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ABSTRACTS

Society for Neuroscience 2018 Satellite Symposium

Neural Mechanisms of Feeding and Swallowing and Their Applications for Neural Rehabilitation

Event Organizers:

Teresa E. Lever, Department of Otolaryngology – Head and Neck Surgery, University of Missouri School of Medicine, Columbia, Missouri, United States

Limor Avivi-Arber, Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada; University of Toronto Centre for the Study of Pain, Toronto, Ontario, Canada

Kazutaka Takahashi, Department of Organismal Biology and Anatomy and Research Computing Center, University of Chicago, Chicago, Illinois, United States

Event Description: Feeding and swallowing are complex, life-sustaining sensorimotor behaviors controlled by the central and peripheral nervous systems. These functions are impaired in many neurological diseases or following injury, with no age or gender boundaries. This symposium provides insights into the latest discoveries in neural mechanisms underlying these orofacial functions and rehabilitation advances in humans and animal models. The following is a link to the symposium website: http://home.uchicago.edu/~kazutaka/SfN2018Satellite.html.

This 4th Symposium on the Neural Mechanisms of Feeding and Swallowing brings together a diverse group of speakers whose research focuses on orofacial behaviors in health and disease. The program included a keynote by P Weissbrod, the director of the Center for Voice and Swallowing at the University of California San Diego, and presentations focusing on 3 main subjects: (1) Swallowing—Cognitive efforts on swallowing (CS Lin), lingual function and physiology in a rat model of post stroke dysphagia (M Cullins), and mouse models of dysphagia (T Lever); (2) Chewing and Feeding—3D kinematics of feeding in rodents (K Takahashi), and neuroplasticity of the orofacial sensorimotor cortex induced by tooth loss (L Avivi-Arber); and (3) Rehabilitation—Biofeedback in dysphagia (L Blumenfeld), and neural encoding of orofacial structures for speech and feeding (E Chung).

PROGRAM

8:30–9:30 Breakfast
9:30–9:45 Opening Remarks; Kazutaka Takahashi (University of Chicago), Limor Avivi-Arber (University of Toronto), and Teresa Lever (University of Missouri)

Session 1
Session Chair: Limor Avivi-Arber (University of Toronto)
9:45–10:30 Chia-Shu Lin (National Yang-Ming University), "Cognitive efforts on swallowing"
10:30–11:15 Limor Avivi-Arber (University of Toronto), "Neuroplasticity of the orofacial sensorimotor cortex induced by tooth loss"
11:15–12:00 Miranda Cullins (University of Wisconsin), "Lingual function and physiology in a rat model of post stroke dysphagia"
12:00–12:15 Panel Discussion
Break
12:15–13:00

Session 2
Session Chair: Teresa Lever (University of Missouri)
13:00–13:45 Liza Blumenfeld (University of California San Diego), "Implementing objective measures in video fluoroscopic swallowing studies"
13:45–14:30 Keynote: Philip Weissbrod (University of California San Diego), "High density laryngeal surface electromyography for assessment of voice and swallowing: early concepts and future directions"
14:30–14:45 Panel Discussion

Session 3
Session Chair: Kazutaka Takahashi (University of Chicago)
14:45–15:30 Josh Chartier (University of California San Francisco), "Encoding of articulatory movements in speech sensorimotor cortex"
15:30–16:15 Teresa Lever (University of Missouri), "Establishing clinicopathological biomarkers of dysphagia in a mouse model of ALS: paving the way for targeted treatments"
16:15–17:00 Kazutaka Takahashi (University of Chicago), "Development of 3D videofluoroscopic techniques to characterize the kinematic relationship between oral environmental changes and alternations in mastication/swallowing patterns of rats"
17:00–17:30 Panel Discussion and Concluding Remarks; Teresa Lever (University of Missouri), Limor Avivi-Arber (University of Toronto), Kazutaka Takahashi (University of Chicago)

SPEAKER ABSTRACTS

Cognitive Efforts on Swallowing

Chia-Shu Lin[1,2]

[1]Department of Dentistry, National Yang-Ming University; [2]Institute of Brain Science, National Yang-Ming University

