

Focused Ultrasound Treatment, Present and Future

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Abstract

The discovery that ultrasound waves could be focused inside the skull and heated to high temperatures at a focal point goes back to 1944. However, because the skull causes the ultrasound waves to attenuate and scatter, it was believed that application of this technology would be difficult, and that it would be impossible to use this approach in the surgical treatment of intracranial diseases. Eventually, magnetic resonance image guided focused ultrasound (MRgFUS) surgery began being used to treat uterine fibroids, breast cancer and bone metastasis and locally confined prostate cancer. In the first ten years of the 21st century, new developments in this technology have been achieved, broadening the scope of practical application, and treatment is now being performed in various countries around the world. In 2011, third-generation transcranial focused ultrasound made it possible to use thermocoagulation and create intracranial lesions measuring 2 to 6 mm in diameter with a precision of around 1 mm. It was also possible to produce MR images which relay information of temperature changes in real time, enabling a shift from reversible test heating to irreversible therapeutic heating. This gave rise to the possibility of a minimally-invasive treatment with outcomes similar to those of conventional brain surgery. This method is paving the way to a new future not only in functional neurosurgery, but in cranial neurosurgery targeting conditions such as epilepsy and brain tumors, among others. In this paper, we describe the current state and future outlook of magnetic resonance image guided focused ultrasound, which uses computed tomography (CT) bone images in combination with MRI monitoring of brain temperature.

Key words: focused ultrasound, functional neurosurgery, brain tumor, epilepsy, blood brain barrier permeability

Introduction

Magnetic resonance image guided focused ultrasound (MRgFUS) has been used to date to treat conditions such as uterine fibroids, breast cancer, and bone metastasis, degenerative joint diseases, and locally confined prostate cancer. In the field of neurosurgery, the concept of using high-intensity focused ultrasound was reported by J. G. Lynn and T. J. Putnam as early as 1944.¹⁾ It was thought, however, that because the skull causes ultrasound waves to attenuate and scatter, application of this technology in intracranial diseases would be problematic. As we moved into the 21st century, however, advances were made in imaging and fusion technologies, making it possible to correct for ultrasound attenuation and scattering, and as a result intracranial treatment has become a reality. MRgFUS is already being used to treat people in various countries around the world.

It is now possible to use thermocoagulation to create an intracranial lesion measuring 2 to 6 mm in diameter with a precision of around 1 mm, and to use MRI to measure changes in temperature in real time in order to monitor positional data and brain temperature data. This provides the control necessary to transition from low-grade and reversible heating, which produces a stimulative effect, to irreversible coagulation heating. As a result, we can now perform minimally an invasive treatment that provides outcomes similar to those of conventional radiofrequency coagulation surgery, without the need for skin incisions or burr holes.

Joint clinical trials applying focused ultrasound thalamotomy for the treatment of essential tremor were initiated at centers in seven different countries in 2013 with the aim of obtaining Food and Drug Administration (FDA) approval, and the results were published in August 2016.²⁾ This paper explores the current state and future outlook of this equipment, as well as upcoming directions in neurosonosurgery.

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Focused ultrasound system

The ultrasound equipment consists of a helmet of 30 cm in diameter with 1,024 transducer elements. The unique pathway of the ultrasound waves caused by the skull geometry can be measured using CT bone images and MR images in conjunction. These measurements allow correcting the phase of each element in a way which produces constructive interference at the focus, yielding a single tight focus, similar to the way that a magnifying glass is able to collect optical light and focus the rays at the natural focus raising the temperature (Fig. 1). The treatment is done inside a 1.5 Tesla or 3.0 Tesla MRI gantry. Using this approach, the advantages of both CT and MRI can be utilized, along with information about the temperature at the target point.

The space between the head and the helmet is filled with ionized, bubble-free water at 15 degrees Celsius, which enables the propagation of the ultrasound waves. The degassed water, which continuously circulates around the skull, is also used to cool the skull. During sonication, the skull absorbs a significant amount of the energy and heats up, raising the temperature of the adjacent dura matter, which may result in headache and nausea. The cold water helps to reduce the temperature of the skull and counteract this phenomenon.

