Neural Circuit Involved in Idiopathic Infantile Nystagmus Syndrome Based on fMRI

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ABSTRACT

Purpose: To identify the neural circuitry of idiopathic infantile nystagmus syndrome (INS), characterized by an early onset alternating series of slow and rapid eye movements that can manifest in different waveforms and genetic lines. The neural circuitry of INS is currently unknown.

Methods: A novel functional magnetic resonance imaging (fMRI) method, referred to as the null zone fMRI technique, was used to identify the neural circuitry for INS. In the null zone fMRI technique, a gaze position with minimal nystagmus within the null zone was linked to the fMRI "off" condition and a gaze position with robust nystagmus outside of the null zone was linked to the fMRI "on" condition. Eye movements were monitored with an fMRI compatible eye tracker and observed in real time to ensure subject compliance in "on" and "off" states. Subjects with INS (n = 4) included three family members (a mother and two daughters) with presumed autosomal dominant INS, as well as age- and gender-matched normal controls (n = 3).

Results: Three of four subjects with INS demonstrated significant increased activation of the decline of the cerebellum, whereas no normal subjects under identical conditions showed activation of the decline of the cerebellum. Both groups showed significant activation in the occipital lobe (Brodman areas 17, 18, 19, and cuneus).

Conclusion: A novel fMRI method demonstrated that the decline of the cerebellum is actively involved in INS. These are the first results to identify the cerebellum, and specifically the decline, as a possible site involved in the ocular motor dysfunction known as INS.


INTRODUCTION

Periodic, involuntary ocular oscillations detected within the first 6 months of life characterize infantile nystagmus syndrome (INS). INS is one of the leading causes of significant vision loss in children and affects 1 in 1,000 to 6,000 births.1,2 INS occurs in 2% to 8% of children with visual impairment or legal blindness who use services for the visually impaired. Forty percent of patients with INS have an autosomal dominant inheritance pattern.1

Nystagmus in early life can present with associated sensory system disease (eg, albinism, retinal degeneration, or optic nerve hypoplasia). INS can only be diagnosed by patient history, neuro-oph-
thalmological examination, eye-movement recordings, brain imaging studies (e.g., computed tomography scan or magnetic resonance imaging [MRI]), and electrophysiological testing (visual evoked response or electroretinogram). Many of these tests are used to rule out possible structural or overt pathological causes for the early nystagmus. A National Eye Institute and National Institutes of Health workshop on the classification of nystagmus (Classification of Eye Movement Abnormalities and Strabismus: CEMAS) recommended the term “infantile nystagmus syndrome” (INS) to describe infants with nystagmus independent of (idiopathic) sensory system disease. INS has replaced “congenital nystagmus” as the most appropriate term to describe the condition.

At least 12 INS eye movement waveforms exist. Jerk INS has an accelerating velocity exponential slow phase, characterized by a slow but accelerating eye movement away from the target and a subsequent high velocity (saccadic) eye movement toward the target. The accelerating eye movement away from the target is considered pathognomonic for INS.

Approximately 70% of patients with INS have a null zone, a direction of gaze in which the intensity (defined as frequency x amplitude) of the nystagmus greatly decreases. Most patients with INS have a null zone within 10° of the primary, straight-ahead, gaze position. The minimum intensity of INS is in the null zone and increases outside of the null zone. Because the presence of a null zone yields an increased foveation duration, patients with INS and without sensory system disease may enjoy relatively good visual acuity, usually better than 20/70 (level of visual impairment). In general, the longer the foveation time on the target the better the visual acuity. A strategy to improve vision in patients with INS is to reduce or eliminate the nystagmus and improve foveation duration. Although much is known about INS eye movement and associated sensory system disease, the cause of idiopathic INS, as well as the generator site(s), remains elusive.

In the current study, we used functional magnetic resonance imaging (fMRI) to localize the anatomical correlates for INS. fMRI measures changes in cerebral blood flow from increased oxygen demands due to neuronal activity. We correlated changes in neuronal activity as a result of eye movements or nystagmus. In general, fMRI is based on a comparison of two states: an off-state when neural activity is minimal and an on-state when neural activity is maximal. The current study is based on a novel fMRI technique referred to as the “null zone fMRI technique.” The null zone is the fMRI “off” condition, and a gaze position where robust nystagmus occurs is the fMRI “on” condition. The anatomical correlates of INS would, theoretically, be identified by having the patient alternate gaze position from within the null zone to outside of the null zone during the fMRI recording. The current study is the first to introduce the null zone fMRI technique and to present preliminary data of its validity for uncovering the ocular motor circuitry of idiopathic INS.

