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Design and validation of a closed-loop, motor-activated auricular vagus nerve stimulation (MAAVNS) system for neurorehabilitation

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ABSTRACT

Background: Studies have found that pairing vagus nerve stimulation (VNS) with motor activity accelerates cortical reorganization. This synchronous pairing may enhance motor recovery.
Objective: To develop and validate a motor-activated auricular vagus nerve stimulation (MAAVNS) system as a potential neurorehabilitation tool.
Methods: We created MAAVNS and validated its function as part of an ongoing clinical trial investigating whether taVNS-paired rehabilitation enhances oromotor learning. We compared 3 different MAAVNS EMG electrode configurations in 3 neonates. The active lead was placed over the buccinator muscle. Reference lead placements were orbital, temporal or frontal.
Results: The frontal reference lead produced the highest sensitivity (0.87 ± 0.07 ($n = 8$)) and specificity (0.64 ± 0.13 ($n = 8$)). Oral sucking reliably triggers MAAVNS stimulation with high confidence.
Conclusion: EMG electrodes placed on target orofacial muscles can effectively trigger taVNS stimuli in infants in a closed loop fashion.

Introduction

Vagus nerve stimulation (VNS) synchronously paired with motor training has shown promise in reorganizing the primary motor cortex after brain injury in animal models and improving functional rehabilitation in stroke patients [1,2]. This restoration of pathologically deficient neural activity is likely due to neuroplastic mechanisms activated by VNS, as the synergistic effects only occur when active stimulation is delivered with paired therapy [3,4]. The vagus nerve can be stimulated non-invasively via the auricular branch in the ear by transcutaneous auricular VNS (taVNS), which has shown similar afferent neural activation patterns as traditional cervical VNS [5]. Recently, taVNS paired with motor rehabilitation has been explored to treat motor function impairment post-stroke [6].

Recently our group has demonstrated the initial safety and feasibility of pairing taVNS with neonatal occupational therapy to improve oromotor function in infants with feeding deficits [7]. However, infant bottle sucking behavior can be difficult to continuously monitor visually and thus effectively pair consistently with neurostimulation. A trained provider must constantly monitor the feeding and then trigger the stimulation manually. This is labor intensive, costly, and introduces variation in different observers. A closed-loop system could provide a more accurate stimulation delivery method while reducing the number of operators required.

Oral feeding uses several facial muscles in concert, including the buccinator, masseter, and temporalis, which can be measured using electromyography (EMG) [8–11]. An EMG-paired taVNS system, triggered by muscles important for functional rehabilitation, has not yet been explored. Functional plasticity in the motor cortex may require intricate timing between targeted movement and applied stimulation [4]. EMG provides indication of muscle activity with high spatial and temporal resolution – pairing these muscle-specific movements in real-time with taVNS may accelerate motor learning and facilitate restoration of deficient neural processes.

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We designed and built a closed-loop motor-activated auricular vagus nerve stimulation (MAAVNS) system and evaluated whether MAAVNS is sensitive enough to detect sucking behavior, and specific enough to discriminate coordinated sucking motor activity from noise and other movements in a neonatal population. For determination of optimal settings, we prioritized sensitivity for nutritive over non-nutritive sucking movements.

Techniques and methods

Overview of motor activated auricular vagus nerve stimulation (MAAVNS) system

Our closed-loop MAAVNS system uses EMG detection of movement of orofacial muscles to trigger taVNS stimulation when these target muscles were activated in a suck-swallow oromotor sequence (Fig. 1a and b). We enrolled 3 neonates in a sub-study comparing 3 different EMG configurations to investigate the utility of MAAVNS and determine the optimal EMG configuration to reliably pair taVNS stimulation with nutritive sucking during bottle feeding.

EMG lead configuration and muscle selection

Three different EMG configurations were tested (Fig. 2a). Small round 20 mm EMG electrodes (Natus) were placed on the left side of the subject's face and connected to a pre-amplifier (NeuroLog NL844). The active EMG lead was placed over the buccinator approximately 5 cm horizontally from the corner of the mouth for all configurations. The reference EMG lead location varied depending on the configuration: A) Orbital Rim, B) Temporal Ridge, C) Frontal Eminence. The common ground electrode was placed in the center of the forehead, approximately 2.5 cm above the brow ridge, for all configurations. Each configuration was tested independently on different treatment days over 3 neonates (n = 3(A), 6(B), 8(C)).

