Kinetic oscillatory stimulation (KOS) in the nasal cavity studied by resting-state fMRI

Tie-Qiang Li[1], Rolf Hallin[2], and Jan-Erik Juto[3]

[1]Department of Medical Physics, Karolinska University Hospital, Karolinska Huddinge, Stockholm, Sweden, [2]Department of Neurophysiology, Karolinska University Hospital, Karolinska Huddinge, stockholm, Sweden, [3]Department of CLINTEC, Karolinska Institute, Huddinge, stockholm, Sweden

PURPOSE: Kinetic oscillatory stimulation (KOS) in the nasal cavity has clinically been shown to be extraordinarily effective for treating acute migraine[1] and inflammation[2]. The purpose of the study is to improve our understanding of the neurological mechanisms underlying the KOS treatment. We used a resting-state fMRI design that fits the treatment protocol inside MRI scanners and a voxel-wise metric based on the number of significant functional connections to quantify BOLD response to KOS treatment.

METHODS: The KOS treatment in nasal cavity is a non-invasive technique for migraine and other inflammatory disorders. In brief, the treatment is aimed to restore the physiological haemostasis in the body by delivering low frequency stimulations in the autonomous nervous system (ANS) via the posterior part of the nasal mucosa, which is rich in innervations and inter-nerve connections. Recently published and on-going random-controlled trials (RCT) for rhinitis and migraine have demonstrated the efficacy of KOS treatment for inflammation and pains. In this study we studied 12 normal controls (female/male=10/2) and 12 acute migraine patients (female/male=9/3). We used a whole-body clinical Siemens 3T MRI scanner (Magnetom Trio) to conduct simultaneous KOS treatment and fMRI measurements. The imaging protocol consisted of multiple sessions of whole-brain BOLD frMRI scans each lasted 10 min. The main acquisition parameters included the following: TE/TR=35/2000ms, isotropic spatial resolution of 3.5 mm, single-shot BOLD EPI with IPAT factor=2, and 300 timeframes. A 32-channel phased-array head coil was used for the signal acquisition. When the patients arrived, the migraine headaches were on-going. Before KOS treatment, the patients were asked to perform two sessions of control scans: a baseline without inserted catheter and a session without treatment but with inserted catheter. One or two KOS treatment sessions were administrated at 95 millibar and 68Hz depending on the patients' symptoms. After each KOS treatment session patients were asked to evaluate their pain level. All patients studied were totally pain relieved after 10-20 minutes KOS treatment. At the end, a control session of resting-state without the inserted catheter was performed. Since the treatment is non-invasive and involves no-chemical agent, we applied also the same procedure and fMRI protocol to the normal controls.

The fMRI data were first pre-processed with a pipeline procedure[3,4] based on AFNI including mainly motion correction, Gaussian smoothing at FWHM=4mm, registration to standard MNI template, low-pass filtering at 0.1Hz and nuisance signal regression. Voxel-wise cross-correlation coefficients (CC) and the number of meaningful functional connections with CC≥0.3 were than computed for each voxel inside the brain. The derived number of functional connection data were statistically assessed voxel-wise using a 3-way ANOVA model with patient (n=2, patients versus normal controls) and treatment (n=4, pre-KOS baseline, probe, KOS, and post-KOS baseline) as fixed effects and subject as random effect (n=12). The statistical significance was assessed with voxel-wise $p<0.05$ and a minimum cluster size of 40 voxels.

RESULTS: Both significant patient and treatment effects were detected with the 3-way ANOVA analysis of the functional connection density. As shown in Figs. 1a and b, migraine patients showed significant enhanced functional modulations within the central control network (the limbic system) for ANS. On averaged, the functional connection density in the significantly affected areas including foci in the thalamus, insular cortex, Para hippocampus and brain stem were nearly doubled during migraine attacks. As depicted in Figs. 1c and d, the KOS treatment effect in the healthy volunteers was mainly manifested as reduced functional connection density in the thalamus, precuneus, motor-sensory, visual, and temporal cortices. Furthermore, these brain regions also exhibited significant patient and treatment interactions indicating significant different response to the KOS treatment between normal controls and migraine patients.

DISCUSSION: The functional modulation in the limbic system, which is the central control network for ANS, is of special interest to the study of migraine and KOS treatment. Migraine patients have a normally regulated ANS when symptom free between attacks. However, during headache attacks they often suffer from the symptoms of unbalanced ANS. Growing evidence from functional imaging studies[5,6] indicates that the limbic system and basal part of the brain (particularly the thalamus, hypothalamus and brain stem) play a very important role in the pathogenesis of migraine attacks. Taking advantage of the innervations in the nasal cavity KOS treatment provides an effective method to relieve acute migraine pain. Follow-up studies of the migraine patients indicate that KOS treatment also significantly reduce migraine frequency. At present, there is no sufficient clinical and fMRI data to clarify whether KOS treatment between migraine attacks is effective or not.

CONCLUSION: With the fMRI results from this study we can conclude the following: 1) Acute migraine attacks are associated with significantly enhanced modulation in the central control network of ANS; 2) KOS treatment in normal volunteers results in significantly reduced functional connections in the thalamus, precuneus, motor-sensory, visual and temporal cortices; 3) The functional response in migraine patients to KOS treatment is significantly different compared to that for healthy controls; 4) Compared with other data-driven analysis, such as ICA, the metric based on the number of functional connections can facilitate quantitative statistics.

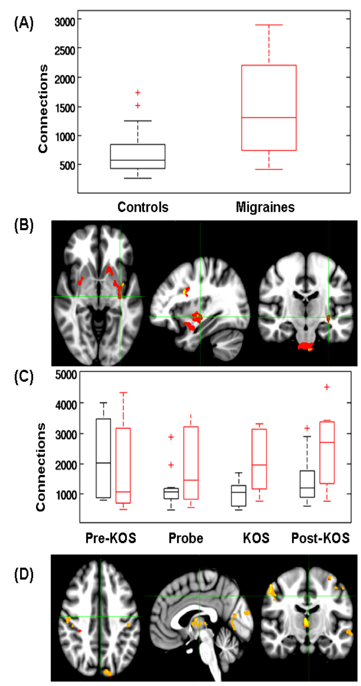

Fig.1. A summary of the 3way-ANOVA results based on the number of function connections (or connection density) derived from voxel-wise CC computation. (A) There is significant patient effect, meaning the functional connection density between healthy controls and migraine patients are significantly different; (B) The brain regions with significant patient effect are largely distributed in the limbic system and the brain stem; (C) There is significant treatment effect, manifested as reduced functional connection density in the normal controls associated with the administration of the catheter and KOS treatment; (D) The brain regions with significant patient and treatment interaction are distributed in the thalamus, precuneus, motor-sensory, visual and temporal cortices.

REFERENCES: 1) Juto J.E. and Hallin R. *Headache,* in press (2014). 2) Juto J.E. and Axelsson M. *Acta Otolaryngol.* **134**:506 (2014). 3) Li X., Li T. Q., Andreasen N., et al. *Sci Rep* **3**:1339, (2013). 4) Wang Y. and Li T.Q. *Plos One* **8**:e76315 (2013). 5) Moulton E.A., Becerra L., Johnson A., et al *Plos One* **9**:e95508 (2014). 6) Kato Y, Araki N, Matsuda H, et al. *J Headache Pain*, **11**:255 (2010).