PATIENTS AND METHODS

Subjects

The subjects included three related women (Fig. 1) and one unrelated man with ages ranging from 21 to 57 years and a mean age of 33 years. The control group consisted of three normal women with ages ranging from 23 to 55 years and a mean age of 34.7 years. The selection process of the subjects with INS was based on the following criteria: patient and family history, ophthalmological examination, eye movement studies, electrophysiology, no history of eye muscle surgery, a visual acuity of 20/70 or better in the worst eye, good binocular alignment, and a null or semi-null zone based on patient chart review and vision tests prior to the fMRI session. Patients with sensory deficits were excluded. The control group all had 20/20 or better visual acuity, no history of eye problems except for refractive error, and no known neurological problems. Fully informed, signed consent was obtained from each subject and
Figure 2. The novel functional magnetic resonance imaging (fMRI) method to assess the anatomical correlates of infantile nystagmus syndrome (INS) referred to as the "null zone fMRI technique." The small dots in the dark boxes at the top represent the fixation point that shifted back-and-forth from outside the null zone in left gaze to within the null zone in right gaze. The middle square waveform represents the fMRI on-off mode of activation. The bottom waveform, a hand-drawn illustration, represents eye movements alternating between the high intensity on-state and the low intensity off-state every 20 seconds.

the study was approved by the Institutional Review Board at Nationwide Children's Hospital, Columbus, Ohio.

Design and Procedures

fMRI Visual Paradigm. The visual paradigm was based on a simple shift of gaze position, a difference of only 10° to 15° visual angle, from the inside (off-state) to the outside (on-state) of the null zone (Fig. 2). The two basic conditions for fMRI were based on the subject's gaze position inside and outside of his or her null zone: in the active on-state, the patient with INS directed his or her gaze slightly outside of the null zone, which yielded vigorous nystagmus. In the off-state, the patient with INS directed his or her gaze within the null zone, which yielded minimum nystagmus.

fMRI Setup. Visual stimulus was programmed using Vision Egg, a Python programming language, on a Toshiba laptop, and was presented by an LCD projector (Sony VPL-X1000; Sony, New York, NY). The image was displayed onto a projection screen mounted on an fMRI compatible frame and visible to the subject through a tilted mirror placed above the subject's head. Motion was restricted by packing firm cushions around the head and securing them with straps. Some movement may still have been possible and was accounted for during the data analysis. Eye movement activity was monitored by an infrared-based fMRI compatible tracker, the ASL Eye-Trac 6 (Applied Science Laboratories, Bedford, MA), to ensure that the subjects followed directions and remained awake. The visual stimulus followed a standard block design, or pseudo-randomized block design, to minimize subject burden and decrease test duration. Figure 3 is an example of the pattern and fMRI response from recent trials of the current study.

fMRI Scanner and Site Localization. The magnetic resonance (MR) scans were performed on a 3.0 Tesla GE imager (General Electric, Fairfield, CT) with an 8-channel array head coil at Nationwide Children's Hospital. Study protocol included an MR brain screening with sagittal T1-weighted and axial T2-weighted images to ensure the absence of any anatomic brain abnormality (eg, Arnold–Chiari syndrome). The fMRIs were undertaken using the blood oxygen level dependent sensitive T2* echo planar imaging sequence to gather whole brain data sets. The Montreal Neurological Institute coordinates and anatomical landmarks were used to define the anatomical sites of activation and deactivation clusters (voxels) derived from different statistical approaches. Identification of these areas was guided by the atlas of Talairach and Tournoux and confirmed by a radiologist.

fMRI Data Acquisition. The acquisition parameters were echo time (TE = 35 ms), relaxation time (TR = 3.0 sec), flip angle = 90° single shot, full k-space, 128 × 128 acquisition matrix with a field of view = 24 cm, which generated an in-plane resolution of 1.875 mm² with a maximum total of 27 axial slices. This produced a total of 120 volumes or time points per patient. Furthermore, for anatomical imaging we used a three-dimensional, spoiled gradient-echo pulse sequence (0.469 mm³) in the axial plane and obtained 1.3-mm thick slices.

fMRI Data Analysis. A multi-stage process for data analysis was performed using FEAT (FMRIB Expert Analysis Tool) Version 5.4 (FMRIB Centre, Oxford, UK). This method involved both individual and higher/group level statistics.