This presentation focuses on a simple but largely ignored point regarding the maintenance of oral functions: chewing and swallowing require cognitive efforts. As an example, for older patients with a substantial deficit in the stomatognathic system (e.g., tooth loss), dental work alone (e.g., installing a new denture) is not sufficient to fully restore oral functions. The patients need to learn or *re-learn* how to adapt themselves to the treatment outcomes. Moreover, they learn how to functionally compensate for these structural deficits. The presentation focuses on the following three aspects. (A) The association between the brain and oral functions, i.e., the 'brain-stomatognathic axis', is very complicated (for review, see C-S Lin, BMC Geriatrics, 2018). To adapt one's oral functions to new conditions, the brain mechanisms of motor learning, i.e., building and refining the association between a motor command and sensory feedback, would play a key role. (B) Evidence from neuroimaging research has revealed that the prefrontal cortex and the cerebellum play a critical role when people are learning a new motor skill. The cerebellum is critical to integrate and fine-tune the sensory and motor information, and eventually, the movement can be automatically performed. The prefrontal cortex is critical to cognitive processing, such as attention to a movement, to switch from one movement to another, and to monitor the progression of a movement. These cognitive factors are critical for older people to maintain their oral functions. (C) A strategy is proposed to explore the mechanisms underlying functional adaptation, by investigating the interaction between structural deficits and functional performance. For example, one could focus on patients with fewer contacts of the posterior teeth, while showing a better masticatory performance. It is hypothesized that in these patients, a greater degree of cognitive effort (e.g., attentional control) is deployed so that they are able to compensate for the deficits of the stomatognathic system. In conclusion, the recent theoretical frameworks and neuroimaging evidence have highlighted the importance of cognitive processing for older people to maintain their oral functions. Understanding the individual differences in the mental/brain mechanisms would be critical to geriatric oral healthcare.

Neuroplasticity of the Orofacial Sensorimotor Cortex Induced by Tooth Loss

Limor Avivi-Arber

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Our studies in male and female rodents have provided novel insights into the neuroplastic capabilities of the orofacial primary sensorimotor cortex (oSM) that may reflect or allow for oral sensorimotor adaptation and learning following intraoral injury affecting the vital oral sensorimotor functions such as biting, chewing, swallowing, and speaking. The oSM is the main brain region involved in generating and modulating these functions. The oSM relies on ongoing sensory and proprioceptive feedback inputs from the teeth since many orofacial muscles lack muscle spindle proprioceptors. We have already documented that extraction of three right maxillary molar teeth induces 4–8 weeks later: (1) altered jaw and tongue movements during natural feeding in awake freely moving female Sprague Dawley (SD) rats; (2) increased perioral mechanosensitivity in male SP rats and C57BL/6 and BXA24 mice but not in female BXA24 mice; (3) widespread genetically-determined sMRI-detected volumetric changes in brain regions involved in processing sensory and motor functions. The latter findings were obtained from a genetically diverse population of female mice of five different strains of the AXB-BXA strains and their two parental strains, the A/J and the C57BL/6, thereby modeling the effect of tooth loss in heterogeneous cohorts of humans; (4) significant sMRI-defined regional volumetric differences between female BXA14 and BXA24 mice. Since the nongenetic, environmental parameters were identical for all mice, the strain-dependent differences suggest a difference in the genetic control of this trait; (5) decreased jaw/tongue motor representations and decreased excitability of oSM in male SP rats and C57BL/6 mice. Such functional neuroplastic changes are analogous to those observed in limb M1 following limb injury which are considered a fundamental mechanism underlying adaptation and learning processes; (6) increased number of astroglia in oSM of male SD rats. We have also shown that oSM neuroplasticity induced by acute dental stimulation can be reversed by application of an astroglial inhibitor to the oSM. Better understanding of the oSM neural and astroglial processes will assist in developing improved therapeutic approaches that target oSM to prevent and manage impaired oral motor functions resulting from tooth loss and other orofacial or central injuries or diseases.

Lingual Function and Physiology in a Rat Model of Post Stroke Dysphagia

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Introduction/Purpose: A better understanding of the effects of stroke on the underlying biology of the lingual muscles may help guide clinical research on post stroke dysphagia as many therapeutic interventions target the lingual muscles. Our goal was to study the impact of stroke on lingual function and physiology using a rat model of cerebral ischemia. Our objectives were to determine (1) whether the middle cerebral artery occlusion (MCAO) rat model of unilateral ischemic stroke models clinical symptoms of dysphagia including lingual weakness and deficits in swallowing function, and (2) the impact of unilateral ischemia on lingual muscle myosin heavy chain (MyHC) fiber type.
Methods: Six-week-old male Sprague-Dawley rats were randomly assigned to either MCAO or sham surgeries. Rats were trained to press an instrumented disk with the tongue for a water reward to determine maximum tongue force, measured at baseline, 1 week, and 8 weeks post-surgery. Swallowing function was assessed by videofluorography at the same time points. Videofluorographic assessments included bolus area, bolus speed, inter-swallow interval, and mastication rate. Lingual muscles were collected bilaterally and snap frozen at 2 and 8-weeks post-surgery. Fluorescent immunohistochemistry was used to assess MyHC muscle fiber types.
Results: MCAO maximum tongue force was significantly less than sham at 1 and 8 weeks ($p = 0.034$ and 0.003 respectively). Average bolus area was significantly smaller in the MCAO versus Sham group at both 1 and 8 weeks ($p = 0.002$, $p < 0.001$). Peak bolus speed was reduced in the MCAO group ($p = 0.006$ and $p = 0.048$ at 1 and 8 weeks). No significant differences between groups were found for inter-swallow interval or mastication rate. The contralateral genioglossus muscles (right) of the MCAO rats had significantly higher percentages of MyHC IIb than the sham group 2 weeks post MCAO ($p = 0.003$), but no difference between groups was found at 8 weeks ($p = 0.97$).
Discussion: The MCAO rat model of post stroke dysphagia develops clinically relevant tongue weakness and deficits in swallowing function. These results support the application of this model to the study of post stroke dysphagia and therapeutic interventions. A transient change in genioglossus muscle fiber type was detected, but further evaluation of the impact of stroke on lingual muscles is needed.

