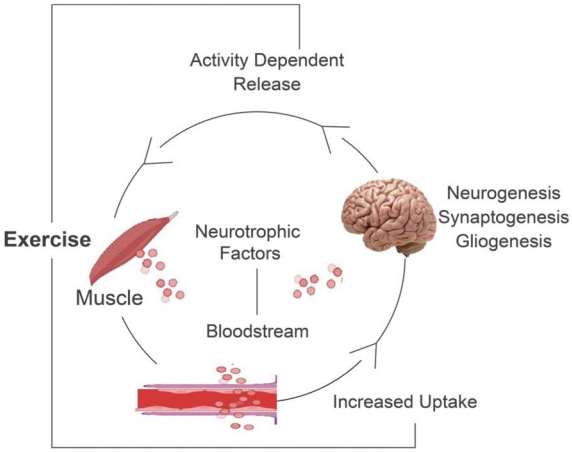
with resistance training in neurons (Gabriel et al., 2006). In addition to neuromuscular adaptations, the neuroplastic potential of exercise is well documented (Kleim & Jones, 2008), and both resistance and endurance training have been reported to induce long-lasting neuroplastic changes (El-Sayes et al., 2019; Nicolini et al., 2021).

Resistance training that targets skeletal muscles triggers a well-established cascade of events that mediates neuroplasticity (Chang et al., 2012; Cotman et al., 2007; Voss et al., 2011). For example, the concentration of neurotrophic factors such as peripheral brain-derived neurotrophic factors (BDNFs) and growth factors such as insulin-like growth factor 1 (IGF-1) is reported to increase in the systemic circulation of healthy adults after a minimum of 4 weeks of physical (strength) training (Cotman et al., 2007; Stillman et al., 2016). These factors enter the systemic circulation, cross the blood–brain barrier, and support neuroplasticity, which, in turn, improves motor performance and muscle recruitment for strength-based tasks (Chang et al., 2012; El-Sayes et al., 2019; Kowiański et al., 2018). BDNF is a neurotrophic protein, and early animal models have reported its association with synaptic plasticity, neuronal growth, neuronal survival, and cognitive processes. Similarly, IGF-1 is an important growth factor that, together with BDNF, supports neuroplasticity. It also plays a crucial role in promoting the survival of neuronal structure and function across the lifespan (Chow et al., 2021; Cotman & Berchtold, 2002; Cotman et al., 2007).

Several experimental studies have demonstrated that BDNF and IGF-1 can cross the blood–brain barrier and influence growth processes including gliogenesis (Cheng et al., 2007), neurogenesis (Van Praag, 2008), and synaptogenesis (Kowiański et al., 2018; Lista & Sorrentino, 2010) within the central nervous system (CNS; Chow et al., 2021; Cotman & Berchtold, 2002; Cotman et al., 2007). Upon reaching the CNS, BDNF binds and activates its receptor, tyrosine kinase receptor B (TrkB), which then triggers the phosphorylation and activation of TrkB in its cytoplasmic and kinase domains. Activation of TrkB leads to the recruitment and activation of specific proteins in the cytoplasm, resulting in the activation of signaling pathways that regulate cognitive processes and synaptic plasticity (Blum & Konnerth, 2005). IGF-1 is believed to function in multiple ways to aid in neuroplasticity. First, it activates specific signaling pathways and interacts with other neurotrophic factors like BDNF to promote various aspects of brain development, adult neurogenesis, neuroplasticity, and neuroprotection. Second, IGF-1 binds to the IGF-1 receptor (IGF1R), resulting in the activation of its IGF1R and contributes to diverse physiological effects such as behavioral modifications, neuroprotection, and neuroplasticity (Llorens-Martín et al., 2010). Additionally, exercise is reported to modulate BDNF and IGF-1 levels in the bloodstream and facilitate their uptake through the blood–brain barrier and into the CNS. Several studies have consistently demonstrated that increased levels of BDNF and IGF-1 in the systemic circulation are sensors for enhanced adult brain plasticity (Chow et al., 2021; Cotman & Berchtold, 2002; Cotman et al., 2007). Figure 1 presents a simplified version of the events involved in physical exercise–induced brain plasticity.

Of the two types, resistance (strength) training is of specific interest to dysphagia rehabilitation. Resistance training for dysphagia rehabilitation targets various swallowing-related muscles and can vary in training specifications (dosage; Burkhead, 2017; Félix-Lusterman et al., 2021; Rogus-Pulia & Connor, 2016). Some dysphagia-targeted resistance training programs include base of tongue exercises, Shaker's exercise, expiratory muscle strength training (EMST), and progressive tongue-to-palate resistance training. Interested readers are referred to the works of Rogus-Pulia and Connor (2016) and, more recently, Félix-Lusterman et al. (2021) for a detailed narrative on other types of resistance exercise used in dysphagia rehabilitation. Although the impact of resistance training on swallowing safety and efficiency remains debated (Huckabee & Lamvik-Gozdzikowska, 2018; Rogus-Pulia & Connor, 2016), these regimes are used globally in routine clinical practice. Moreover, strength training is the standard of care for remediating dysphagia (Burkhead et al., 2007; Carnaby & Harenberg, 2013; Rangarathnam & Desai, 2020; Rumbach et al., 2017) even when a lack of strength or amplitude of movement is not the primary dysfunction within the swallow. One intriguing perspective on the use of strength-based exercises in dysphagia rehabilitation is the potential connection to experience-dependent neuroplasticity. Although the primary focus of strength training

Figure 1. A simplified mechanistic model of exercise-induced neuroplasticity.



is often on improving muscle function, it is possible that such exercise in swallowing musculature yields similar neuroplastic potential to what has been reported in limb exercise research from exercise sciences (Chang et al., 2012; El-Sayes et al., 2019). This potential connection between strength training and neuroplasticity suggests that resistance exercises may have broader implications beyond simply targeting muscle strength. By augmenting the adaptive capacity of the CNS, these exercises hold the potential to facilitate improvements in swallowing function through neural reorganization, thereby providing an indirect avenue for rehabilitation.

Among the resistance exercises, there is a growing body of evidence suggesting EMST (Sapienza, 2008; Sapienza et al., 2011) is efficacious in remediating dysphagia and preventing age- and disease-induced swallowing function decline (Brooks et al., 2019; Eom et al., 2017; Hutcheson et al., 2018; Mancopes et al., 2020; Patchett et al., 2017; Plowman et al., 2019). By design, EMST incorporates several exercise training principles, such as progression, overload, repetition, detraining, and transference (Burkhead, 2017; Rogus-Pulia & Connor, 2016) and meets the requirements of a resistance training regime (Félix-Lusterman et al., 2021; Rogus-Pulia & Connor, 2016). Mechanistically, EMST targets the expiratory musculature, specifically the abdominal and the internal intercostal muscles. In line with the expectations of resistance training, EMST results in increased (strength) force production capabilities, functionally measured as the maximum expiratory pressure (MEP; Sapienza & Hoffman, 2020). Furthermore, studies have shown that EMST can induce musculoskeletal and neural adaptations similar to those exhibited by resistance training that target skeletal muscles (Pauloski & Yahnke, 2021; Sapienza & Wheeler-Hegland, 2006). Although it is recognized that the ultimate goal of speech and swallowing targeted exercises is neuroplastic changes that facilitate sustained improvements in functional behavior (Macrae & Humbert, 2013; Zimmerman et al., 2020), quantitative evidence remains sparse. Moreover, no mechanistic models incorporate multimodal quantitative data to explain how these targeted exercises may induce neuroplasticity. This knowledge gap limits our ability to design and precisely optimize exercises to remediate swallowing disorders due to aging and disease.