The pre-statistical process involved slice-timing correction using Fourier-space time-series phase shifting. Motion correction was achieved with MCFLIRT (FMRIB Centre), a mean-based intensity normal-
ization of all volumes by the same factor. High-pass temporal filtering and Gaussian-weighted least squares fit straight line fitting were also employed. To investigate the possible presence of activation or unexpected artifacts, an Independent Component Analysis based exploratory data was conducted using MELODIC (FMRIB Centre). Additionally, FILM (FMRIB Centre) with local autocorrelation correction was used to perform time-series statistical evaluation. The Gaussianized T/F or Z images were thresholded using clusters determined by an average Z > 5.1 and a corrected cluster significance threshold of $P = .01^{26-28}$ while the registration to high resolution and/or standard images was performed with FLIRT (FMRIB Centre). To further minimize motion, the subjects were given instructions not to speak during the fMRI trial unless an emergency occurred or the subject wanted to withdraw from the study. However, we did compare the relative displacement of anatomical images for each subject to assess image motion over time.

To assess the individual subject and session level, we used a general linear modeling approach. The input stimulus function on-off model from Figure 2 was convolved with a Gaussian (sigma 2.8 sec and peak lag 5 sec) to yield the regressor for the general linear modeling. This was to form the hemodynamic response function, which blurs and delays the original waveform to match the difference between the input stimulus waveform and the output measured fMRI hemodynamic response function (ie, to create a single contrast on-state versus off-state). The higher-level group statistics were performed using fixed effects.

**Psychophysics.** Monocular visual acuity was measured using an ETDRS visual acuity chart using a 10-alternative forced choice procedure as described previously. Contrast sensitivity functions were measured using a Vistech 6500 (Vistech Consultants, Inc., Dayton, OH) wall-mounted chart utilizing a 3-alternative forced choice procedure as previously described. Subjects with INS undertook psychophysical tests with free head and body posture and were not constrained in any way to maximize visual function.

**Eye Movements.** Eye movements were recorded with an MRI compatible eye tracker (LRO Eye Tracker; Applied Science Laboratories, Bedford, MA) positioned at the rear of the MRI bore. Imaging was limited to the patient's right eye via a front surface mirror attached to the MRI head coil. Eye movements, fixation, and eye closure were monitored in real time throughout each trial.

**Procedure**

Following fully informed signed consent, each subject underwent visual acuity and contrast sensitivity function measurements on each eye. Next, each subject with INS was positioned in front of an examiner and, with binocular viewing, the intensity of nystagmus was evaluated as the subject fixated on a pen light that was positioned throughout the patient’s visual field to locate the null zone and areas of robust nystagmus. A map was generated of the subject's null zone or semi-null zone and areas of high intensity nystagmus for use in the MRI scanner to approximate corresponding zones of minimal and maximum nystagmus. When the subject with INS was placed in the scanner, the null zone map was fine tuned with the use of the fMRI compatible eye tracker and fixation points within and outside of the subject's null zone were determined for use in the experiment.

Subjects with INS were run in the fMRI study first, followed by the normal subjects. Normal subjects' fixation positions for the fMRI study were based on their age- and gender-matched INS subject's gaze positions so that gaze positions were similar between the INS and normal subjects.

Following the completion of the psychophysical data, subjects were taken to the MRI scanner. Subjects were positioned on the MRI scanner bed and the head was constrained with pillows and a head strap. Once the subject was placed in the scanner, the stimulus viewing mirror was adjusted so that the subject could binocularly view the stimulus screen. Another front surface mirror was adjusted to align the eye tracker, positioned behind the scanner, with the subject's right eye. For the INS subjects, the nystagmus map obtained earlier was used to provide a rough estimate of null zone and areas of robust nystagmus. Based on eye tracker monitoring in real time, two small fixation points were adjusted to identify gaze positions corresponding to robust nystagmus outside of the null zone and minimal nystagmus within the null zone.