Microbubbles can be created due to interaction between the tissue and the ultrasonic field. These air bubbles oscillate and grow in size in response to the alternating regions of high and low pressure

induced by the ultrasonic wave, and when the acoustic pressure is high enough these microbubbles may collapse, creating a shock wave, known as cavitation. The Exablate system is designed to monitor a large spectrum of frequencies and automatically stop the sonication when abnormal readings are detected around half the operating frequency (680 KHz). Cavitations may occur due to pineal body calcifications, basal ganglia calcifications, calcifications of the cerebral ventricles and calcifications of the cerebrum/dura mater, as well as intracranial calcifications such as paranasal sinuses, primarily frontal sinuses. In addition, some elements are shut down if the calculated beam path to the focus passes through the membrane, through air around the membrane or through areas delineated by the treating physician as “no-pass regions” (NPR) (Fig. 2). Conditions that are required in order to increase the temperature at the target focal point are as follows: there must be a total of at least 700 effective elements, and the skull area through which the ultrasound waves pass must be at least 250 cm² (Fig. 3).

During the treatment, feedback regarding the patient’s neurological symptoms and thermal images of the brain using MRI are provided in real-time. Initially, low-stimulation heating is performed and the target position is corrected. For position correction, heating is performed at least three times, and the

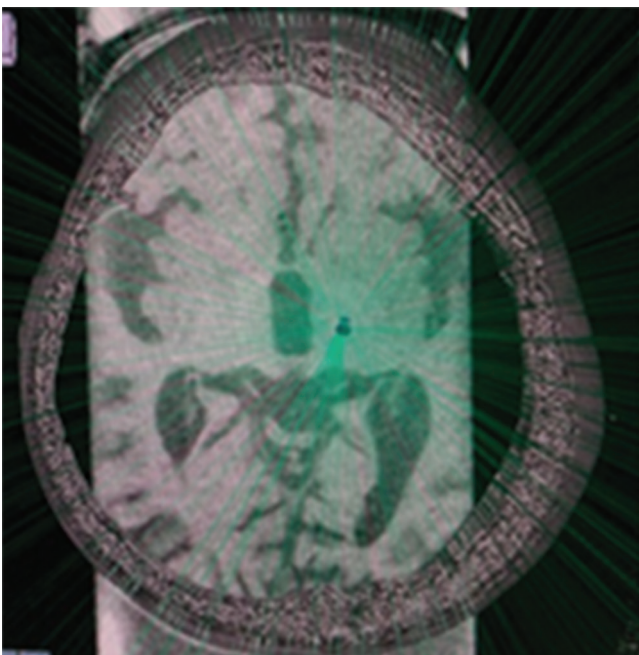


Fig. 1 Focused ultrasound. Description: Ultrasound waves are shown focused on the left thalamic Vim nucleus.



Fig. 2 No-pass region. Description: The *black circle* indicates air around the membrane, and the *red circle* indicates the membrane itself.

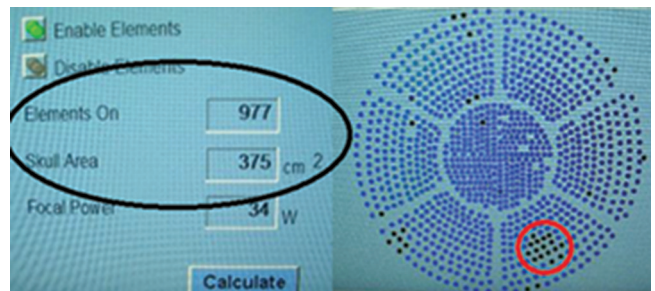


Fig. 3 Display of elements that are on, and skull area. Description: This shows elements that are operating, and the permeable surface area of the brain.

