Title: Feasibility Study: fMRI Evaluation of Auricular PENFS for Fibromyalgia
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Version Date: 6/21/2017

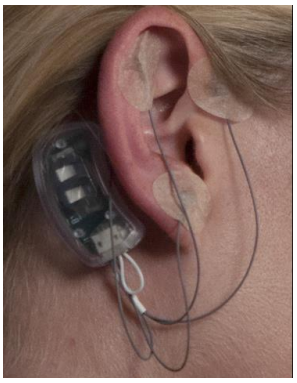
Research Design and Methods

Subjects: Subjects will be divided into two groups (N=20; 10 per group): control (standard therapy) vs. PENFS treatment for this feasibility study. It is expected that all 20 subjects will be recruited by the end of year 1. Age, gender and comorbid conditions may have differential effects on neurological response to pain. Thus, subjects will be block randomized, stratified by age and sex. This should provide an adequate sample size while minimizing confounding variables between groups. Standard therapy includes pharmacologic treatments such as anticonvulsants (i.e. gabapentin, pregabalin), non-steroidal anti-inflammatory medications (i.e. ibuprofen, meloxicam), acetaminophen, topical agents and physical therapy individualized to patient co-morbidities and preferences, as prescribed by a pain management practitioner. An age of 60 years old is set as a limit to minimize brain structural changes due to aging. Subjects age 20-60, male and female with a diagnosis of fibromyalgia by the American College of Rheumatology 2010 criteria for the diagnosis of fibromyalgia will be included in the study. Diagnoses of fibromyalgia will be obtained from chart review (from patients' problem list) and the diagnoses will be confirmed by a qualified pain practitioner.[70,71] Further details regarding inclusion are described in the human subjects section. Patients will be excluded if they are older than 60, have contraindications/relative contraindications to device placement or MRI, or have significant cognitive deficits by mini-mental status exam or co-morbidity that may affect assessments.

Procedures: All study protocols will be approved by the Emory University/VA institutional review board (IRB) and VA R&D committee. Patients will be prescreened using chart review of patients at the Atlanta VAMC and then invited via a phone call for a face-to-face screening session. At the screening session, an informed consent will be signed in accordance with ethical principles from the Declaration of Helsinki and the Ethical Committee at Karolinska Institutet. Then, the study physician (A.W.) will make assessments according to the stated inclusion and exclusion criteria. Subjects who meet study criteria will return for baseline assessments including MRI, collection of biobehavioural information such as cognitive and psychological assessments, eating, sleeping and drinking habits, PROMIS measures including "physical function," "anxiety," "depression," "fatigue," "sleep disturbance," "social function," "pain interference," "global health", and measures from the realms "Activity and Participation" from the International Classification of Functioning, Disability, and Health, arm curl, 30s chair stand, handgrip strength tests, Defense and Veterans Pain Rating Scale (DVPRS) and documented baseline analgesic consumption. Stratification based on age and sex will be performed to account for differential pain perception and neurological responses to pain based on age and gender. Both men and women are included because despite the preponderance of women with fibromyalgia in the general population, there are more male veterans within the V.A. setting. Subjects will be stratified based on age and sex and block-randomized to either standard therapy as defined above or PENFS (series of 4, weekly – manufacturer recommended) treatments, then assessed for changes in pain and function at 1 month and 3 months following treatment without maintenance after the 4-week series. The 1 month time-point is chosen because more profound effects will likely be seen immediately following treatment, based on prior MRI studies of acupuncture for pain. However, the 3-month time point is chosen to evaluate the possibility of longer-term changes. A follow-up MRI will be obtained to evaluate for long-term changes in functional connectivity within 2 weeks after the final intervention. Treatments will be performed by Dr. Kalangara, a pain physician trained to apply PENFS. The PI, Dr. Woodbury, is a pain physician qualified to perform the pain and functional assessments and will perform these, blinded to treatment and control groups.