Neuroimaging is an effective approach to assessing neuroplasticity, which helps recognize brain structure and function changes over time. Among the various modalities employed to measure neuroplasticity, functional magnetic resonance imaging (fMRI) and diffusion-weighted magnetic resonance imaging (DW-MRI) allow noninvasive and precise identification of brain function and structural changes due to training (or exercise). fMRI indirectly measures neural activity by detecting blood oxygen level–dependent (BOLD) level changes in response to an experimental task or stimulus while offering high spatial resolution (Norris, 2006). On the other hand, DW-MRI measures the diffusion of water molecules along the white matter (WM) tracts to describe their structural properties. More specifically, diffusion tensor imaging establishes a framework for obtaining, analyzing, and quantifying microstructural properties and organization of WM tracts (Basser & Jones, 2002). BOLD activity measured through fMRI and WM properties assessed using DW-MRI can collectively inform about neuroplastic changes. In addition to neuroimaging, behavioral measurements help elucidate the relationship between brain structure, function, and behavior. Multimodal studies, such as those combining neuroimaging and behavioral measures, can augment our understanding of neuroplastic changes (Auriat et al., 2015; Reid et al., 2016).

Research Objectives

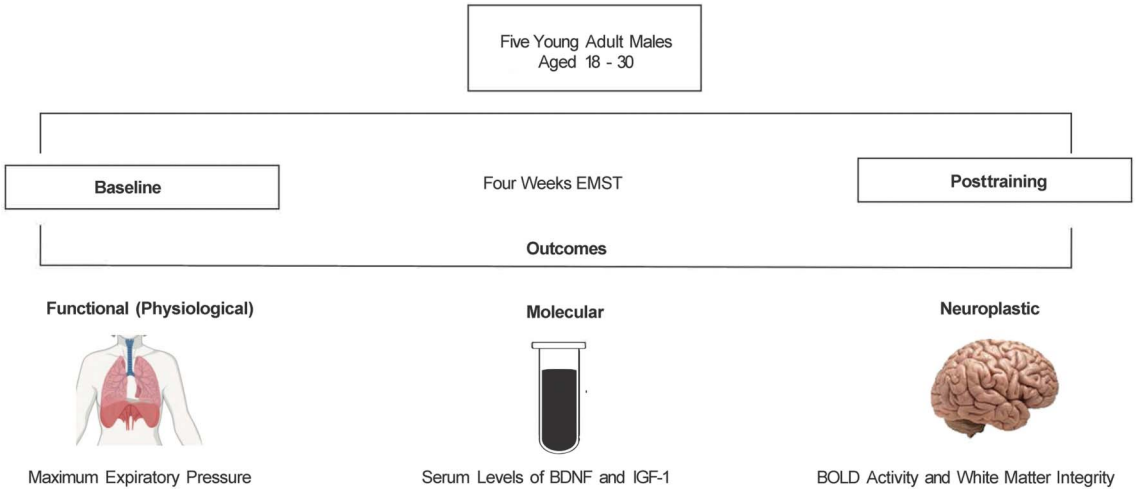
Histologically, expiratory musculature, the target of EMST, are also skeletal muscles (Sapienza & Hoffman, 2020), and previous studies have established that the expiratory musculature's patterns of adaptation to resistance training are similar to that of skeletal muscles (Pauloski & Yahnke, 2021; Sapienza & Wheeler-Hegland, 2006). Building upon established models of physical exercise–induced neuroplasticity, this study investigates whether expiratory EMST can induce similar molecular, functional, and neuroplastic adaptations. This study aims to gather preliminary multimodal data on molecular and functional changes associated with the neuroplastic effects of a 4-week EMST in healthy young adults. The specific objectives of the study are as follows: (a) to identify differences in pre- and posttraining concentrations of peripheral serum BDNF and IGF-1 levels and subsequent functional changes in MEP, (b) to characterize changes in pre- and posttraining BOLD signal activity at a whole-brain level and within swallowing sensorimotor networks (Huang et al., 2022; Lowell et al., 2012), and (c) to identify pre- and posttraining microstructural changes in the WM tract at a whole-brain level via tract-based spatial statistics (TBSS) and in specific WM tract implicated with swallowing (Alvar et al., 2021) via fractional anisotropy (FA).

Method

Study Design

This study used an exploratory pre–post within-group repeated-measures design. Figure 2 shows an overview of the current study. The study protocol was approved by the University of Nebraska–Lincoln institutional review board (#23042).

Figure 2. Methodological overview and outcomes. EMST = expiratory muscle strength training; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor 1; BOLD = blood oxygen level dependent.



Participants

Five healthy young adults assigned male at birth aged between 19 and 35 years, *M* (*SD*) = 28.8 (2.68) years, were recruited from the community, and all participants signed a written informed consent form. Based on previously reported meta-analytic findings on MEP by Templeman and Roberts (2020), a priori sample size calculation (G*Power Version 3.1.9.4) indicated that a power of 0.8 required three participants. Biological sex and age differences have been reported in the functioning and performance of respiratory muscles (Watsford et al., 2007), and the roles of hormones and muscle mass may also influence the training regime (Kraemer & Ratamess, 2005; Roberts et al., 2020); hence, only young adult men were included to minimize confounding variables and enhance the study's internal validity. All participants had lung volumes and capacities within the normal range as measured using the Spirometry module of PowerLab (Model 16/35, AD Instruments, 16-bit, ± 5 V, 1 KHz) with LabChart software (Version 8.1.9, AD Instruments) on a laptop computer (WIN10). They also had a body mass index (BMI) in the healthy range, *M* (*SD*) = 21.86 (1.06), and were in good pulmonary health with no smoking history by self-report. Furthermore, voice disorders and swallowing dysfunction were ruled out using the Voice Handicap Index-10 (Rosen et al., 2004) and the Dysphagia Handicap Index (Silbergleit et al., 2011), respectively. Table 1 shows each participant's demographic characteristics.

All participants were right-handed (based on the Edinburgh Handedness Inventory; Oldfield, 1971) and recreationally active based on McKay et al.'s (2022) physical activity classification framework. A strong positive correlation has been reported between physical fitness (exercise) status and strength performance (McKay et al., 2022), and there is a positive bidirectional relationship between exercise status and circulating blood serum levels of BDNF (Cotman et al., 2007) and IGF-1 (Vega et al., 2010). Although reported results are somewhat inconsistent, literature on physical exercise suggests that short-term (single-bout) physical activity can influence circulating BDNF and IGF-1 levels (Fernández-Rodríguez et al., 2022; Jiang et al., 2020). Participants were instructed to refrain from performing exercises that were not part of their normal routine to control this extraneous variable. Furthermore, participants were instructed not to perform physically demanding activities such as lifting or moving heavy-weight objects during training. All participants maintained a daily log of their physical activities for the training period.

EMST

The EMST-150 device (Aspire Respiratory Products) was used to deliver the targeted resistance training to expiratory musculature. Before beginning the training, the

Table 1. Demographics of five male participants.

Participant	Age (years) *M* (*SD*) = 28.8 (2.68)	BMI *M* (*SD*) = 21.86 (1.06)	Race
1	26	22.86	Asian
2	30	20.06	Caucasian
3	32	21.91	African
4	26	22.16	Asian
5	30	22.33	Caucasian

Note. BMI = body mass index.

participant's MEP was assessed using instrumentation reported in Dietsch et al.'s (2024) study. The training followed the procedure described and reported by Sapienza (2008), and each training session was performed under a controlled dosage of five sets of 5 breaths × 5 days/week at $75\%_{MEP}$ over 4 weeks (Sapienza, 2008; Sapienza et al., 2011). Participants' MEP was measured at the end of each week, and the load for subsequent training weeks was progressively adjusted to match any changes in respiratory strength gains.

Outcome Measurements

The following biochemical, behavioral/physiological, and neuroimaging measures were obtained before and after training. Figure 3 shows the timeline of measurements.