Once the gaze positions were identified for the subjects with INS, the scanner protocol was established such that the fMRI data acquisition on-state and off-state matched the corresponding gaze positions as outlined in Figure 2. During data acquisition, each subject's eye movements and fixation were monitored in real time to ensure that subjects followed instructions.

For intra-patient comparison, the minimum and
maximum nystagmus were used as the off and on states, respectively. The age- and gender-matched controls looked in the same gaze direction as the patients (eg, gaze left then right). The control subjects could not voluntarily move their eyes at the frequency of the patients, so this proper control of fixation was chosen.

RESULTS

Psychophysical Data

Visual Acuity. A summary of visual acuity results is shown in Figure 4. Normal subjects had a mean visual acuity of -.08 logarithm of the minimum angle of resolution (LogMAR) (range: -.02 to -.2; 20/12 to 20/18) in the right eye and -.10 LogMAR (range: -.02 to -.18; 20/18 to 20/13) in the left eye. The subjects with INS had a mean visual acuity of .245 LogMAR (range: .4 to .02; 20/50 to 20/22) in the right eye and .305 LogMAR (range: .56 to .02; 20/70 to 20/18) in the left eye.

Contrast Sensitivity Function Data. Contrast sensitivity function data are presented in Figure 5. The contrast sensitivity functions from the right and left eyes were similar for the normal subjects and for the subjects with INS. Note that the patients with INS exhibit a loss of contrast sensitivity restricted to the higher spatial frequencies, referred to as a Type I contrast sensitivity function loss, compared with the normal subjects.

Eye Movement Data. Representative eye movement recordings from the subjects with INS are shown in Figure 6 for the “On” condition (left side), where gaze was directed outside of the null zone and where nystagmus was robust, and for the “Off” condition (right side), where gaze was directed within the null zone and where nystagmus was reduced or absent. Although it was not the purpose of the study to quantify the intensity of the nystagmus, quantification of one of the INS subject’s nystagmus by hand scoring revealed that nystagmus frequency was 4.56 beats/sec outside of the null zone (range: 4.5 to 4.75) and 1.63 beats/sec within the null zone (range: 0 to 2.75), depending on the trial.
Figure 7. Mean activation seen across all sessions in controls (left column) and in patients (right column) \((P = .01; \text{Z-score} > 5.1)\). Crosshairs pointing to coordinates \((x = 44, y = 23, z = 27)\) of the decline of vermis for the controls and coordinates \((x = 53, y = 26, z = 26)\) of the decline for the patients. The prominent activation superior to the decline of vermis is the lingual gyrus in the control group. The other activation seen in the patient group relative to the decline are the middle occipital gyrus (BA18) (most superior), fusiform gyrus (most posterior and superior), and lingual gyrus (slightly posterior and superior).

**fMRI Data.** Because of the small number of subjects, we performed fixed-effects statistics on the individual subjects and group data on the entire brain with a specific interest in the cerebellum. The first step of the multistage analysis consisted of comparing the gaze in the null zone versus outside the null zone for each individual. In this case, three of the four patients showed activation in the decline \((P = .01, \text{Z-score} > 5.1)\). None of the controls showed this activation \((P = .01, \text{Z-score} > 5.1)\). The second stage consisted of taking the mean activation (one-sample \(t\) test) of all of the patients and comparing to the mean activation of all of the controls. In this case, activation was seen in the group of patients (including the nonfamily member) in the decline \((P = .01, \text{Z-score} > 5.1)\). Figures 7 to 10 illustrate four different regions of mean activation for controls (left columns) and patients (right columns) overlaid onto a standard brain template. Additional regions that were activated on average across all of the patients included middle occipital, lingual, and fusiform gyri \((P = .01, \text{Z-score} > 5.1)\). Our novel fMRI method demonstrated that the decline of the cerebellum is actively involved in INS. In normal controls, there was activation of the decline of vermis with saccadic eye movements consistent with previous work (oculomotor vermis). The current results identify the cerebellum, specifically the decline, as a significantly activated site for oculomotor dysfunction associated with INS.