target correction is done in three directions (Fig. 4). Next, heating is done on a trial basis, which produces a stimulation effect on the target, and the neurological findings are checked. At this point, if the target is at an appropriate position (for example, the Ventral intermediate (Vim) nucleus for essential tremor, and the Vetrooralis posterior (Vop) nucleus for focal dystonia), this suggests that a valid area is being targeted, and this contributes to the effectiveness of the coagulation treatment. Similarly, if heating occurs at a dangerous position (for example, the pyramidal tract), adverse neurological symptoms such as paralysis may occur, and sonication can be discontinued at the point of reversible test heating, thus maintaining safety. Once an appropriate target position has been identified, the sonication power is further increased to the level where irreversible coagulation heating, meaning therapeutic heating, is achieved. During each sonication, MR images are taken, and the increase in the temperature at the target focal point and position information are simultaneously checked. By controlling the ultrasound delivery in real time in this manner, side effects caused by coagulation can be avoided. Moreover, this method eliminates the risks posed by drilling burr holes, such as in deep brain stimulation and deep brain coagulation, for example, brain trauma resulting from penetration, blood vessel trauma and infection, and there is no need to consider an entry trajectory, as there is in surgery.

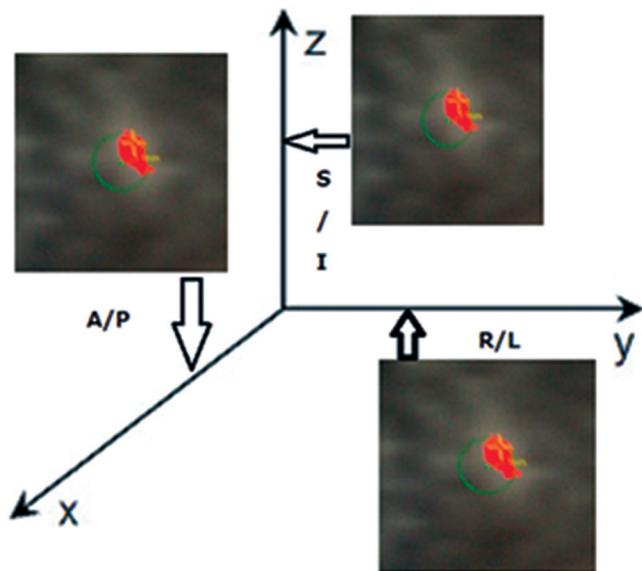


Fig. 4 3-dimensional position correction. Description: Sagittal or coronal images are used to correct in the superior/inferior direction (S/I), and axial or sagittal images are used to correct in the anteroposterior direction (A/P). Coronal or axial images are used to correct in the horizontal (left-to-right) direction.

Focusing on a single point minimizes the scattering of heat to surrounding tissue. Coagulation is maintained within 1 mm of the target position 84% of the time, and within 0.72 mm on average³). At a distance of 0.2 mm from the coagulated tissue, the preservation of histopathologically normal tissue has been confirmed. This verifies the accuracy of the treatment, and sharp margins of the treated volume.

These advances tie in to the minimal level of invasion, the precision, and the reversibility of the treatment, and contribute to the low level of risk of this approach.

Present and Future

Clinical research results (Present)

To date, reports have been published involving essential tremor, tremor-dominant Parkinson's disease, neuropathic pain, obsessive-compulsive disorder, and brain tumors. In this paper, we review each of these in turn. (Table 1)

Essential tremor

Reports have been published describing three pilot studies and one double blinded, randomized controlled pivotal study targeting essential tremor. The most comprehensive of these reports was published by Elias et al. in August 2016.²⁾

Efficacy was evaluated using the Clinical Rating Scale for essential Tremor (CRST) as the first endpoint and the Quality of Life in Essential Tremor (QUEST) questionnaire as the second endpoint. In the CRST evaluation, improvement was seen in all categories, which include speaking, eating, drinking, hygiene, dressing, writing, working and social activities. Particularly strong improvement was seen in social activities. Similarly, in the

Table 1 Implementation stages of transcranial focused ultrasound (including Japan and other countries)

Preclinical	Clinical trials	Approved
Hydrocephalus	Alzheimer's disease	Essential tremor
Multiple sclerosis	Brain tumors	Neuropathic pain
Stroke	Depression	Parkinson's disease
Traumatic brain injury	Epilepsy	
Trigeminal neuralgia	Neuropathic pain	
	OCD	
	Parkinson's disease	
	Pediatric neuroblastoma	

QUEST evaluation, improvement was seen in all of the categories, which include speaking, work and finance, hobbies and leisure, physical and psychosocial, with particularly strong improvement seen in the psychosocial category.