Intervention: Peri-auricular PENFS will involve the application of a NSS purchased by the VA through an established contract from Innovative Health Solutions consisting of a battery pack secured via adhesive to the back of the ear to provide continuous stimulation at pre-programmed frequencies and intensities through electrodes sterilely, percutaneously placed at neurovascular bundles (Figure 5). PENFS will be placed by collaborator Dr. Kalangara, a VA pain management physician. All PENFS points will be located through transillumination, with one grounding electrode applied to the posterior concha and three electrode points placed in regions to stimulate the respective auricular nerve endings (greater auricular, auricular branch of vagus and auriculotemporal) for fibromyalgia-related pain. Figure 5 shows one sample placement of the electrodes, however, several configurations for placement exist. The NSS uses a needle array instead of a single pin to help provide a field effect. Due to the effects of "field stimulation," the entire auricle and its cranial nerve branches, including the vagal branch, receives stimulation. The skin will be disinfected with alcohol. Peri-auricular PENFS consists of an EAD (External Auricular Device) which is an FDA cleared neuromodulating generator targeting acute and chronic pain with a frequency of 1-10 Hz, pulse width of 1 ms, amplitude of 3.2 v, impulse of 100 mw, length of stimulation of 120 hrs, duty cycle of 2 hrs.on / 2 hrs off, a wire harness, which consists of three 4-pin arrays and one single pin ground wire connected by wire leads to a connector which attaches to the generator. Steri-Strip© liquid adhesive will be used to adhere the electrode arrays and single pin ground wire to the skin to help assure proper energy transfer. Oval and Tegaderm ™ bandages will be used to hold the arrays and ground pin in place to help affix the wires. The EAD generator is cleared and FDA-approved for a targeted population of acute and chronic pain. These devices are designed to stimulate neurovascular bundles of peripheral branches of cranial nerves found in the peri-auricular area (external ear) including the vagus (X), trigeminal (V) facial (VII), glossopharyngeal (IX, via communication with lesser occipital) and occipital nerves and branches of the posterior auricular and superficial temporal arteries.

Figure 5. Sample NSS



Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) scans will be collected within 2 weeks prior to commencement of treatment and also within 2 weeks of the final treatment to evaluate changes in resting state connectivity, using metrics our group has previously associated with chronic pain severity. BOLD fMRI images will be acquired on a 3T Siemens Trio scanner with a 32-channel phased array head coil and a gradient echo-planar imaging (EPI) sequence to yield ten minutes of resting state fMRI data for stable estimation of connectivity networks. T2/FLAIR scans also will be performed to evaluate any white matter disease that may occur in older veterans using validated evaluations for leukoaraiosis. Those with significant leukoaraiosis based on methodology established by Junque et al. will be excluded due to the potential effects of white matter disease on resting state connectivity metrics. [72,73]. Recent studies have shown alterations in white matter connectivity in fibromyalgia patients. In addition to resting-state scan, we may also acquire diffusion weighted imaging (DWI) scans to quantify the white matter tracts connecting key areas involved in pain processing. Since pain processing involves changes in cerebral blood flow [1](predominantly vasoconstriction), and neurometabolities (such as glutamate and GABA), we will acquire resting cerebral blood flow using pseudo Continuous Arterial Spin Labeling (pCASL) MRI technique, and MEGA-PRESS MRS technique to measure tonic glutamate and GABA concentrations. We may acquire a measure of global venous blood oxygenation to evaluate whole brain changes in oxygen metabolism using T2 Relaxation Under Spin Tagging (TRUST) MRI. We will also acquire appropriate scans to correct for EPI distortions during post-processing.

Prior to scanning, subjects will be asked to rate the intensity of their fibromyalgia pain as part of the DVPRS, a validated measure of pain for military and veteran populations. In the scanner, foam cushions will be used to reduce head movement and headphones to dampen scanner noise. Patients will be asked to keep their eyes open, to help insure that they do not fall asleep during the 10 minute resting state scan. Physiological data

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[1]Montoro CI[1], Duschek S[2], de Guevara CM[1], Reyes Del Paso GA[3]. Patterns of Cerebral Blood Flow Modulation During Painful Stimulation in Fibromyalgia: A Transcranial Doppler Sonography Study. Pain Med. 2016 Dec;17(12):2256-2267. doi: 10.1093/pm/pnw082. Epub 2016 May 31.

will be collected simultaneously to the fMRI data (time-locked), as cardio-respiratory fluctuations are known to artifactually influence fMRI intrinsic connectivity estimation within several brain networks.[74,75] Cardiac data will be acquired using an MR-compatible infrared pulse oximeter attached to the right middle finger. Respiratory rate data will be acquired using an MR-compatible respiratory rate monitor and plethysmograph. We will use validated correction algorithms (see below).