EMG signal processing

EMG raw signal was passed through a 4 channel AC pre-amplifier (NeuroLog NL844) and into an Isolator (NeuroLog NL820A) for signal amplification (× 10000) (Fig. 1b). The signal was filtered using low pass and high pass filters (NeuroLog NL136 & NL144) to remove signals outside the target frequency. The filtered signal was passed through a signal conditioner (NeuroLog NL530) to add gain and offset controls. Using an integrator (NeuroLog NL703) the amplified EMG response is converted into an analog voltage signal corresponding to the amount of motor activity at a sampling rate of 100 ms. This analog signal is full-wave rectified to ensure the voltage output is positive. The signal is then passed through a gated amplitude discriminator (NL201 Spike Trigger) which enables the calibration of an activation threshold by setting the "window height". Adjustments to the "window height" allow for the fine tuning of trigger sensitivity. The window height was set to approximately 0.4 V and was used to calibrate stimulation trigger sensitivity prior to each trial. The amplitude discriminator converts analog EMG signal spikes (target muscle activation) into trains of digital pulses that pass to a delay module (NL405 without delay) that produces adjustable TTL Logic output

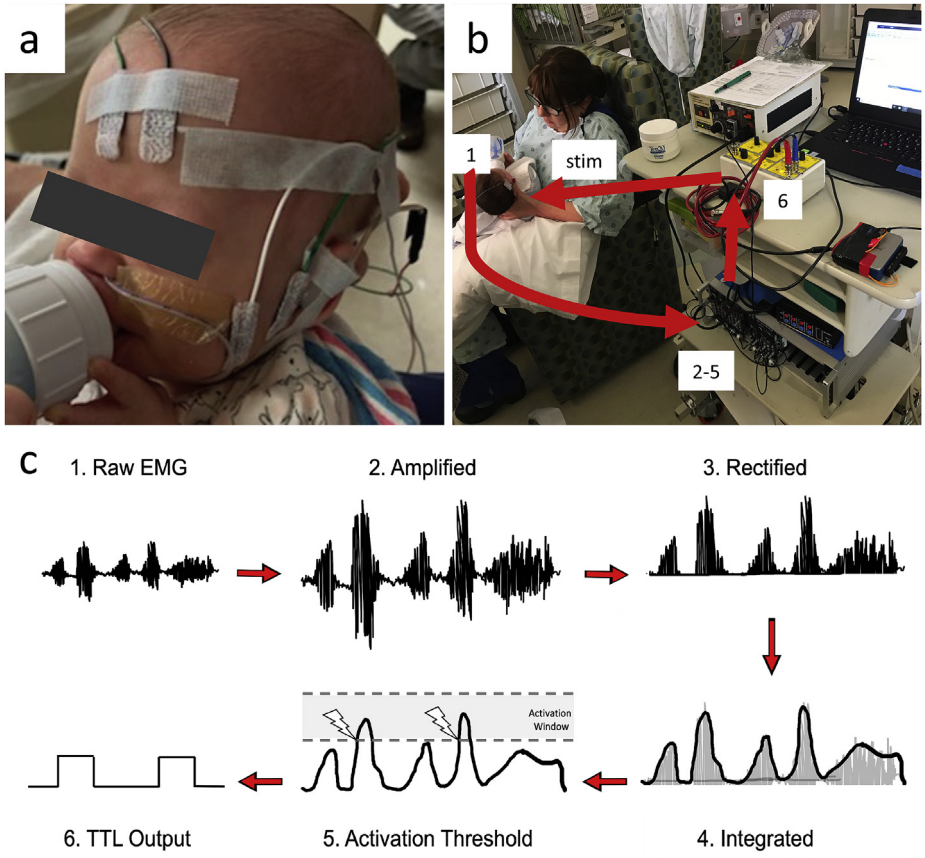

Fig. 1. a) EMG lead placement for position C. Active lead on buccinator, reference lead on frontal eminence, ground lead in center of forehead. b) Overview of MAAVNS set up. EMG signals from facial muscles (1) were processed (2–5) and used to trigger stimulation (6, stim). c) Raw EMG signal was processed by amplifying, rectifying and integrating the signal. An activation threshold was set and calibrated to a visual suck, delivering a TTL output when a suck was detected.