- Behavioral/physiological measure: The primary outcome of interest was the MEP (in cmH_2O).
- Biochemical assay: A registered phlebotomist collected blood (nonfasting) samples from the participant's antecubital vein at the Nebraska Medicine, University Health Center. The drawn blood samples were stored in sterile serum separator tubes at room temperature for 20 min to allow for clotting and then centrifuged for 10 min at 4°C to obtain serum. The separated serum samples were placed in aliquots and stored at −80°C until analysis.
- Neuroimaging: Multiband whole-brain echo planar imaging MRI scans were obtained on a Siemens 3 T Magnetom Skyra at the University of Nebraska–Lincoln's Center for Brain, Biology, and Behavior. High-resolution T1 anatomical, swallowing task–based, and diffusion-weighted images (DWIs) were collected. The technical specifications of T1 anatomical, swallowing task-based imaging runs are described elsewhere (see Dietsch et al., 2023). The imaging parameters for DWI were as follows: flip angle/echo time/repetition time/acquisition time/the field of view = 90°/88 ms/8,320 ms/5:59 min/256 × 256 mm; b = 1,000 s/mm^2. A block design was employed in the fMRI experiment, with participants completing three functional runs in each neuroimaging session. Each run comprised 10 saliva swallow blocks ("SWALLOW") alternating with rest periods ("NO SWALLOW"), which are 10 s each in duration and a jittered intertrial interval (3, 4, or 5 s) presented in a pseudorandom order. These cues were presented through PowerLab (Model 16/35, AD Instruments) with LabChart software (v8.1.9, AD Instruments) on a laptop computer (WIN10). Swallowing compliance was monitored using BIOPAC's MRI-compatible surface electromyography (sEMG) set and AcqKnowledge data acquisition system (BIOPAC Systems, Inc.). The positive and negative electrodes were placed on the participant's submental muscle, and the ground electrode was placed on the clavicle. Each functional run was about 3.6–4 min long, and the entire session lasted about 12 min.

Analysis

Biochemical Assays

The analysis began by acclimatizing the serum samples, which were thawed in ice for further processing. BDNF and IGF-1 levels analysis followed the manufacturer's guideline for recombinant protein assay (Unconjugated, lyophilized) sandwich enzyme-linked immunosorbent assay for BDNF and IGF-1 (ABCAM). Assays were performed in triplicates, blinded to the participant's condition, and the levels of BDNF concentrations will be reported as pg/ml and IGF-1 in ng/ml.

Neuroimaging

Anatomical images were reconstructed and segmented using the FreeSurfer processing pipeline (Desikan et al., 2006). Functional imaging reconstruction, processing, and analysis were conducted using the Analysis of Functional Neuroimages package (AFNI; Cox, 1996). Figure 4 shows the neuroimaging analysis pipeline used in the current study.

After processing, a whole-brain analysis was performed to evaluate differences in pre- and posttraining BOLD activity. Along with a whole-brain analysis, we also investigated differences in BOLD activity for regions frequently implicated in swallowing (Huang et al., 2022; Lowell et al., 2012). Further details of the fMRI processing are described in Appendix A. The DWIs were preprocessed and analyzed using the DIPY pipeline (Garyfallidis et al., 2014), FMRIB Software Library (FSL), and the

Figure 3. Timeline of measurement. MEP = maximum expiratory pressure; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor 1; MRI = magnetic resonance imaging.

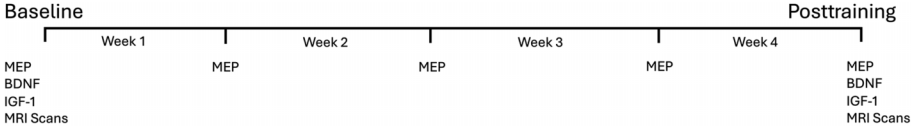
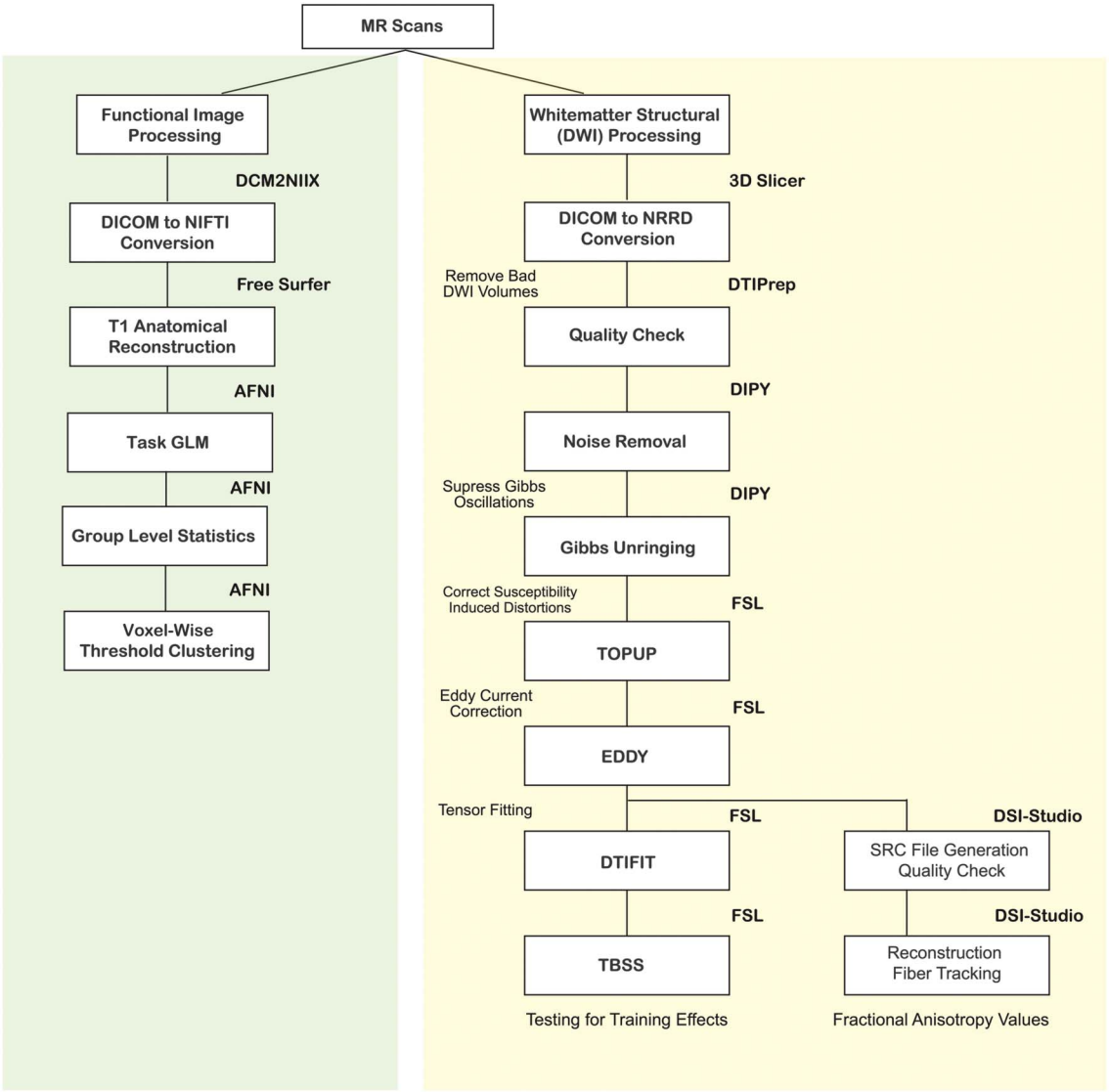


Figure 4. Analysis pipeline for processing structural and functional neuroimaging. MR = magnetic resonance; DWI = diffusion-weighted image; AFNI = Analysis of Functional Neuroimages; GLM = general linear model; FSL = FMRIB Software Library; TBSS = tract-based spatial statistics.



DSI Studio (Yeh et al., 2013) to obtain FA values for WM tracts implicated in swallowing (Alvar et al., 2021) as shown in Figure 4. The following is a brief description of the steps involved in preprocessing: (a) conversion of DWI DICOM data to NRRD, (b) brain mask generation and removal of nonbrain tissue, (c) DWI quality control check to remove DWI volumes with artifacts, (d) motion correction and Gibbs unringing, and (e) correction for susceptibility-induced distortions and eddy current.

TBSS

The preprocessed and eddy current corrected data were used to fit the diffusion tensor model for each participant's data at the voxel level using the FSL's *dtifit* function. Following the tensor fitting, the output FA images were further analyzed using TBSS (Smith et al., 2006), where individual diffusion maps were prepared for voxel-based group analysis. This was done by aligning all participants' FA images to a template of averaged FA images (FMRIB-58) in Montreal Neurological Institute space using a nonlinear registration algorithm. Then, a grouped mean FA image was created and thinned to generate a grouped mean FA skeleton of the WM tracts. Finally, all participant's aligned FA images were projected onto the grouped mean FA skeleton by filling the grouped mean FA skeleton with FA values from the nearest relevant tract center. This second local co-registration step

improves alignment problems and reduces significant intersubject variability. A design matrix and a contrast file were generated to compare baseline and posttraining changes, and voxel-wise statistics on the skeletonized FA data were performed using the randomise function with threshold-free cluster enhancement option. The randomise function of TBSS tests for group differences, for example, baseline versus posttraining. The output contrast-1 from the randomise function tests for the assumption, baseline > posttraining, and contrast-2 tests for posttraining > baseline.