Gait disturbance and paresthesia were seen as typical adverse events. These were most obvious on the day of treatment and the following day. In 75% of the cases in which gait disturbance was seen, the gait disturbance disappeared within 12 months, and in 63% of cases that demonstrated paresthesia, the paresthesia disappeared within 12 months.

Nir Lipsman et al. (2013), reported that improvement of the tremor and numbness occurred as a result of ultrasound sonication at the stage when MRIs did not yet show a coagulation lesion. These results suggest that ultrasound may affect neurological functions other than producing coagulation (the stimulative effect of ultrasound).³⁾

Wintermark et al. (2013), in describing the characteristics of ultrasound-induced lesions as they appeared on images, reported the formation of coagulation layers in three zones. Edema occurred in the outermost layer, but it reached a peak within three months, and as the edema disappeared, there was a corresponding decrease in the tremor improvement rate, and adverse effects were eliminated.⁴⁾

It has been suggested that the size of the coagulation lesion is not governed by the number of sonications and the attending energy. The relationship between lesion size and sonication is an issue that will require further study. At the same time, the ability of ultrasound to penetrate bone has been an issue in realizing this treatment from the outset, with skull volume and skull density being factors that affect penetration. However, the possibility that bone thickness and shape cause defocusing to occur has also been suggested, and the relationship between bone, ultrasound, amount of heat and coagulation lesion are topics to be addressed in future studies.^{2,5,6)} In this report, it is mentioned the skull density and ultrasonic permeability, and the lower the ratio of the cancellous bone to the dense bone of the skull (Skull density ratio), the lower the ultrasonic permeability and the tendency of the increase in the brain temperature tends to be difficult.

Vim coagulation for essential tremor preceded clinical research in transcranial focused ultrasound, and was the first approach for which usefulness was scientifically verified. Currently, more cases are being treated worldwide by means of transcranial ultrasound than any other approach, and research is underway that will bring this treatment to further heights of advancement.

Tremor dominant parkinson's disease

Anouk Magara et al., (2014) and Ilana Schlesinger et al., (2015) have published reports on tremor dominant Parkinson's disease. Anouk Magara reported on the usefulness of pallidothalamic tractotomy (PTT) using focused ultrasound in tremor dominant Parkinson's disease, describing the treatment of a total of 13 cases. In the first four cases, there was only one therapeutic sonication (temperature at target: 52°C to 59°C). Neurological confirmation three months post-treatment showed obvious recurrence. Also, at the three-month point, the treated area was no longer visible on images. In the subsequent nine cases, therapeutic sonication was done four or five times. Improvement in tremor was observed three months post-treatment based on the Unified Parkinson's Disease Rating Scale (UPDRS) score, and for these patients, the lesion was still visible on images. The report suggests that multiple therapeutic sonications are necessary for coagulation at the specified target. The authors report that, like high-frequency stimulation of the subthalamic nucleus (STN-DBS) and internal globus pallidus DBS (Gpi-DBS), focused ultrasound is effective not only for tremor, but also for rigidity and akinesia.⁷⁾

Ilana Schlesinger⁸⁾ published a report on coagulation treatment of the Vim nucleus using focused ultrasound in patients with tremor dominant Parkinson's disease. In this report, the authors stated that, as with conventional coagulation of the Vim nucleus using high frequencies, focused ultrasound is effective for tremor, but is not effective for rigidity or akinesia. They also reported unstable gait and numbness as adverse events accompanying treatment. The report cited the same adverse events with essential tremor as those seen in reports describing Vim coagulation.⁸⁾