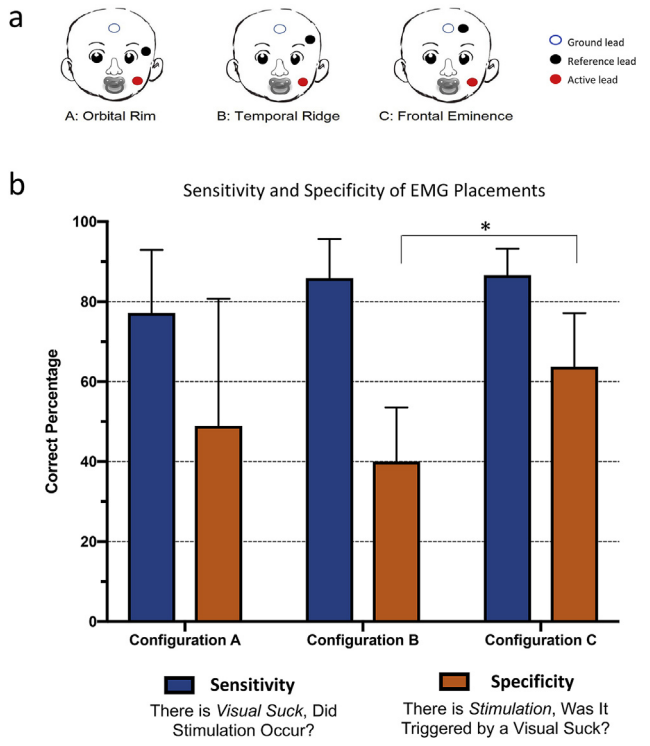

Fig. 2. a) EMG lead placement for Configurations A, B, and C. b) Sensitivity and Specificity of EMG lead Configurations A, B, and C. This data demonstrates that both Configurations B and C had a sensitivity greater than 86%, however, Configuration C had a significantly greater specificity than Configuration B (64% compared to 40%).

used to trigger taVNS stimulation. Fiber optic wires connect all the modules to minimize latency of signal transmission.

Administering taVNS

The TTL output signal generated from the EMG signal processing steps (prior section) is relayed to a TTL Train Generator (Digitimer Model DG2A) which triggers the constant current stimulator (Digitimer DS7AH) and initiates stimulation at pre-set parameters (3 s trains of 25 Hz stimulation at a 500μs pulse width). Stimulation is delivered at 0.1 mA below individual perceptual threshold via custom neonatal taVNS electrodes described in Badran Jenkins et al., 2019 [7] (under review – Frontiers in Human Neurosciences). Perceptual threshold was determined prior to each treatment by increasing the current intensity in 0.1 mA increments until the physical acknowledgment of the stimulation by the subject was observed (head turn, wince, etc.). The amount of stimulation that was delivered during each treatment session was dependent on the activity of the subject during the feed. If the subject did not have an effective feed, then the amount of stimulation that was delivered during that feed was decreased due to lack of oromotor activation. Refer to supplemental video for operational demonstration.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.brs.2020.02.028.

Determination of optimal EMG lead configuration

At the beginning of each trial, the window height of the EMG Signal Processing system was calibrated such that taVNS stimulation was triggered when a nutritive suck was visually observed. The window height ranged from 0.3 to 0.6 V depending on the strength of the subject's oromotor function associated with a nutritive suck. A designated observer was tasked with identifying nutritive sucks and whether they were correctly paired with the EMG-driven stimulation. Nutritive sucks that failed to trigger stimulation were also recorded. A positive nutritive suck/stimulation pairing was also indicated if the suck occurred within an ongoing 3 s train of stimulation.