The fMRI data will be analyzed using AFNI and FSL software tools, including correction of bulk head motion, physiological noise correction, spatial normalization, smoothing of the images, ICA-based identification and correction of motion artifacts, smoothing, and low pass filtering. In order to quantify intrinsic brain brain connectivity, the pre-processed fMRI data will analyzed with both a dual regression ICA and seed voxel approach.

The DWI data analysis will be accomplished with AFNI and FSL software tools, including correction of bulk head motion and eddy current effects, and visualization of tracts and quantification of fractional anisotropy to determine white matter microstructural integrity. The pCASL data analysis will be accomplished with Matlab, AFNI, and FSL, including motion correction, smoothing of the images, spatial normalization, subtraction of control and label images, and conversion of difference signal into physiological units. The subject specific high-resolution T1-MPRAGE will be used to segment the grey matter ribbon, on which further ROI selection and statistical analysis will be performed. The MEGA-PRESS data will be analyzed with Matlab and LCModel, including pre-phasing of spectra, spectral registration, alignment of edit and control spectra on the creatine (Cr) peak, 2Hz appodization to improve SNR, and fitting of the data to a linear combination of simulated basis sets describing a predefined set of metabolites.

Statistical Analysis Plan

Seed-voxel Functional Connectivity Approach: Areas of the DMN found to be relevant in prior studies regarding fibromyalgia are the inferior parietal lobule (IPL) and posterior cingulate cortex (PCC).[18] Based on this existing data, seed-based resting connectivity analyses of the posterior insula and relevant areas of the DMN (IPL and PCC) will be performed. The seeds will be spherical, 1-cm diameter and centered on the MNI peak coordinates of regions of activity defined from prior studies.[18] The same seeds[18] will be eroded to include only gray matter voxels using the Johns Hopkins University-International Consortium of Brain Mapping white-matter atlas.[79] All voxel time series within the seed will be averaged using AFNI to obtain an averaged time series. We will then correlate the averaged time series from the seed region (posterior insula) with IPL and PCC using AFNI. The resultant cross-correlation coefficients will be converted to z-scores, which will act as the dependent variables for the primary outcome analysis with fcMRI (see Tests of A Priori Hypotheses below). Exploratory analysis of more traditional structures will also be performed, including placement of seeds in the ventral posterior medial nucleus of the thalamus and primary and secondary somatosensory cortices to investigate connectivity between these regions. The average time series from these distinct regions-of-interest is used as a regressor in a whole brain GLM to find which other regions contain correlated time series. Areas of significant correlation with seed regions at pre-treatment scans will be tested for change in connectivity by comparing pre- and post-treatment z-scores, corrected for false discovery rate. While this approach can yield additional inferences, there is some bias in the choice of exact seed location and contour[148]. Thus, a limited number of seeds has been carefully chosen based on results of previous studies[18] and known pain pathways.

We will also perform a linear regression with z-scores from fcMRI correlations from seed voxels and baseline pain levels (DVPRS) in order to evaluate links between baseline resting insula connectivity and baseline individual differences in pain sensitivity. Specifically, using the z-scores collected for insula-IPL connectivity and insula-PCC connectivity, we will find the correlation between insula-IPL connectivity and DVPRS scores, controlling for effects of insula-PCC connectivity. We will likewise find the correlation between insula-PCC connectivity and DVPRS scores, controlling for insula-IPL connectivity. We will also use a linear regression model to explore any association between treatment-modulated clinical pain and the change in the posterior insula resting brain connectivity. All group analyses will use AFNI.

