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Research report

Cross-activation and detraining effects of tongue exercise in aged rats

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HIGHLIGHTS

- Swallow exercise used to improve aspects of swallowing and voice in aging rat model.
- Increased tongue forces found at all ages.
- Gains diminished after detraining in old rats.
- Minimal cross-system activation effects were observed in the larynx.
- Neuroplastic benefits shown in old rats with exercise.

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ABSTRACT

Voice and swallowing deficits can occur with aging. Tongue exercise paired with a swallow may be used to treat swallowing disorders, but may also benefit vocal function due to cross-system activation effects. It is unknown how exercise-based neuroplasticity contributes to behavior and maintenance following treatment.

Eighty rats were used to examine behavioral parameters and changes in neurotrophins after tongue exercise paired with a swallow. Tongue forces and ultrasonic vocalizations were recorded before and after training/detraining in young and old rats. Tissue was analyzed for neurotrophin content.

Results showed tongue exercise paired with a swallow was associated with increased tongue forces at all ages. Gains diminished after detraining in old rats. Age-related changes in vocalizations, neurotrophin 4 (NT4), and brain derived neurotrophic factor (BDNF) were found. Minimal cross-system activation effects were observed. Neuroplastic benefits were demonstrated with exercise in old rats through behavioral improvements and up-regulation of BDNF in the hypoglossal nucleus. Tongue exercise paired with a swallow should be developed, studied, and optimized in human clinical research to treat swallowing and voice disorders in elderly people.

1. Introduction

Clinicians use exercise-based therapies to treat a variety of age-related cognitive and sensorimotor impairments [10,19,20,37,83], including impairments in voice and swallowing [5,9,11,24,32,68,69,76]. However, treatment efficacy for swallowing problems (dysphagia) and voice problems (dysphonia) has not been optimized because the underlying functional changes associated with exercise in the cranial sensorimotor system are unknown. As a result, clinicians have limited evidence available when choosing an exercise-based treatment for the specific needs of their patients. Thus, clinicians are required to try a plethora of "possible" exercises to see if one of them will lead to improvement, resulting in inefficient use of therapy time and a lack of evidenced-based therapy guidelines [11,48,67]. Without a clear understanding of changes to underlying neural substrates with exercise and age, clinicians are at a disadvantage because they lack physiological and mechanistic evidence to support the decision to use specific therapy parameters or to determine when and if exercise follow-up should occur [11,18]. Thus, research must systematically examine therapy parameters and the resulting changes to neural substrates to provide evidence needed to guide clinical decision-making, maximize therapeutic outcomes, and encourage neuroplasticity.

Neurotrophic factors, or neurotrophins, represent molecular candidates for neural substrates responsible for neuroplastic change. Neurotrophins are the molecular mediators of synaptic plasticity within the motor system [85], contribute to maintaining and restoring synaptic function in neurons of both the central

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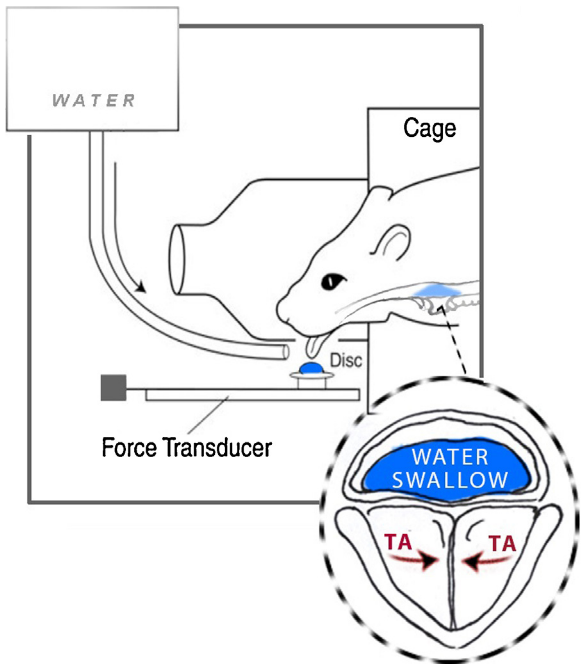

Fig. 1. Schematic of tongue force operandum. Image demonstrates tongue exercise followed by a water swallow in the rat. Image highlights activation of the thyroarytenoid muscle (TA) to protect the airway, following licking, during the water swallow. Image adapted by TG.

and peripheral nervous systems [2,34], and have been proposed as mechanisms of exercise-based change in the limb sensorimotor system [30,31]. However, little information exists regarding the potential for neuroplastic change in the cranial sensorimotor system and the role of neurotrophins in this context, making development of mechanistically-based neuroplastic therapy approaches for voice and swallowing challenging.