Neuropathic pain

Daniel Jeanmonod et al. (2012) reported on central lateral thalamotomy performed in 2012 on 11 patients with neuropathic pain. In the first two cases, a small lesion was created, and in the subsequent nine cases, true coagulation of the thalamus was achieved using transcranial focused ultrasound. In the first two cases, the maximum temperature at the target was 53°C, where in the nine subsequent cases, the temperature achieved ranged from 55°C in the lowest case to a maximum of 64°C. At the three-month point, the mean pain relief for the nine cases was 49%, and for the eight cases that reached the one-year point, improvement of 42% was reported. In the report, the authors pointed out that with focused ultrasound, an appropriate temperature must be reached in order to create an irreversible lesion, and that MRI imaging and

monitoring of the temperature at target are necessary with focused ultrasound in order to ensure safety and efficacy.⁹⁾

Obsessive-compulsive disorder

In 2014, H. H. Jung et al., reported a study in which capsulotomy was performed using focused ultrasound in cases of obsessive-compulsive disorder. Among the subjects, four patients underwent bilateral capsulotomy. Six months post-treatment, none of the patients exhibited any adverse neurological events, and improvement was seen across the board on the Yale-Brown Obsessive Compulsive Scale (Y-BOBCS), the Hamilton Depression Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A). The report describes adverse events that occurred with capsulotomy using high-frequency coagulation as intracranial hemorrhage (necessitating cerebral ventricle drainage), reduced cognitive function, confusion, personality changes, and weight loss, among others. With capsulotomy using the Gamma Knife, there was radiation injury caused by an increase in the radiation dosage and in the cubic volume of the irradiated site, as well as adverse events similar to those described for high-frequency coagulation. In the four cases in which capsulotomy was done using focused ultrasound, none of these adverse events were seen six months post-treatment, and one case was reported to have experienced weight increase. The report also includes a comparison of surgical stress and radiation injury.¹⁰⁾

Brain tumor

Daniel Coluccia et al. (2014) and Nathan McDannold et al. (2010) reported their research using MRgFUS for brain tumors. In their research, they reported that with the high-frequency focused ultrasound currently used (650 kHz), the strong central convergence of the ultrasound created a small lesion, and also, it was only possible to achieve a temperature increase for lesions close to the center of the skull. Because of this, lesion selectivity was high for lesions with a large volume, such as brain tumors, and the tumor had to be in the center of the skull, such as tumors of the thalamus. As a result, the report suggested that at the current point in time, focused ultrasound can possibly be applied in the treatment of brain tumors. Two possible approaches would be to use microbubbles to produce more powerful ultrasound waves, to use low-frequency focused ultrasound, or to use target drug delivery by destruction of the blood-brain barrier. Focusing the ultrasound waves on microbubbles may boost focal heating, while the use of low-frequency ultrasound waves, increases the penetration of the ultrasound

waves, making it possible to create a larger lesion. Temporarily opening the blood-brain barrier boosts drug permeability, and delivers the drug to a specific site. If these technologies can be realized, focused ultrasound could possibly be effective in the treatment of brain tumors.^{11,12)}

Future clinical research and status of approval in various countries (Future)

Looking at the status of approval of transcranial focused ultrasound in various countries, at present, the treatment has been approved by the United States (US FDA, Jul 2016), Europe (CE mark), Korea and Canada. Recently (Dec 2016), it also received approval by the Japanese Ministry of Health, Labour and Welfare for the indication of medication refractory essential tremor.

Clinical research in transcranial focused ultrasound is underway in a number of countries, and after clinical research focusing on essential tremor and tremor accompanying Parkinson's disease (Vim) has been completed, efforts will begin, particularly in the US, in clinical research relating to Parkinson's disease (GPi), epilepsy, brain tumors, opening of the blood-brain barrier, and other targets. In other efforts, physician-led clinical research is planned at various facilities (in Japan, this research will target dystonia and other conditions).

Some reports indicate that research will also target the feasibility of focused ultrasound in treating temporal lobe epilepsy. S. Monteith et al., (2016) describe research in which a gel-simulating tissue was injected into the cadaver skull bone to create temporal lobe models, and focused ultrasound was used to examine the feasibility of focal ablation in temporal lobe epilepsy. In this study, long sonications of 30 seconds were used to successfully increase the temperature at target, but the results suggested that temperature also increases at the base of the skull. The report pointed out the necessity for preventing temperature increases at the middle of the cranial base.¹³⁾ If temperature increases at the middle of the cranial base, the temperature of the cranial nerves on the surface of the skull could increase, and vertigo or other adverse events could occur if the temperature of the semicircular canal of the inner ear increases.