Dual Regression ICA Approach (Exploratory): The within- and between-subject resting state fMRI data analysis will be performed using ICA through Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC, an FSL tool) and a previously validated dual regression approach[146]. This dual regression technique allows for voxel-wise comparisons of resting state functional connectivity by first temporally concatenating resting fMRI data from all subjects, followed by back-reconstructing the group networks for

individual subjects, which are then used for within- and between-subject group and difference maps. This technique has shown high test-retest reliability in previous studies[147]. This process will be completed for the network of interest (DMN) – which will serve as our primary outcome metric for this study. The medial visual network, MVN, will be evaluated as a negative control, as we expect PENFS to have no effect on this primary visual sensory network. Group analyses will be performed to evaluate how intrinsic brain connectivity covaries with clinical pain, and how networks change following PENFS and standard therapy. The results will be threshold at $p < 0.05$, cluster-corrected for multiple comparisons. For exploratory analyses, dual regression ICA also will be run with other empirically derived networks (corrected for multiple comparisons), which will provide an unbiased data-driven analysis that can be used to generate new hypotheses for future studies and grant submissions. Generally, we expect no group differences at pre-treatment, but expect that between-group differences will emerge for networks specified a priori as well as exploratory analyses at post treatment scan.

Tests of a Priori Hypotheses. *Primary outcome (fMRI as a biomarker for pain).* The primary outcome measure is connectivity between the insula and DMN. Based on previous research[10,39,67,18], we hypothesize that PENFS will decrease connectivity between the insula and DMN structures relative to standard treatment. Z-scores from two correlations described above (i.e., between the posterior insula and the IPL and between the posterior insula and the PCC) will be used as the dependent variables for this outcome analysis. Hence, changes in z-scores for the two correlations will be tested for each group using pairwise comparisons. We expect that post-treatment connectivity between the posterior insula and DMN structures will be reduced from pre- to post-PENFS treatment (i.e., they will look more like normal subjects after treatment). We do not expect to see similarly significant changes for standard therapy at 2 weeks following the final treatment. Each of the two correlations will be FWE corrected to $p<.05$ for two comparisons for each group. Patient-reported changes in pain will be evaluated using 1) DVPRS severity scores and 2) analgesic consumption before and after treatment (2 weeks) and at long-term follow-up (6 weeks, 12 weeks) following the 4th week of treatment for each group. We will use a 2 groups (PENFS vs. control) x 4 times (pre- and post- treatment at 2, 6 and 12 weeks follow-up) analysis of the variance to compare outcome for the groups over time. We will employ a linear mixed effects (LME) modeling framework to fit the ANOVA model to the data. LME's are more robust than traditional ANOVA methods when there is a possibility for imbalance in the effects due to attrition. Missing data resulting from dropout and other losses to follow-up can be addressed more easily in LMEs and give a stronger estimate of the fixed group effect while controlling for time as a random effect in the model. After all analyses have been performed, we will use *[Spearman Rank]* correlation coefficients to investigate the predictive ability of baseline resting insula connectivity to predict post-PENFS changes in pain levels. Baseline connectivity will be extracted as z-scores from imaging data.

Secondary outcome (functional improvements). We also intend to investigate whether functional improvements occur with the application of PENFS, as the ultimate goal of reducing pain (primary outcome) is to improve function. Secondary dependent variables for the evaluation of functional improvements with PENFS include previously described PROMIS and International Classification of Functioning, Disability, and Health measures, the arm curl, 30-s chair stand and handgrip strength tests at 2, 6 and 12 weeks follow-up after the completion of the 4-week treatment period. The secondary hypothesis is that PENFS will show significant improvements post-treatment relative to pre-treatment in multiple domains as compared to standard therapy. To test this hypothesis, pairwise repeated measures comparisons between post- and pre-treatment DVPRS, analgesic consumption and functional assessments will be performed within each group, FWE corrected to $p<0.05$. Similar analyses will be conducted at 6 and 12 weeks follow-up. Data from each time point can be considered its own family of comparisons for this purpose. Further, analysis of sample characteristics for the groups (PENFS vs. control) will be conducted to assess comparability of the samples. Categorical variables such as gender and biobehavioral data will be assessed using Fisher's exact test, but continuous variables such as age will be assessed using two-tailed t-tests. All reported p-values will be 2-tailed and considered significant at the 0.05 level, FWE corrected. Data collected and analyzed regarding functional changes related to PENFS treatment will be assessed for new hypothesis generation.

Power Analysis. The purpose of this study is to test the feasibility of using fMRI to evaluate the neural correlates of PENFS outcomes. Hence, its purpose is to provide better estimates of effect size and power calculations for sample size in future studies.