Research in our laboratory has demonstrated that aging results in degenerative changes to the nucleus ambiguus (NA), hypoglossal nucleus (HN), and muscles involved in voice and swallowing [3,36,62,73,74,79] and that 8 weeks of tongue exercise leads to increased tongue forces across the lifespan in a rat model [4,17,72]. In addition, our research suggests that brain derived neurotrophic factor (BDNF) and its receptor TrkB are a putative mechanism underlying age and exercise related change in tongue function, because the HN showed decreased TrkB with age and increased BDNF with exercise in adult rats [72]. However, questions exist regarding the enduring benefits and generalizability (cross-activation potential) of tongue exercise paired with a swallow. Furthermore, it is unknown how neurotrophic factors mediate adaptations in sensorimotor function with age and exercise, and how other neurotrophic factors, such as neurotrophin 4 (NT4) [1] exert effects through the TrkB receptor in the cranial sensorimotor system.

To examine exercise specificity and cross-activation in our study, tongue exercise paired with a swallow was used as the exercise-based therapy intervention. This exercise is relevant, because exercises that use cross-activation of shared inputs during training to induce treatment efficiency are being explored in the clinical world for dysphagia and dysphonia [21,22]. For the exercise task trained in this study, muscles of both the tongue and larynx were activated during the exercise to allow for a safe and accurate swallow (Fig. 1), because the vocal folds are known to close to protect the airway during the swallow [23,47,51,64,78,82]. In addition, muscles involved in both vocalization and swallowing receive input from similar neural control elements and are both involved in respiration [52,53,60]. Therefore, the task used in this study had the potential to affect both lingual and laryngeal structures and their sensorimotor outputs. As such, it is theoretically possible and reasonable that our exercise, which targets a specific component, the tongue, within a larger sensorimotor framework (swallowing) may provide cross-system benefits to other components not specifically targeted but activated, such as the larynx [53]. However, based on the principles of specificity and saliency proposed in a seminal paper outlining the 10 principles of neuroplasticity [44], it was hypothesized that changes in physiological and underlying neural substrates would be greater in measures involving the tongue (genioglossus (GG) muscle, tongue forces, and HN) after tongue exercise than for those involving the larynx (thyroarytenoid (TA) muscle, vocalization acoustics and NA), because this exercise was specific to tongue activation, and resulted in a greater proportion of tongue presses, with laryngeal activation occurring passively during the swallow.

To examine the lasting benefits of exercise in the cranial sensorimotor system and to provide clinical evidence to support maintenance programs after exercise-based therapy, a detraining protocol was also used in this study. Periods of 2 and 4 weeks of detraining were chosen because they represent both short term (2 weeks) and long term (4 weeks) detraining [56,57]. It was hypothesized that all outcomes would decrease following detraining, with greater reductions at 4 weeks versus 2 weeks, based on the "use it or lose it" and timing principles of neuroplasticity [44]. This hypothesis is also supported by previous human clinical studies showing that tongue forces were decreased following 2–4 weeks of detraining following a 9-week lingual strengthening protocol [15].

Therefore, the goal of this study was to obtain a better understanding of the effects of age, exercise specificity, and detraining on neurotrophic factors and behavioral measures within the cranial sensorimotor system, using a rat model. Although this work was performed in an animal model, the level of evidence provided will serve as a foundation for future clinical studies and will provide the evidence needed to direct more focused hypotheses for future human clinical studies related to treatment of dysphagia and dysphonia.

2. Methods

All procedures were performed in compliance with the NIH Guide for the Care and Use of Laboratory Animals, Eighth Edition [59] and approved by the University of Wisconsin School of Medicine and Public Health Animal Care and Use Committee.

A total of 80 Fischer 344/Brown Norway male rats were obtained from a National Institute on Aging (NIA) aging animal colony. This inbred strain of rat is used most frequently in aging research because they are genetically identical and are raised in identical conditions. Two age groups were studied: 40 young adult (9-month old) and 40 old (32-month old). The 32-month old group represented advanced senescence because the median lifespan for this strain of rats is 33 months [81]. Only male rats were used because the female estrus cycle may affect vocalization acoustics [50]. The rats were equally and randomly assigned to either a tongue exercise group ($n = 20$; 10 young adult and 10 old), 2-week detraining group ($n = 20$), 4-week detraining group ($n = 20$) or a no-exercise control group ($n = 20$).

2.1. Behavioral tongue exercise and tongue force acquisition

Rats had access to water gradually restricted to only 3 h a day over 14 days [80]. Rats also had light and dark cycles reversed to ensure exercise was provided at the time of most activity. All rats were trained during a 2-week acclimation period to lick with