fMRI of Acupuncture for Salivation

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Introduction: One common side effect of radiation therapy to head and neck cancers is xerostomia – the impaired ability to produce saliva. Xerostomia has been treated successfully by the application of acupuncture at the LI2 point (1). However, the neuronal network responsible for acupuncture in the treatment of xerostomia is unknown. We hypothesized that the neuronal activation areas stimulated by the acupuncture will be similar to those from gustatory stimuli.

Materials and Methods: We performed a randomized controlled study using fMRI to understand the salivation mechanism as stimulated by acupuncture of the LI2 point. 20 right-handed healthy volunteers (10 males, 10 female, mean age 34.8 years) participated. Stimulations for the true and placebo acupunctures were a 5-cycle boxcar design, composed of 5 resting and 5 activation periods, with total time of 540 seconds. For the 60 second activation period, a needle was inserted into the LI2 and manually manipulated for the true acupuncture paradigm. A placebo (Streitberger) needle was inserted into a sham acupoint for the placebo paradigm. During the resting periods, the needles were pulled out immediately, and the subjects rested for 40 seconds. LI-2 is located on the radial side of the second digit in slight flexion and in the depression anterior to the metacarpophalangeal joint. The sham acupoint is on the ulnar side of the ipsilateral forearm. A 1.5 Tesla scanner (GE Signa Twinspeed with a quadrature head coil) was used for the study. To minimize head movement, two plastic pads were inserted into the space between the subjects' heads and the coil, and tape was used for further fixing of the heads inside the coil. High resolution T1-weighted images were obtained using a SPGR pulse sequence (TR/TE=30ms/14ms, 90 degree flip angle, 256 x 256 matrix, 144-160 axial slices, 1.5 mm slice thickness with 0 cm gap for whole brain coverage) and co-registered with the BOLD fMRI data acquired by using a T2* weighted EPI sequence (TR/TE = 5000ms/40ms, 90 degree flip angle, 128 KHz bandwidth, 128x128 matrix size, 45 axial slices, 4.5 mm slice thickness with 0 cm gap) while running the stimulations. The amount of saliva generated in the true and placebo stimulations was collected by placing two gauze sponges with known weights into the two sides of the mouth of the subjects prior to the fMRI acquisitions. The sponges were collected from the mouth and weighed immediately after the scans. The weight differences of the sponges indicated the saliva weight for the true or for the placebo stimulation. The functional MRI data were analyzed using AFNI (2005_11_18_1920) (2). The data processes included motion correction. The motion curves (the displacement (mm) vs the fMRI scanning time) were analyzed. 7 subjects (6 females and one male) with motion larger than 5 mm were eliminated from all further processing. The individual and group analyses were applied to the 26 data sets, resulting from the remaining 13 subjects with each performed two paradigms. A cross correlation coefficient (r) between the time course of each voxel and the input functions based on the stimulations' time patterns was calculated. The r value for the corresponding p value less than 0.05 was selected for the individual and for the group analysis to threshold the activation areas. The group analysis was performed by applying an ANOVA algorithm and by using two fixed factors (i.e., the true and placebo acupunctures) and 13 random factors (i.e., the thirteen subjects). The activated areas for the individual subjects were colored and overlaid on the high resolution SPGR images. Then, the activation areas determined by the group analysis were overlaid to a standard Talairach brain. The coordinates for a certain activation area (i.e., cortex) were determined by selecting the middle point in the area for the slice with the most activation pixels, and were labeled based on the Talairach space.

Results: There are ten activation areas determined from the group analysis on the data during LI2 stimulation. These areas were overlaid onto the Talairach Brain and shown in Figure 1, with the corresponding coordinates in the Talairach Space listed in Table1. The LI2 stimulation was preformed on only one hand, but the activation areas were bilaterally symmetrical. Neither activation nor deactivation was found from the group analysis on the data during placebo acupuncture. Mean salivation in grams during the true and the placebo acupuncture phases was 2.92 (SD:1.38) and 2.52 (1.30) respectively, and the saliva was significant more during the acupuncture stimulation (p=0.0008). Sixteen subjects (80%) had greater salivation during acupuncture stimulation than during placebo stimulation (p= 0.012). Hence, the activation areas determined from the group analysis on the data during LI2 stimulation appear to be associated with the cortical network of salivation.