FA

DSI Studio (Yeh et al., 2013) was used to extract FA values for specific WM tracts implicated with swallowing (Alvar et al., 2021). Each participant's preprocessed and eddy current corrected DWI images were converted to create a .src file, which was further examined using a quality control procedure to ensure its integrity and quality. To obtain a .fib file, these image files were analyzed using the DSI Studio's reconstruction and fiber tracking steps. Finally, the .fib file was used to extract FA values for specific WM tracts using the tract profiles function. A glossary of technical terms is provided in Appendix B.

Statistical Analysis

The expected independent variable was the training condition (baseline and posttraining). The expected dependent variables (DVs) were MEP, serum level concentrations of BDNF and IGF-1, BOLD signal activity, and WM FA values. Age and BMI were used as covariates. A linear mixed model (LMM) with fixed effects for baseline and posttraining was performed. Each DV (MEP, serum levels of BDNF and IGF-1, BOLD signal activity, and WM FA values) was considered separately in the model. Participant ID was included as a random effect to account for the repeated measures within the same participant.

Results

Molecular and Functional Adaptations

A posttraining review of the participants' daily exercise logs did not reveal any deviations from their normal routine. Table 2 shows MEP, BDNF, and IGF-1 level changes from baseline to posttraining. The results of the LMM revealed that there was a statistically significant effect of training on MEP, $F(1, 4) = 82.388$, $p < .001$; $\eta^2 = .83$, and serum BDNF levels, $F(1, 4) = 29.045$, $p = .006$; $\eta^2 = .58$, but not on serum IGF-1 levels, $F(1, 4) = 0.004$, $p = .951$; $\eta^2 = .09$. Participants had significantly higher MEP and serum BDNF levels at posttraining compared to the baseline. Figure 5 shows each participant's weekly gains in MEP, and Figure 6 shows the violin plots for MEP, BDNF, and IGF-1 levels across the baseline to posttraining conditions. The LMM estimates for MEP, BDNF, and IGF-1 are shown in Table 3.

Table 2. Mean (standard deviation) of maximum expiratory pressure, brain-derived neurotrophic factor, and insulin-like growth factor 1 levels across baseline and posttraining.

Measure	Baseline	Posttraining	% Change
MEP (cmH_2O)	89.22 (5.54)	138.91 (11.97)	55.6
BDNF (pg/ml)	1090.52 (63.76)	1187.11 (35.43)	9
IGF-1 (ng/ml)	3.915 (0.58)	4.1 (0.1)	4.7

Note. MEP = maximum expiratory pressure; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor 1.

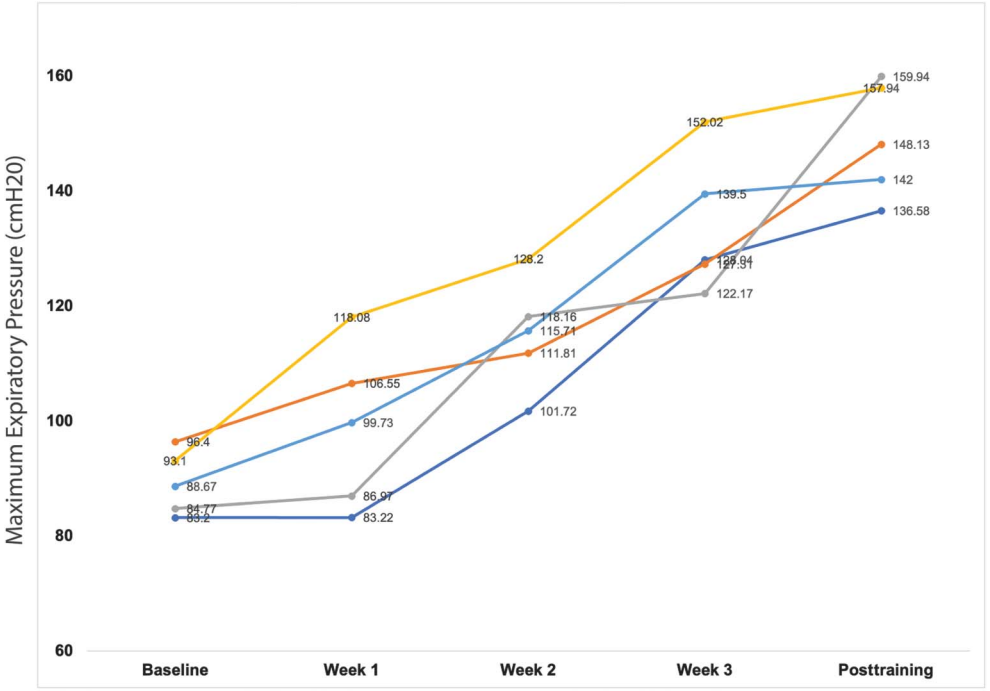
Neuroplastic Adaptations

A visual inspection of the sEMG signal confirmed that all participants swallowed during the fMRI task. Furthermore, participants confirmed through self-reporting that they performed an actual swallow during the scans. A multivariate modeling was performed within AFNI using the *3dMVM* program (Chen et al., 2014) with conditions (swallow vs. no swallow) and time (baseline vs. posttraining) as within-subject factors. Further details of the analysis and modeling are described in Appendix A. This analysis revealed a significant interaction in eight regions (cluster-adjusted p value of .05) at a whole-brain level. The pattern of this interaction effect was such that we observed a significantly larger difference between the swallow and no-swallow tasks posttraining compared to the baseline. Figures 7–10 show the eight significant regions and changes in their beta-weights across baseline and posttraining conditions. Table 4 shows their coordinates, cluster size, and effect descriptors. A sub-objective of the study was to characterize changes in baseline and posttraining BOLD signal activity within established swallowing sensorimotor networks (Huang et al., 2022; Lowell et al., 2012). However, swallowing sensorimotor networks, including the primary motor cortex (M1), the primary somatosensory cortex (S1), the insula, and the cerebellum, were consistently identified after applying cluster corrections. Therefore, separate ROI analyses were not performed.

WM Microstructural Adaptations

Figure 11 shows the TBSS results for contrast-2 (posttraining > baseline), and this analysis did not reveal significant voxel-wise differences between baseline and posttraining conditions. Table 5 shows WM tracts of

Figure 5. Weekly gains in maximum expiratory pressure for each participant.



interest and their FA values across baseline and posttraining conditions. When comparing the FA values of individual WM tracts of interest, we observed a minimal increase in mean FA from baseline to posttraining across all the tracts. However, the effect was not statistically significant.

Discussion

Functional and physiological adaptations to targeted exercises such as the EMST have been extensively studied (Pauloski & Yahnke, 2021; Sapienza et al., 2011; Sapienza & Wheeler-Hegland, 2006), and convergent findings from numerous studies suggest that EMST is efficacious in remediating swallowing deficits in a wide range of conditions (Brooks et al., 2019; Eom et al., 2017; Hutcheson et al., 2018; Mancopes et al., 2020; Patchett et al., 2017; Plowman et al., 2019). In addition to functional and physiological adaptations, exercise science literature reports adaptations at molecular and neural levels due to targeted resistance training. The current study aimed to investigate whether EMST induces similar changes at a molecular level and whether these changes collectively lead to beneficial neuroplastic changes.

Functional Adaptations

A resistance training regime aims to increase functional strength and achieve peripheral or muscular adaptation. As expected, EMST significantly increased functional

Figure 6. Changes in maximum expiratory pressure (left panel), serum brain-derived neurotrophic factor (middle panel), and serum insulin-like growth factor 1 (right panel) across baseline and posttraining. MEP = maximum expiratory pressure; BDNF = brain-derived neurotrophic factor; IGF-1 = serum insulin-like growth factor 1.