Human Subjects

1. Risks to subjects

Human subjects involvement and characteristics

All study subjects will be veterans. Subjects will be case-matched for age, gender and comorbid conditions since these may have differential effects on neurological response to pain. An age of 60 years old is set as a limit to minimize brain structural changes due to aging.

Inclusion criteria are as follows:

- Subjects must be male and female veterans age 20-60 with a diagnosis of fibromyalgia as diagnosed by a clinician, by chart review, and by the most recent American College of Rheumatology 2010 criteria for the diagnosis of fibromyalgia. [70,71]
- Subjects must self-report consistent, daily pain (greater than 5 on the VAS) >90 days.
- Subjects must have intact skin free of infection at the site of implantation.
- Subjects must be willing to participate and understand the consent.
- Subjects must be right-handed in order to provide consistency in brain structure and function.

Exclusion criteria are as follows:

- Subjects must not be currently pregnant, since effects of fMRI and electrical current on the developing fetus are not well-known.
- Subjects must not have an implanted electrical device such as a vagal stimulator, pacemaker, or spinal pain pump, which are not compatible with MRI.
- Subjects must not have a history of seizures or neurologic condition that may alter the structure of the brain.
- Subjects must not have a history of drug abuse or severe, uncontrolled psychiatric illness such as schizophrenia or major depressive disorder with suicidal ideation.
- Subjects must not have psoriasis vulgaris or other skin conditions that may increase the risk of infection at the implantation site.
- Subjects must not have severe anxiety, claustrophobia, or other conditions that may prevent their ability to lie at rest in an MRI scanner. This will be determined after discussion with the patient regarding their own perceived ability to lie at rest in an MRI scanner without the use of additional sedating medications.
- Subjects must not introduce new medications or treatments for fibromyalgia symptoms during the course of the study to prevent confounding results.
- Subjects must not have a concurrent autoimmune or inflammatory disease that causes pain such as systemic lupus erythematosus, inflammatory bowel disease or rheumatoid arthritis, since this could decrease the effect of treatment.

Sources of materials

The research materials include the PENFS devices, which will be obtained through the prosthetics department via an existing VA contract with Innovative Health Solutions. Each PENFS device requires removal and reinsertion of a new device on a weekly basis for 4 weeks. Each device is sterilely pre-packaged and will be sterilely applied. Old devices will be disposed of in a sharps container as biological waste. Data will be specifically obtained for research purposes, but will also be available in patient records as part of their pain treatment.

Potential Risks

Physical risks are minor. Adverse events are unlikely, but would include minor irritation to the skin, excessive bleeding or vasovagal syncope on initial application. If vasovagal syncope occurs, the practitioners are well-trained in resuscitation techniques since both Dr. Kalangara and Dr. Woodbury are anesthesiologists with ACLS training. The procedure would be aborted and the patient would not be included in the study. If skin irritation or excessive bleeding occurs, the device will be removed and the patient will be appropriately treated and removed from the study. A potential for physical risk related to MRI exposure exists, but there is insufficient evidence to conclude that significant risks are posed with MRI exposure unless the patient has an implanted MRI-incompatible device, in which case they will be excluded from the study. Research risks include possibility of a security breach and misuse of patient data. Patient data will be de-identified and protected according to HIPAA regulations. Psychological risks include possibility of claustrophobia or PTSD related to a small space in the MRI scanner, hence patients with significant anxiety related to the MRI scanner will be excluded.

2. Adequacy of Protection from Risk

Recruitment and Informed Consent
All study protocols will be approved by the Emory University/VA institutional review board (IRB) and VA R&D committee. Patients will be prescreened using chart review of patients at the Atlanta VAMC and then invited via a phone call for a face-to-face screening session. At the screening session, risks, benefits and alternatives regarding the study will be described to the patient, and an informed consent will be signed by patients agreeing to become study particpants in accordance with ethical principles from the Declaration of Helsinki and the Ethical Committee at Karolinska Instituet. Then, the study physician (A.W.) will make assessments according to the stated inclusion and exclusion criteria. Subjects who meet study criteria will return for baseline assessments including resting state fMRI, collection of biobehavioural information such as cognitive and psychological assessments, eating, sleeping and drinking habits, arm curl, 30s chair stand, handgrip strength tests, Defense and Veterans Pain Rating Scale (DVPRS) and documented baseline analgesic consumption. Case-matching will be performed due to the differential pain perception and neurological responses to pain based on age and gender. Both men and women are included because despite the preponderance of women with fibromyalgia in the general population, there are more male veterans within the V.A. setting, so the intention of the study is to reflect the veteran population and not to exclude either gender group. Subjects will be randomized to either standard therapy as defined above or PENFS (series of 4, weekly – manufacturer recommended) treatments and case-matched, then assessed for changes in pain and function at 1 month and 3 months following treatment without maintenance after the 4-week series.