**DISCUSSION**

The current study used a novel fMRI technique, referred to as the null zone fMRI technique, to localize the anatomical correlates of INS. The null zone fMRI technique capitalizes on the variable
Figure 9. Mean activation seen across all sessions in controls (left column) and in patients (right column). \( P = .01; Z \text{-score} > 5.1 \). Crosshairs pointing to coordinates \((x = 45, y = 26, z = 41)\) of the cuneus including BA18 for the controls and coordinates \((x = 42, y = 19, z = 41)\) of the cuneus including BA17 for the patients. The activation seen in the sagittal view of the control group is the declive of vermis. The activation seen in the sagittal view of the patient group is the lingual gyrus including BA17 and BA18. The activation seen in the axial view of the patient group are the lingual including BA18 and middle occipital including BA18 gyri along with the superior part of the declive.

Figure 10. Mean activation seen across all sessions in controls (left column) and in patients (right column). \( P = .01; Z \text{-score} > 5.1 \). Crosshairs pointing to coordinates \((x = 54, y = 26, z = 23)\) of the uvula in both groups. The uvula is activated in the patients but not the controls. The area of activation seen in the coronal view of the control group is the cuneus including BA30. The area of activation seen in the axial view of the patient group is the middle temporal gyrus BA21. The other areas activated in the sagittal view of the patients are the lingual, fusiform including BA18, middle occipital including BA18 gyri, and the declive.

The intensity of the nystagmus based on gaze position: whether gaze is directed to the null zone where nystagmus is minimal or directed to outside of the null zone where nystagmus is robust. By linking these two gaze positions to the fMRI off-condition and on-condition, respectively, the brain site(s) related to INS were revealed.

With respect to patient and control comparisons, the controls could not voluntarily move their eyes at the frequency of the patients, so the proper control of fixation was chosen. By having both the patients and controls “fixate,” we could isolate the involuntary nystagmus, slow and fast eye movements of INS.

These preliminary data reveal that the declive of the cerebellum is related to the nystagmus associated with INS. The declive was not activated in age-matched normal controls under identical viewing conditions. The current results are the first to identify the cerebellum and specifically the declive as part of the ocular motor network involved in INS. Previous fMRI studies of ocular motor dysfunction localized other regions of the cerebellum. Patients with downbeat nystagmus had floccular deficiency and showed reduced activation in the parafloccular lobule. Also, the fastigial nucleus was found to be related to opsoclonus specifically in deep cerebellar nuclei.

Based on heredity and genetic studies of INS and given the number of different INS waveforms that may exist, it is evident that INS comprises a heterogeneous population of patients with associ-
ated ocular pathologies, and idiopathic nystagmus dysfunction. For example, INS is associated with albinism, an abnormality that includes the obvious ocular pathology (lack of melanin) as well as an abnormal misrouting of optic nerve fibers from the temporal retina of each eye to the contralateral hemisphere. INS has also been implicated in patients without a chiasm based on MRI. These patients were not the focus of the current study. Only patients with idiopathic INS from one primary family were evaluated. The patients in the current study had good visual acuity and did not have other ocular pathologies associated with INS. We do not know whether the current fMRI results are specific to just one subtype of INS, which affects the family with the three members who participated in the study. A much larger fMRI study of patients with INS is planned to assess whether there is one type or multiple types of INS based on fMRI.

The range of visual acuity values found within the subjects with INS in the current study agree with visual acuity estimates of subjects with INS reported previously. Additionally, the contrast sensitivity function findings of a loss of contrast sensitivity restricted to the higher spatial frequencies, known as a Type I contrast sensitivity function loss, is in agreement with the obtained visual acuity in the subjects with INS. These data further substantiate that the subjects with INS did not have associated visual pathology, which would have caused further losses of visual acuity and/or loss of contrast sensitivity function. Family history, involving four generations as outlined in Figure 1, is suggestive of autosomal dominant INS, although formal genetic testing has not been undertaken on the family.

It has been postulated that INS may involve a pursuit eye movement system abnormality leading to pendular and pendulomotor waveforms. A possible vestibular abnormality in some patients with INS may lead to linear jerk nystagmus. INS has been modeled as an undamped velocity oscillation in the pursuit system and as a “pursuit-system nystagmus.” Others have modeled INS as a saccadic system abnormality or argue that no current models of normal oculomotor control can explain all of the waveforms seen in INS. Although most non-fMRI evidence favors a pursuit eye movement abnormality in INS (e.g., undamped velocity oscillator), one reason for different models of INS is partly due to the fact that little is known about the anatomical correlates of INS. The limited nature of the current study and the small number of subjects prevents detailed discussion regarding the most appropriate model of INS.