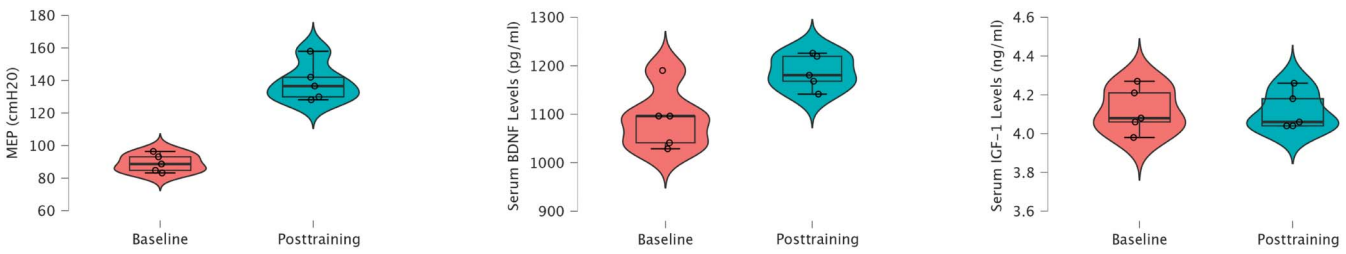


Table 3. Linear mixed-model fixed-effects estimates.

Measure	Estimate	*SE*	*t* (1, 4)	*p* value
MEP	24.845	2.737	9.077	< .001
BDNF	48.293	8.961	5.389	.006
IGF-1	0.002	0.030	0.066	.951

Note. *SE* = standard error; MEP = maximum expiratory pressure; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor 1.

strength (MEP) from baseline to posttraining in the current study. MEP gains observed in the current study align with the expectations of a strength training regime and are consistent with previous studies (Baker et al., 2005; Sapienza & Wheeler-Hegland, 2006; Templeman & Roberts, 2020). Two peripheral mechanisms contributing to strength gains are muscle fiber shifts and muscular hypertrophy (Folland & Williams, 2007; Plotkin et al., 2021). In addition to these mechanisms, neural factors such as increased and synchronous motor unit firing and increased motor unit recruitment also contribute to strength gains, particularly during the initial stages of training (Gabriel et al., 2006). Although the present study did not evaluate the changes in muscle fiber composition or the cross-sectional area, we believe such adaptations might not have occurred in the periphery. Instead, we suspect that the gains observed in the current study may be due to increased neural involvement from the training. This speculation is based on the dosage of our training protocol, which may not have been sufficient to induce measurable changes in muscle fiber size or composition within the timeframe of our study.

Studies on physical strength training suggest that significant hypertrophy of (limb) skeletal muscles typically requires more extended training periods (typically greater than 12 weeks) and potentially higher training volumes (intensity greater than 85%$_{Max}$ and up to 10 repetitions per set) than those used in our study (Folland & Williams, 2007; Plotkin et al., 2021; Schoenfeld, 2010). However, strength training, even over relatively short durations such as our 4-week protocol at 75%$_{MEP}$, elicits neural adaptations early in the training process. Such neural adaptations can enhance muscle force production by improving

Figure 7. Bilateral insular clusters and its beta-weights associated with the interaction effect. Whiskers represent standard error; the color bar reflects *F* values. MNI = Montreal Neurological Institute.

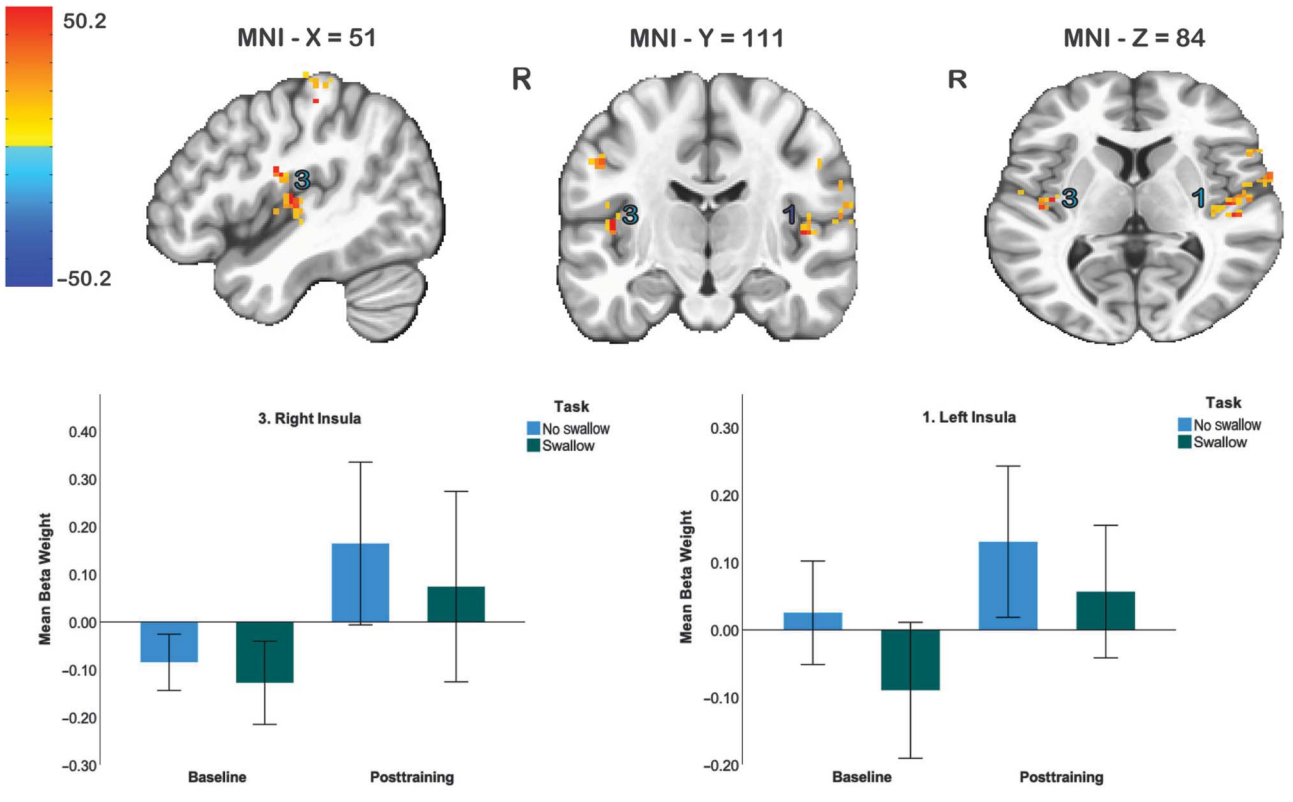
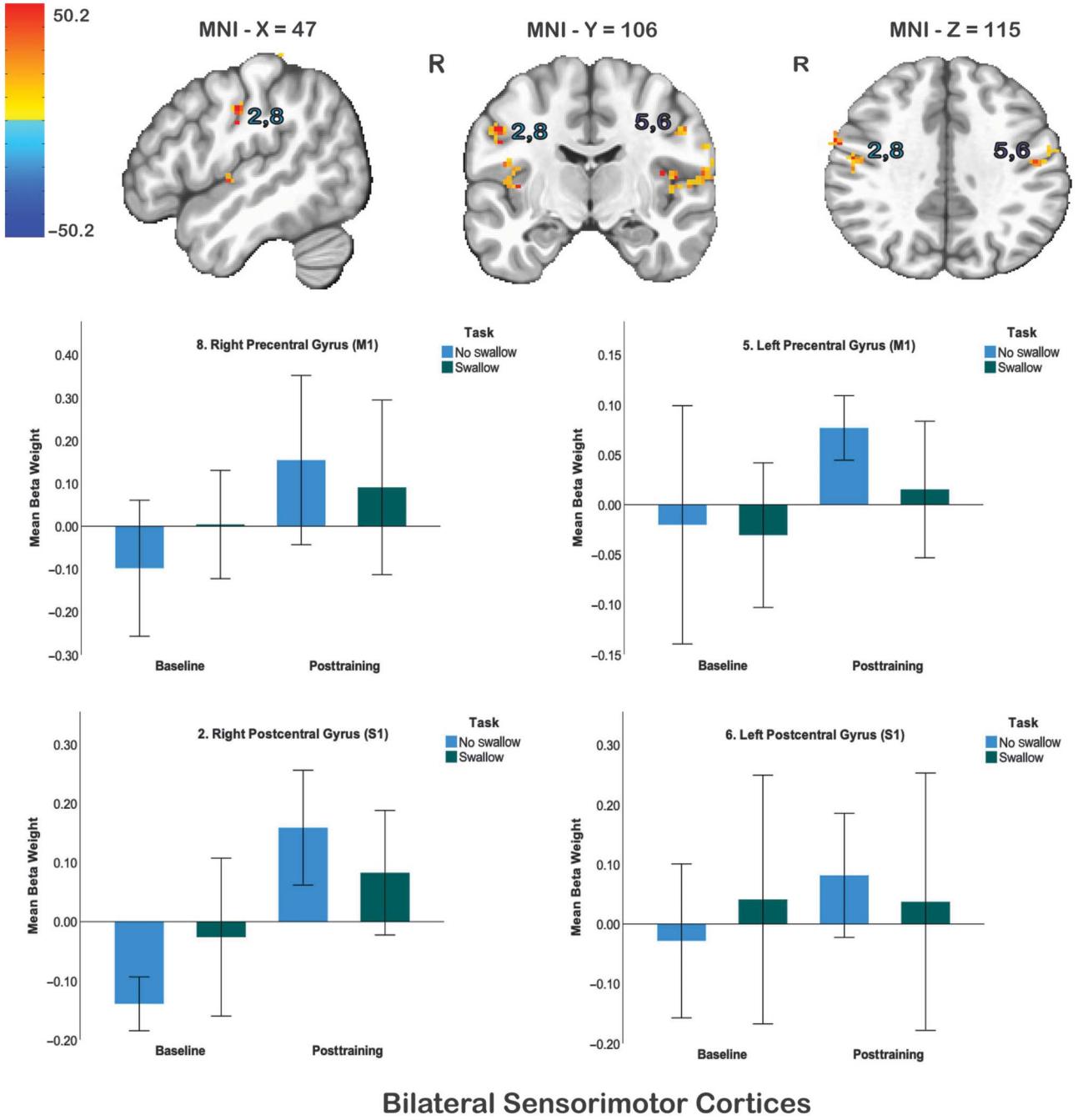
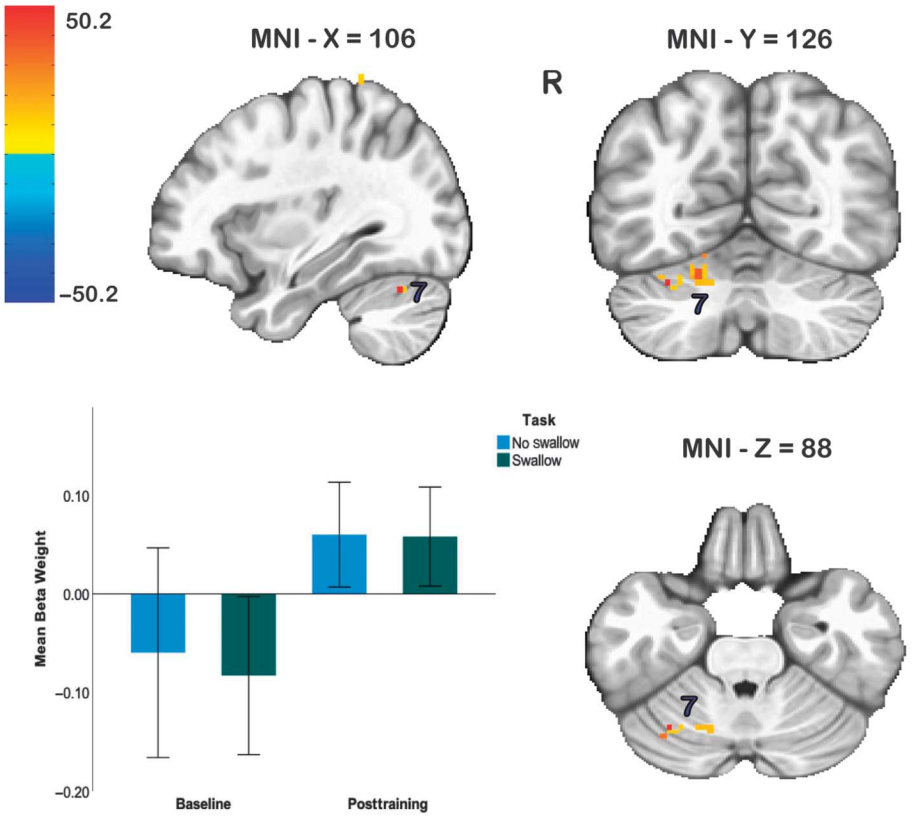