Protection Against Risk
The utmost will be done to minimize potential risks to the patient. Patient information will be de-identified with numerical identifiers for data analysis. Data analysis will occur at Emory and VA facilities in compliance with HIPAA regulations. All individuals in contact with patients for the study will be required to undergo HIPAA training and appropriate CITI training regarding human subjects. Complications of treatment will be documented in patient records and the patient will be referred to appropriate individuals for further treatment. Complications will also be recorded using de-identified records for the purposes of the research study.

Potential benefits of research to subjects and others
For the subjects, the immediate benefit of the proposed research is the possibility of long-term pain control using a non-narcotic modality for pain, improving function and decreasing side effects from pharmacologic therapy. Another potential benefit is receiving fMRI analysis that may unearth underlying neurological disease processes leading to early diagnosis and referral to appropriate physicians for further treatment. Patients will also be selected for early referral to the pain clinic, where the pain therapies will be optimized under the guidance of Drs. Kalangara and Woodbury, independent of whether they are in control or treatment groups. Benefits to others include understanding of the neural correlates for fibromyalgia and chronic pain processes and wider application to the general population for improving pain management and designing targeted therapies. Other potential benefits include improvement in function and return to work, possibly decreasing the need for social security disability, lost wages and missed work days. The risks to the patients are minimal in comparison to the potential benefits to the subjects and others.

Importance of knowledge to be gained
Understanding neural correlates for fibromyalgia and chronic pain and the process of analgesia for non-narcotic therapies are important to optimize targeted therapy for pain control. Prescription drug-related side effects including overdose and death from narcotics is a significant problem within the United States and especially the veteran population, where opioid use disorder is common. Fibromyalgia patients are often prescribed narcotics from primary care providers when other modalities have failed, though narcotics have not been shown to provide long-term benefit in these patients. If the minimally invasive auricular therapy described in this study provides long-term analgesia, it could prove to be a valuable tool for treatment. If the therapy does not provide significant analgesia, then it would save both patients and the V.A. costs in terms of deterring further use of a therapy that is already being utilized by the military and V.A. systems through an existing contract. Though the device is FDA-approved due to its minimal risks, evidence-based analysis of this treatment does not exist and is necessary given the associated costs of the device (and of the disease process it is treating) to the system. Additionally, an understanding of its potential mechanisms for creating analgesia can be applied to future treatment plans.

Data and Safety Monitoring Plan
Patients from both standard therapy and treatment groups will be followed-up weekly during the 4-week treatment intervention period. Patients will also be given the clinic phone number and the P.I.'s cell phone number to contact if potential issues arise during treatment. If complications occur, the procedure will be aborted and the patient would not be included in the study. The practitioners are well-trained in resuscitation techniques since both Dr. Kalangara and Dr. Woodbury are anesthesiologists with ACLS training. Phone reminders and telephone contact will be made on a regular basis in order to encourage follow-up and compliance. Compliance can be easily assessed as described in the research protocol, since device removal is apparent and the device cannot be reinserted except by a skilled practitioner. Follow-up by phone will also be performed following the final fMRI to assess for any potential delayed reactions related to the device or to the MRI exposure. Travel to study sites will be reimbursed as part of patients' visit to the pain clinic. The study sites (VA and Emory) are within walking distance of each other, though participants will not be required to walk. Data will be monitored by collaborator Dr. Jerry Kalangara during the treatment period. Dr. Anna Woodbury, P.I., will be blinded to treatment and control groups for fMRI acquisition and data analysis.

Women and Minorities
Women and minorities will naturally be included in the study as fibromyalgia does not discriminate among ethnic or racial groups, and predominantly affects females, though in the veteran population there is less of a female to male discrepancy.

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