Timbie et al., (2015) reported on the possibility of using focused ultrasound for the blood-brain barrier. Using focused ultrasound (FUS) in combination with contrast medium microbubbles enabled temporary, non-invasive destruction of the blood-brain barrier, and the report indicated that it was possible to transport material measuring 100 nm to the central nerves when medication was administered

systemically. By using this technique in combination with magnetic resonance imaging, it will be possible to deliver a certain medication accurately to a selected target in the brain. Focal and transient destruction of the blood-brain barrier using MRgFUS could possibly hold the key to dramatic changes in the treatment of brain diseases when used in combination with nanotechnology. This report looks at research in destruction of the blood-brain barrier from a comprehensive standpoint, and examines possibilities for application of this technology in the future.¹⁴⁾

Conclusion

This review summarizes the current state of and future outlook for MRgFUS. Diseases of the central nervous system have been classified into the preclinical study stage, clinical study stage and approved treatment stage. The authors anticipate further clinical application in numerous areas, and look forward to the further development of this treatment approach.

Conflicts of Interest Disclosure

Dr. Taira, receiving lecture fees from Daiichi-Sankyo, Eisai, GlaxoSmithKline, Otsuka, Pfizer, Hisamitsu, Dainippon-Sumitomo, Takeda, and Kyowa-Hakko, and grant support from St. Jude Medical. No other potential conflict of interest relevant to this article was reported.

References

- 1) Lynn JG, Putnam TJ: Histological and cerebral lesions produced by focused ultrasound. *Am J Pathol* 20: 637–649, 1944
- 2) Elias WJ, Lipsman N, Ondo WG, et al.: A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* 375: 730–739, 2016
- 3) Lipsman N, Schwartz ML, Huang Y, et al.: MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol* 12: 462–468, 2013
- 4) Wintermark M, Druzgal J, Huss DS, et al.: Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. *AJNR Am J Neuroradiol* 35: 891–896, 2014
- 5) Chang WS, Jung HH, Kweon EJ, Zadicario E, Rachmilevitch I, Chang JW: Unilateral magnetic resonance

- guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J Neurol Neurosurg Psychiatr* 86: 257–264, 2015
- 6) Jung HH, Chang WS, Rachmilevitch I, Tlusty T, Zadicario E, Chang JW: Different magnetic resonance imaging patterns after transcranial magnetic resonance-guided focused ultrasound of the ventral intermediate nucleus of the thalamus and anterior limb of the internal capsule in patients with essential tremor or obsessive-compulsive disorder. *J Neurosurgery* 122: 162–168, 2015
- 7) Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D: First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound* 2: 11, 2014
- 8) Schlesinger I, Eran, A, Sinai A, et al.: MRI guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease. *Parkinsons Dis* 2015: 219149, 2015
- 9) Jeanmonod D, Werner B, Morel A, et al.: Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus* 32: E1, 2012
- 10) Jung HH, Kim SJ, Roh D, et al.: Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. *Mol Psychiatry* 20: 1205–1211, 2015
- 11) Coluccia D, Fandino J, Schwyzer L, et al.: First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound. *J Ther Ultrasound* 2: 17, 2014
- 12) McDannold N, Clement GT, Black P, Jolesz F, Hynynen K: Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery* 66: 323–332, 2010
- 13) Monteith S, Snell J, Eames M, Kassell NF, Kelly E, Gwinn R: Transcranial magnetic resonance-guided focused ultrasound for temporal lobe epilepsy: a laboratory feasibility study. *J Neurosurg* 125: 1557–1564, 2016
- 14) Timbie KF, Mead BP, Price RJ: Drug and gene delivery across the blood-brain barrier with focused ultrasound. *J Control Release* 219: 61–75, 2015

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