Figure 8. Bilateral sensorimotor cortices clusters and its beta-weights associated with the interaction effect. Whiskers represent standard error; the color bar reflects *F* values. MNI = Montreal Neurological Institute.



synchronous motor unit firing and increasing motor unit recruitment without concurrent increases in muscle fiber size or cross-sectional area (Gabriel et al., 2006). Although the sEMG signals recorded in our study could provide information about changes in motor unit activation after training, it is essential to note that the sEMG instrumentation did not allow for high-density recording. They were primarily used to monitor swallowing when the participants were in the MR scanner. Additionally, the MR scanner noise was also captured, potentially compromising the data. Consequently, we refrained from analyzing the sEMG amplitudes. We suggest future studies investigate expiratory muscle histological changes alongside motor unit activation following EMST. Understanding these

Figure 9. Right cerebellar clusters and its beta-weights associated with the interaction effect. Whiskers represent standard error; the color bar reflects *F* values. MNI = Montreal Neurological Institute.



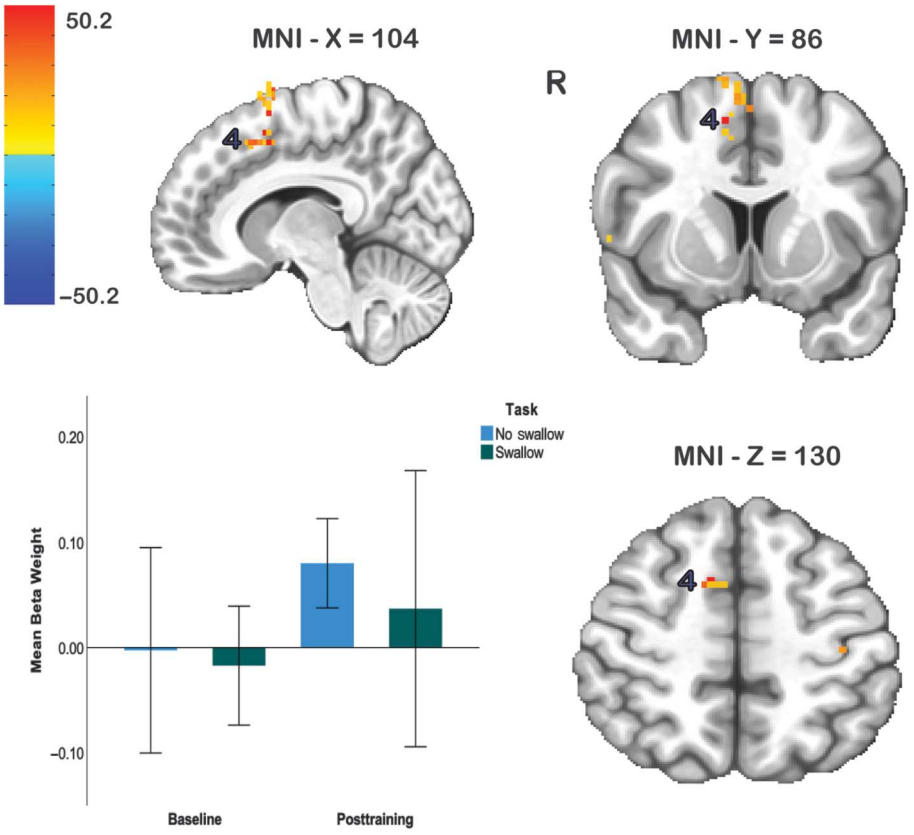
dynamics is essential to gaining insights into neuromuscular adaptations, which are crucial for optimizing training regimes.