The decline is part of the vermis and one or both have been identified as involved in optokinetic nystagmus and saccadic eye movements based on fMRI. In addition, Ettlinger et al. have identified the vermis as involved in prosaccadic gain based on gray matter volume of the cerebellar hemisphere and vermis. Other cerebellar regions responsible for optokinetic nystagmus, such as the superior semilunar lobule, simple lobule, quadrangular lobule, inferior semilunar lobule, and cerebellar tonsil, have also been reported.

Pathological conditions involving the cerebellum, such as Arnold-Chiari malformation in which the cerebellar tonsils herniate into the upper cervical spinal tract, have been associated with other types of nystagmus including down beat nystagmus and periodic alternating nystagmus. Anagnostou et al. found deep cerebellum lesion involvement in Langerhan’s cell histiocytosis relapse, in which a patient demonstrated high frequency square-wave jerks averaging approximately 1.5 Hz, along with impaired smooth pursuit. Baumann et al. showed that patients with cerebellar lesions due to stroke had dysmetric saccades and saccadic smooth pursuit eye movements compared with normal controls. Sander et al. showed that patients with vermis lesions due to stroke had impaired conjugate smooth pursuit eye movements, as well as impaired slow convergence eye movements while maintaining normal fast vergence eye movements.

Although numerous studies have identified the cerebellum, vermis, or decline as involved in saccadic eye movements, few studies have identified one or more of these structures as involved in smooth pursuit eye movements. Tanabe et al. have identified the cerebellum as involved in normal smooth pursuit eye movements. Several other research groups have shown a relation between abnormal smooth pursuit eye movements and cerebellar abnormalities as discussed previously.

Recently, Schlindwein et al. undertook a fluorodeoxyglucose PET scan combined with a structural MRI scan to assess visual motion suppression of oscillopsia in a 31-year-old patient with congenital pendular nystagmus. They found that there was a significant increase in regional cerebral glucose me-
tabolism in the cerebellar nodulus with maximum nystagmus. It is known that the cerebellar nodulus, along with the ventral uvula, exert control on optokinetic nystagmus and on the torsional vestibuloocular reflex.61

The current study has two possible areas of improvement: temporal and spatial resolution (the ability to distinguish between two points on the brain). The current paradigm is based on a block design that allows us to monitor blood flow down to a few seconds. However, future designs may include rapid event related paradigms that would allow the capture of events at the millisecond resolution. This may be deemed more accurate for capturing oculomotor responses. Also, the scanning protocol could be optimized to improve the spatial resolution and improve the location of activation. However, the current protocol was sufficient to validate the new technique.

The null-zone fMRI technique first reported here may be used to assess the ocular motor circuitry of other types or subgroups of patients with INS, as well as patients with different types of nystagmus, provided that the patients have a null zone or semi-null zone whereby nystagmus intensity is altered based on gaze position. The current fMRI procedures may also be used to identify subgroups of patients with idiopathic INS. By linking gaze position with the on-off fMRI sequence used by the blood oxygen level dependent fMRI technique, further information will become available about the underlying circuitry associated with the specific type of nystagmus and the most appropriate types of models for better understanding INS and nystagmus in general. By identifying these ocular motor circuits, it may eventually be possible to alter the function of these ocular motor circuits surgically, pharmacologically, via transcranial electrical stimulation, or via other methods to minimize the nystagmus and increase saccade time and maximize visual function in these patients.

REFERENCES

16. Leguire LE, Kashou NH, Fogi N, et al. Neural circuit involved in idiopathic nystagmus syndrome based on fMRI. Paper presented at: ARVO Reducing Disparities in Eye Disease and Treatment; May 3-7, 2009; Fort Lauderdale, FL.
The answer to *What's Your Diagnosis?* is congenital bilateral dacryocystocele. Congenital dacryocystocele is an uncommon condition of predominantly female neonates; bilateral presentations are extremely rare. It was treated initially with gentle massage and then probing. If not recognized and treated in a timely manner, dacryocystitis can develop within a few days or weeks. Another serious complication is respiratory compromise, occurring due to a large intranasal cystic component causing blockage of the nasal cavity.

**REFERENCES**