Sensitivity and specificity scores were used to determine the relative effectiveness of each EMG lead configuration. Sensitivity was defined as the number of correctly paired stimulations divided by the total number of visually-confirmed sucks recorded. Sensitivity scoring reflected whether the EMG lead configuration could trigger taVNS stimulation even with sucks that appeared weaker but were related to a swallow.

Specificity was defined as the number of correctly paired stimulations divided by the total number of stimulation trains. Specificity scoring reflected whether the configuration could determine a nutritive suck from other movement/noise. An unpaired *t*-test was performed comparing the sensitivities and specificities of configurations A, B and C.

Results

Demographics

The 3 neonates enrolled had a mean gestational age (GA) at birth of 33.57 ± 3.37 weeks (mean ± SD). Mean GA at enrollment was 40.43 ± 2.85 weeks. 2 subjects were black, and 1 subject was white. All 3 subjects were female.

sensitivity and specificity

We recorded from 17 independent 30-min taVNS-paired feeding sessions. Each session, on average had a mean of 268 suck-related events that were recorded and analyzed for sensitivity and specificity. The sensitivity of the 3 tested EMG configurations were (mean ± SD) A: 0.77 ± 0.16 (n = 3), B: 0.86 ± 0.10 (n = 6), and C: 0.87 ± 0.07 (n = 8). The specificity of the 3 tested EMG configurations were (mean ± SD) A: 0.49 ± 0.32 (n = 3), B: 0.40 ± 0.14 (n = 6), and C: 0.64 ± 0.13 (n = 8) (Fig. 2b). All sites captured the majority of visually confirmed sucks with greater than 75% confidence (Fig. 2b), however Placement C (frontal eminence) provided the highest specificity while maintaining sufficient sensitivity in capturing weaker sucks. The specificity of Placement C was significantly different compared to Placement B (P = 0.0018). Sensitivity of Placements A, B and C were not significantly different.

Discussion

We have designed and tested a closed-loop motor activated auricular vagus nerve stimulation (MAAVNS) system that uses real-time EMG signals from orofacial muscles to trigger taVNS in a motor rehabilitation setting. Three different EMG configurations demonstrated that MAAVNS was sensitive enough to capture small, visible suck-swallow sequences. The EMG reference electrode placed on the frontal eminence was the most specific.

Using real-time EMG activation paired with taVNS in a closed-loop fashion as described may facilitate motor learning and restoration of aberrant neural circuitry. This closed-loop system provides reliability, consistency, and reproducibility throughout treatments minimizing human error and ultimately leading the way towards automated clinic- and home-based neuromodulation therapy. MAAVNS is relatively inexpensive and was developed as an open-source platform for researchers to build laboratory-based systems in future trials.

Limitations

We observed a sensitivity-specificity trade off when determining the best window height adjustment. We determined that not missing a nutritive suck was a priority for our objective to optimize treatment for motor learning. This was reflected in the results of all three configurations. Another potential source of variability in specificity was that placement of the electrode may be at the junction of the masseter and the buccinator at our target location. However, both muscles are involved in the suck -swallow sequence.

Conclusion

A closed loop MAAVNS system is feasible with reasonable sensitivity and specificity. In the future, EMG could possibly be used to trigger other brain stimulation modalities that need to be paired with motor function. The MAAVNS system can be applied to any taVNS-paired motor rehabilitation paradigm - as long as the desired muscle action can be isolated, and EMG leads can be adhered to quantify activation.

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Declaration of competing interest

DNC, MSG, DDJ, BWB are listed as inventors on pending patents assigned to the Medical University of South Carolina on the methods described in this manuscript.

CRediT authorship contribution statement

Daniel N. Cook: Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Sean Thompson:** Methodology, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Sasha Stomberg-Firestein:** Data curation, Writing - original draft. **Marom Bikson:** Writing - review & editing, Supervision. **Mark S. George:** Conceptualization, Writing - review & editing, Supervision. **Dorothea D. Jenkins:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Bashar W. Badran:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.02.028.

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