Molecular Adaptations

In the current study, we hypothesized that functional strength gains due to EMST would be accompanied by increased circulating serum BDNF and IGF-1 levels. Our data partially support this hypothesis, showing a 9% increase in serum BDNF levels and a 4.7% increase in IGF-1 levels from baseline to posttraining. However, only the increase in serum BDNF levels reached statistical significance. The observed increase aligns with previous studies that have demonstrated exercise-induced upregulation of BDNF, particularly in response to resistance training protocols (Chow et al., 2021; Cotman & Berchtold, 2002; Cotman et al., 2007; El-Sayes et al., 2019). Our findings indicate that EMST may be a potential intervention to modulate (prime) BDNF neurotrophic signaling pathways associated with functional strength gains and neuroplasticity. Furthermore, the pattern of results observed in our study can be attributed to two key factors: exercise target specificity and temporal dynamics of BDNF and IGF-1 release–uptake cycles. Additionally, while the small sample size must be acknowledged, a potential ceiling effect for IGF-1 may have influenced our findings.

EMST is designed to target expiratory musculature and enhance neuromuscular control specific to expiratory force generation. This targeted neuromuscular training likely explains the significant increase in serum BDNF levels. BDNF is a key neurotrophin that supports the survival, growth, and differentiation of neurons and is frequently implicated in the mechanisms underlying learning, memory, and functional strength gains (Cotman & Berchtold, 2002; Cotman et al., 2007). The specificity of EMST in stimulating neural adaptations could be well aligned with the role of BDNF, which may account for the observed significant increase. In contrast, IGF-1 is a systemic growth factor that responds more robustly to training modalities that induce substantial muscle hypertrophy, such as whole-body strength

Figure 10. Right supplementary motor area clusters and its beta-weights associated with the interaction effect. Whiskers represent standard error; the color bar reflects *F* values.



training. The targeted nature of EMST may not provide a sufficient stimulus for significant changes in systemic IGF-1 levels, resulting in the nonsignificant increase observed (Chow et al., 2021; Cotman & Berchtold, 2002; Cotman et al., 2007; Llorens-Martín et al., 2010).

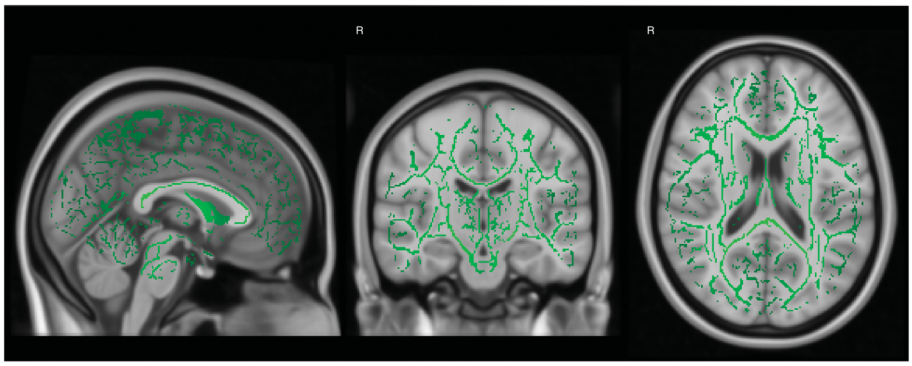
Temporal dynamics could also be crucial in the observed differential effects. BDNF levels can respond quickly to neural activity and exercise, often showing acute increases following training sessions (Fernández-Rodríguez et al., 2022). This immediate responsiveness

Table 4. Coordinates, cluster size, and effect descriptors for eight regions associated with the interaction effect.

Sl. No	Cluster	Coordinates (MNI-152–2009)			Volume (mm^3)	Direction of change
		RL	AP	IS		
1	Left insula	–53	7	7	153	PT > BL
2	Right postcentral gyrus	–59	6	31	94	PT > BL
3	Right insula	43	12	7	78	PT > BL
4	Right supplementary motor area (SMA)	–8	–9	60	73	PT > BL
5	Left precentral gyrus	19	41	69	61	PT > BL
6	Left postcentral gyrus	41	25	60	52	PT > BL
7	Right cerebellum (ventral dentate nuclei)	23	63	–22	27	PT > BL
8	Right precentral gyrus	55	9	37	18	PT > BL

Note. MNI = Montreal Neurological Institute; BL = baseline; PT = posttraining; RL = right–left; AP = anterior–posterior; IS = inferior–superior.

Figure 11. Results of tract-based spatial statistics testing. The grouped mean fractional anisotropy skeleton is represented in green and overlaid on an Montreal Neurological Institute–125 template.



aligns with the significant increase in serum BDNF levels posttraining. On the other hand, IGF-1 levels may exhibit more complex temporal dynamics, with changes potentially requiring a longer duration to become evident. Additionally, IGF-1 is a generic growth factor; its levels are reported to be influenced by a variety of factors, such as nutrition, sleep, and overall health, which can introduce variability and potentially mask the effects of the training within the timeframe of our study (Pickersgill et al., 2022; Stein et al., 2018). Another important consideration is the potential ceiling effect for IGF-1 levels. Our participants were recreationally active, healthy young adults who likely had baseline IGF-1 levels already within an optimal range. This high baseline could limit the potential for further significant increases in response to training, as physiological limits on IGF-1 production may have been reached. Expanding participant sample size and diversity to include older adults and women could mitigate these effects.

Neuroplastic and WM Microstructural Adaptations

In line with the study's hypothesis, an increase in activation was observed in brain regions from baseline to the posttraining period, suggesting the neuroplastic potential of EMST. The whole-brain analysis revealed a significant interaction in eight regions (see Table 3), such that there was a greater difference between the swallow and no-swallow tasks posttraining than the baseline. This suggests that the training had a significant effect on these regions, resulting in increased differentiation between the two tasks after training. The regions that showed significant activation were bilateral sensorimotor cortices, the insula,

Table 5. Effect of expiratory musculature-targeted resistance training on fractional anisotropy values of white matter tracts of interest.

WM tract of interest	FA	
	BL	PT
Right Superior Longitudinal Fasciculus (R_SLF)	0.535 (0.01)	0.542 (0.01)
Left Superior Longitudinal Fasciculus (L_SLF)	0.526 (0.02)	0.531 (0.02)
Corpus Callosum (CC)	0.700 (0.03)	0.718 (0.03)
Right Corona Radiata (R_CR)	0.476 (0.02)	0.483 (0.02)
Left Corona Radiata (L_CR)	0.458 (0.02)	0.463 (0.01)
Right Internal Capsule (R_IC)	0.580 (0.04)	0.583 (0.03)
Left Internal Capsule (L_IC)	0.624 (0.01)	0.63 (0.02)
Right External Capsule (R_EC)	0.478 (0.01)	0.483 (0.05)
Left External Capsule (L_EC)	0.566 (0.04)	0.573 (0.04)
Right Corticospinal Tract (R_CST)	0.590 (0.04)	0.596 (0.01)
Left Corticospinal Tract (L_CST)	0.637 (0.02)	0.646 (0.03)
Right Cingulum (R_Cng)	0.588 (0.04)	0.595 (0.04)
Left Cingulum (L_Cng)	0.596 (0.01)	0.61 (0.02)
Right Uncinate Fasciculus (R_UF)	0.550 (0.03)	0.563 (0.02)
Left Uncinate Fasciculus (L_UF)	0.533 (0.04)	0.535 (0.04)

Note. Fractional anisotropy (FA) values are presented as mean (standard deviation). WM = white matter; BL = baseline; PT = posttraining.

and the cerebellum. Interestingly, these regions are also reported to be a part of the swallowing network (Huang et al., 2022; Lowell et al., 2012). Overall, the observed plasticity within these regions suggests their involvement in motor control adaptation, learning, and sensory processing mechanisms, all of which may contribute to the increased MEP and cross-systemic benefits on swallowing.