Fig 1. Coronal, sagittal, and axial views of the activation areas: the red color areas, determined from the group analysis on the data during LI2 stimulation.

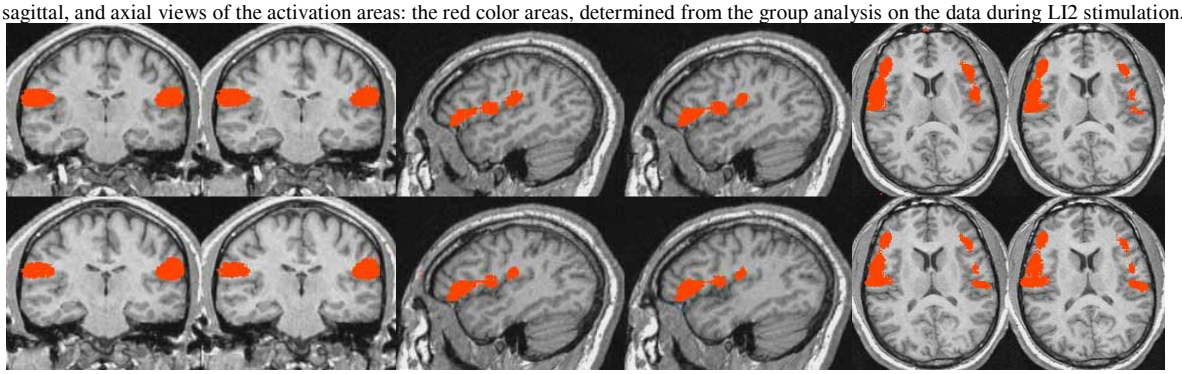

Table 1. Activation areas for acqupuncture at LI2.

Cortex	Left inferior frontal gyrus (mm)	Right inferior frontal gyrus (mm)	Left Pre Central Gyrus (mm)	Right Pre Central Gyrus (mm)	Left Insula (mm)	Right Insula (mm)	Left Middle Frontal Gyrus (mm)	Right Middle Frontal Gyrus (mm)	Left Post Central Gyrus (mm)	Right Post Central Gyrus (mm)
X(R-L)	-44(L)	44(R)	- 46(L)	55(R)	- 46(L)	44(R)	-35(L)	44(R)	-60(L)	50(R)
Y(A-P)	25(A)	35(A)	6(A)	-3(P)	1(A)	-11(P)	40(A)	35(A)	-22(P)	-19(P)
Z(S-I)	4(S)	11(S)	8(S)	8(S)	12(S)	15(S)	9(S)	16(S)	26(S)	26(S)

Discussion and Conclusion: Our data demonstrate that acupuncture at the LI2 point commonly used to treat xerostomia in clinical practice was prominent cortical activation, whereas placebo acupuncture was not associated with any activation or deactivation. In addition, the activation seen in our study was essentially identical to the fMRI activation described in prior studies for gustatory stimuli (3, 4). The true acupuncture also induced saliva production significantly more than the placebo. It is known that salivation involves gustatory, olfactory and visual stimuli which lead to cortical activation (3). Salivation is the physiological response for pure gustatory and somato-gustatory stimuli. These stimulations excite neuronal activity in the primary gustatory cortices, which include the insula and the adjacent operculum (3, 4). The primary gustatory cortex appears to be where information related to gustation and salivation is integrated at the cortical level. Insula and rolandic operculum receive a direct projection from the thalamic gustatory relay through bifurcate neurons (5). Neuronal activity in this region is modulated by sensory input from taste receptors and lingual somatosensory receptors (3). Our data connected the underlying neuronal matrix modulated by the acupuncture and a relevant intermediate biological endpoint to its original clinical application, and should have potential in determining the cause and the treatment for xerostomia.

References: 1.Dawidson I., J. Oral Rehabil., 1997, 24(3): 204-8. 2.Cox RW., Comput Biomed Res., 1996, 29(3):162-73. 3.Ogawa H., et.al.., Chem. Senses., 2005, 30(7):583-92. 4.Cerf-Ducastel B., et.al ., Chem. Senses., 2001, 26(4):371-83. 5.Pritchard TC., et. al., J. Comp Neurol., 1986, 244(2):213-28.