Implementing Objective Measures in Video Fluoroscopic Swallowing Studies

Liza Blumenfeld

Division of Otolaryngology Head & Neck Surgery, Department of Surgery, University of California San Diego

The presentation initially reviewed the significant burden that dysphagia carries in terms of morbidity, mortality and cost. Symptoms often have a deleterious impact on overall quality of life and can prolong hospitalization and increase likelihood of long-term care. Dysphagia assessment is traditionally performed by a speech-language pathologist and includes the Clinical Swallowing Assessment (CSE), Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and Video Fluoroscopic Swallowing Study (VFSS). The VFSS is designed to allow for observation of swallow biomechanics and their relation to safe and efficient transport of material along the upper aero digestive tract. The program described the prominent role that VFSS findings play in directing clinical management of patients with dysphagia including medical and surgical interventions. It went on to highlight the subjective nature of traditional VFSS interpretation and data that reflects poor inter and intra-rater reliability which has provided a cogent argument for a standardized protocol that allows for objective interpretation. The presentation introduced Swallowtail, a novel software application that allows for quantitative analysis of swallow timing and displacement measures obtained during VFSS studies. The presentation provided an overview of how Swallowtail can be used to objectively assess discreet swallow gestures and draw comparisons against normative data. The presentation concluded with a description of how the program could be utilized in a variety of clinical settings to objectively quantify the effects of targeted modalities on swallowing function and rehabilitation.

High Density Laryngeal Surface Electromyography for Assessment of Voice and Swallowing: Early Concepts and Future Directions

Philip A. Weissbrod[1], David J. Bracken[1], Gladys Ornelas[2], Todd P. Coleman[2]

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Introduction/Purpose: Voice and swallowing are highly complex events which are reliant on neuromuscular function and coordination. Currently, there are few tools that are widely used to objectively study neurologic activity during voice and swallowing. Needle based laryngeal electromyography is an option but not frequently used due to patient discomfort, high technical requirement for application and interpretation, and short task duration. Traditional surface electromyography, while non-invasive, has a number of limitations including loss of spatial specificity. High-density surface electromyography (HDsEMG) is an evolving technology that utilizes a dense array of electrodes to simultaneously record signal from a given region. Here, we review our experience to date with HDsEMG for use in evaluation of voice and swallowing.
Methods: HDsEMG arrays of varying electrode density were applied to the anterior neck of healthy adult subjects. Voice tasks included low and high pitch phonation. Swallow tasks included deglutition of different consistencies including dry swallow, thin liquids, puree, mixed texture, and solids. Anterior neck neuromuscular activity was

monitored during tasks and comparisons were made with respect to EMG amplitude, laterality, cranial-caudal distribution, duration of signal, and wave morphology.
Results: Electrode energy varied in regard to low and high pitch phonation across most subjects. Activation in high pitch phonation, as expected, was typically centered around the presumed location of the cricopharyngeal muscle. Swallow results indicate increased duration of swallow commensurate with texture complexity. Early results suggest electromyographic signal morphology also differs between textures.
Discussion: HDsEMG represents an evolving new technology for quantitative analysis of neuromuscular function. Our findings suggest an ability to reliably identify individual muscle groups of the anterior neck and differentiate them from each other. Ongoing work is focused on further validating this technology and integrating machine learning paradigms for a variety of applications, including neurodiagnostics and therapeutic biofeedback.