WM networks can undergo dynamic, experience-dependent changes, as demonstrated by both human and animal neuroimaging studies (Blumenfeld-Katzir et al., 2011; McKenzie et al., 2014; Sampaio-Baptista et al., 2013; Scholz et al., 2009). Furthermore, recent studies have established that WM plasticity offers a complementary route through which training can modulate brain networks (Ekerdt et al., 2020; Hofstetter et al., 2013). Although we observed a modest increase in mean FA values across all WM tracts of interest following EMST, this effect did not reach statistical significance in the TBSS analysis or individual tract FA value comparison between baseline and posttraining conditions. This lack of significance could be attributed to factors such as the limited sample size, variability within the data, and the training dosage. Further exploration with longer training durations beyond 4 weeks may be warranted. For example, Scholz et al. (2009) demonstrated that participants who underwent 6 weeks of motor learning training exhibited significant increases in FA values. Extending the training period in future studies could yield more pronounced and statistically significant changes in FA values. Future studies must systematically manipulate dosing variables such as frequency, intensity, and duration from a neuroplasticity perspective. By exploring how dose–response relationships influence neuroplastic adaptations resulting from EMST, we can aim to develop targeted dosage prescriptions that enhance neuroplasticity.

Conclusion and Future Directions

Data from our study provide preliminary evidence that targeted resistance training of expiratory muscles results in molecular and neuroplastic adaptations similar to exercise targeting skeletal muscles. However, the sample size was inadequate for observed changes in IGF-1 and WM microstructure to reach statistical significance. Although our study provides valuable insights into the molecular, functional, and neuroplastic effects of EMST, results must be interpreted cautiously. First, we acknowledge the study's limited sample size, which limits its generalizability. Moreover, with a small sample size, the ability to detect significant changes may be compromised, especially if the effect size is modest, as observed in IGF-1 levels and FA changes. A larger sample size would increase statistical power and improve the likelihood of detecting significant differences. Since our study lacked a control group, we must also consider whether the observed changes are solely due to EMST or if other nonspecific factors and/or placebo effects may have influenced the findings. Future studies should include a control group to isolate the effects of the intervention better and accurately assess its efficacy. Additionally, including both sexes and a broader age range could mitigate the impact of individual variability and enhance the generalizability of the findings.

Our findings suggest that serum BDNF levels can potentially be a biomarker of EMST-induced neuroplasticity, and its production–uptake cycle can be modulated by EMST. However, several future avenues remain to be explored. Firstly, other neurotrophic factors, such as vascular endothelial growth factors (VEGFs), could also accompany functional and neuroplastic changes. Future studies should consider studying the effects of EMST on VEGF levels. Correlating changes in serum BDNF and IGF-1 levels with functional and neuroplastic outcomes and investigating genetic factors such as polymorphisms related to these molecules in mediating individual responses to EMST can further refine and personalize interventions. Although EMST is linked to peripheral neuroplastic changes shown here as well as a host of functional improvements in swallowing (Brooks et al., 2019; Eom et al., 2017; Hutcheson et al., 2018; Mancopes et al., 2020; Patchett et al., 2017; Plowman et al., 2019), it is worth investigating whether other swallowing-related strength-based exercises, such as the effortful swallow or progressive tongue-to-palate resistance training, would also exhibit similar adaptive patterns.

An interesting observation is that the regions of functional activation seen in the current study are part of the swallowing network, which supports EMST's multisystemic potential. These findings heighten the possibility that EMST may prime neuroplasticity within the swallowing network, aiding recovery and functional improvement. Modern approaches view the brain as a network of interconnected structures rather than isolated modules. Each specialized region interacts dynamically with others, facilitating seamless information processing and transmission throughout structurally and functionally linked brain areas. Recognizing this complexity, we suggest future studies investigate changes in functional and structural (WM) connectivity within swallowing sensorimotor networks. It is also worth investigating whether similar adaptative patterns occur when EMST is used to treat dysphagia of neurological origin. Furthermore, it is also crucial to explore various dosages and study the dose–response relationships. Together, these efforts are essential to identifying markers of aging and disease-induced changes, optimizing treatments and personalizing rehabilitation regimes.

Data Availability Statement

The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Appendix A

Functional Magnetic Resonance Imaging Preprocessing

The functional magnetic resonance imaging (fMRI) data were processed using the Analysis of Functional Neuroimages (AFNI; Cox, 1996) and the FreeSurfer processing pipeline (Desikan et al., 2006; Fischl et al., 2004). The AFNI processing pipeline, implemented using the afni_proc.py script, involved a series of processing blocks, each with specific parameters tailored to optimize data quality and minimize artifacts. First, the raw fMRI data underwent despiking to remove large amplitude spikes and were skull stripped. Slice timing correction was then performed to account for differences in slice acquisition times. After that, the functional data were aligned to a common space (MNI152_2009c) using affine and nonlinear transformations. Motion artifacts were corrected through volume registration, where each volume was aligned to a reference volume with motion parameters estimated and applied. Motion scrubbing was implemented to remove time points with excessive motion using a threshold of 0.3 mm Euclidean norm of the motion derivatives to improve the data quality further.

Additionally, spatial smoothing using a 4-mm FWMH Gaussian kernel was applied to improve the signal-to-noise ratio, and intensity normalization was used to ensure consistency in signal intensity across subjects and voxels. Using anatomical data from the FreeSurfer processing pipeline, a brain mask was created to focus the analysis solely on brain voxels. Finally, we applied a general linear model (GLM) to analyze the hemodynamic response elicited by "SWALLOW" and "NO SWALLOW" tasks. In our GLM, we utilized the "BLOCK" basis function, which characterizes the temporal dynamics of the task-related activity. Specifically, the "BLOCK" basis function had a duration of 20 s and a peak amplitude of 1. These regressors were incorporated into the GLM to capture the neural responses associated with the task and condition. A whole-brain analysis was conducted using this model to examine the different brain activation patterns in response to the two conditions and time points of the study.

fMRI Analysis and General Linear Model

A multivariate modeling was performed within AFNI using the 3dMVM program (Chen et al., 2014) with conditions (swallow versus no swallow) and time (baseline versus posttraining) as the within-subject factor. We estimated the spatial smoothness of the residuals for each participant using a Gaussian plus mono-exponential function implemented with 3dFWHMx. The spatial autocorrelation function values were determined for each participant using the "-ACF" option, and the mean values across participants (0.745862, 2.138274, 6.548944) were calculated (Cox et al., 2017). We used a cluster-based approach to correct for multiple comparisons (Forman et al., 1995) and generated ten thousand random maps with the smoothness parameters. Based on these estimations, we applied a cluster threshold to our data at a minimum cluster size of 18 contiguous voxels with a bi-sided NN = 2 option and a voxel-wise p value of .005, resulting in a corrected two-tailed alpha of $p < .05$. Finally, we extracted the beta weights of each surviving cluster associated with the interaction effects (condition*time).

Appendix B

Glossary

- Diffusion-weighted magnetic resonance imaging (DW-MRI): A special MRI technique that uses the movement of water molecules within tissues to create contrast in the images.
- Diffusion tensor imaging (DTI): An advanced MRI technique that builds on DW-MRI. DTI measures not just the total movement of water molecules in tissues but also the direction of that movement. This allows visualization of pathways and connections within the brain, particularly white matter tracts.
- Fractional anisotropy (FA): A numerical value (between 0 and 1) used in diffusion tensor imaging (DTI) to describe the diffusion of water molecules within a tissue. A value closer to one reflects a greater degree of organization or directionality of these movements, whereas a value of zero reflects that molecules move freely in all directions.
- Neurotrophic factors: A family of proteins that play a critical role in the development, survival, and function of neurons. These factors are essential for the growth and differentiation of neurons during development, as well as for the maintenance and repair of neurons in the adult brain.
- ELISA (enzyme-linked immunosorbent assay): A laboratory test that uses antibodies and enzymes to detect and measure specific molecules, such as antibodies, antigens, proteins, and hormones, in blood, plasma, serum, urine, or saliva samples.
- TrkB (tyrosine kinase receptor-B): A protein found in humans that acts as a high-affinity receptor for several neurotrophins, signaling molecules that help nerve cells grow and survive. Phosphorylation: An important process that regulates TrkB function. It involves adding a phosphate group (PO_4) to a molecule.