Establishing Clinicopathological Biomarkers of Dysphagia in a Mouse Model of ALS: Paving the Way for Targeted Treatments

Teresa E. Lever[1,2], Kate Osman[1], Ian Deninger[1], Kazutaka Takahashi[3,4], Brayton Ballenger[1], Nicole Nichols[2], Lori Lind[2]

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Introduction/Purpose: Our group studies a mouse model of amyotrophic lateral sclerosis (ALS) called LCN-SOD1 (low copy number transgenic superoxide dismutase 1). This model displays a highly variable pattern of disease onset and progression similar to human ALS. We previously showed this model develops tongue motility deficits at disease end-stage. The purpose of this study was to characterize the dysphagia phenotype of LCN-SOD1 mice and identify pathological correlates to target in our future pre-clinical dysphagia treatment studies with this model.
Methods: LCN-SOD1 mice underwent our established videofluoroscopic swallow study (VFSS) protocol at disease end-stage (i.e., 20% body weight loss), along with age-matched littermate controls, to quantify several swallow metrics. A small cohort of control mice was surgically implanted with electrodes on the skull and submental muscles to establish a swallow evoked potential (SwEP) protocol to investigate the neural substrates of swallowing in freely behaving mice during VFSS testing. Following testing, post-mortem assays of the tongue (morphometry) and brainstem hypoglossal nucleus (immunohistochemistry) were conducted.
Results: Compared to age-matched controls, LCN-SOD1 mice had significantly ($p < 0.05$) slower lick and swallow rates, longer inter-swallow intervals, and longer pharyngeal transit times. In controls, the SwEP waveform consisted of five peaks within 6 ms immediately preceding the onset of EMG swallowing activity; methodology refinement is underway before proceeding to LCN-SOD1 mice. Tongue weight, dorsum surface area, and length were significantly ($p < 0.05$) reduced in LCN-SOD1 mice compared to controls. In addition, LCN-SOD1 mice had a 32% loss of hypoglossal neurons compared to controls. Correlation analyses revealed that LCN-SOD1 mice with lower body weights had smaller/lighter weight tongues, and those with forelimb paralysis and slower lick rates died at a younger age.
Discussion: LCN-SOD1 mice developed significant oral and pharyngeal stage dysphagia at disease end-stage and corresponding tongue atrophy and degeneration of the hypoglossal nucleus. These findings are congruent with the clinicopathological features of human ALS, thus highlighting the translational potential of this mouse model in ALS research. Lesion analysis studies are underway to identify the corresponding motor versus sensory brainstem nuclei contributing to each SwEP peak. Once optimized, we envision our freely behaving SwEP protocol may be a useful tool to quantify the effect of various treatments on the neural substrates of swallowing in mouse models of ALS and other neurological diseases/disorders. The ultimate goal of this pre-clinical work is to accelerate the discovery of targeted treatments for neurogenic dysphagia.

Development of 3D Videofluoroscopic Techniques to Characterize the Kinematic Relationship Between Oral Environmental Changes and Alternations in Mastication/Swallowing Patterns of Rats

Naru Shiraishi[1,2], Limor Avivi-Arber[3], Niam Kataria[3], Alexandra Zimerman[3], Teresa E. Lever[4], Makato Inoue[2], Callum Ross[1], Kazutaka Takahashi[1,5]

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Introduction/Purpose: It is considered that tooth loss and its sensory deprivation affect oral behavior during oral stage swallowing. However, it remains unclear if and how such oral environmental changes and dental implants can affect the oral stage of swallowing across days and weeks. Therefore, we used a rat model of tooth loss to develop an unconstrained feeding paradigm to capture changes in orofacial kinematics in response to tooth loss and subsequent replacement with dental implants.
Methods: Sprague-Dawley rats were chronically implanted with 0.5 mm tantalum beads into the skull, mandible, and tongue to analyze 3D kinematics during unconstrained feeding of flavored radiopaque $BaSO_4$ infused kibble using high-speed biplanar videofluoroscopy (XROMM). Patterns of mastication and swallowing cycles and tongue movement were assessed at three time points: baseline, after tooth extraction, and after dental implant.
Results: Animals were not affected by serial radiation exposure during the experimental period. Oral environmental changes resulted in differences in behaviors. Power spectrum analysis showed a statistically significant shift in peak frequencies of tongue displacement and tongue shape kinematics (t test, $p < 0.001$). Tongue shape dynamics were much faster than individual mandible and tongue markers. At baseline, the duration of chew gape cycles and those of swallowing were statistically different (t test, $p < 0.001$). Compared to baseline, there was no statistically significant difference in chew cycle duration 3 days after tooth extraction; however, swallowing cycle duration was significantly longer (t test, $p < 0.001$). Although the mean duration of chew cycles did not change, the variances in duration and gape phase transition patterns did change from baseline to postoperative day 3.
Discussion: We have preliminarily shown that oral environmental changes resulted in altered patterns of mastication and swallowing

cycles and tongue movement during natural feeding. We are in the process of characterizing the daily progression of observed changes to identify when those changes plateau after tooth extraction and placement of dental implants. Furthermore, development of machine learning methods is in progress to accelerate digitization of XROMM data and extraction of 3D kinematics.