A Memorial Tribute to Kyoung-Min Lee: An Outstanding Behavioral Neurologist and Cognitive Neuroscientist

Kyoung-Min Lee, MD, Ph.D, the previous editor-in-chief of the *Journal of Clinical Neurology*, died in Boston, Massachusetts, United States of America (USA) on July 23, 2022 aged 59 years. His death is a tremendous loss to behavioral neurology, cognitive neuroscience, and numerous related research areas, since Professor Lee was one of the most active leaders in uniting disparate fields through multidisciplinary approaches and diverse research methodologies. Professor Lee also made a distinguished contribution to the remarkable growth of the *Journal of Clinical Neurology* as a highly cited international journal while he served as editor-in-chief from 2015 to 2020. In remembrance of Professor Lee, here we provide a biography and summarize his extensive scientific research.

Professor Lee was born on April 20, 1963 in Gwangju, Republic of Korea. He received his MD degree at the Seoul National University College of Medicine in Seoul in 1987, then moved to the USA and received his Ph.D degree in neuroscience under the supervision of Professor Peter H. Schiller at the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology (MIT), Boston, Massachusetts. He completed a neurology residency at the New York Hospital-Cornell Medical Center and a Behavioral Neurology/Functional Neuroimaging fellowship at Cornell University Medical College and Memorial Sloan-Kettering Cancer Center in New York. In 1997 he returned to Seoul National University in Seoul as an assistant professor of neurology and the Interdisciplinary Program in Cognitive Science (Fig. 1). He was promoted to a full professor in 2008. He served as the director of the Institute for Cognitive Science at Seoul National University from 2017 to 2019. Professor Lee also worked as a research scientist at the Smith-Kettlewell Eye Research Institute in San Francisco, California, USA from 2003 to 2010.

**Neuroscience of Visual Perception, Eye Movement, and Response Selection**

Professor Lee was an outstanding scientist in the field of neurophysiology and made exceptional contributions to improving the understanding of the neural mechanisms underlying visual perception, eye movement, and response selection throughout his life. His initial studies on visual information processing and eye movement in nonhuman primates were conducted with renowned neurophysiologist Professor Schiller during his Ph.D studies at MIT. In their earliest paper published in *Science* in 1991, they reported that ablation of the primate extrastriate area (V4) in rhesus monkeys led to severe deficits, particularly in tasks involving the selection of target stimuli that were smaller or had a lower contrast or slower rate of motion. The results suggested that V4 is involved in more complex aspects of visual information processing than previously thought. They subsequently revealed selective functions of the midget and parasol systems in visually guided eye movements, which include the lateral geniculate nucleus, V4, and middle temporal regions. Professor Lee also worked with Dr.
Fig. 1. Selected photographs of Professor Kyoung-Min Lee. A: Professor Lee in his office at Seoul National University Hospital in 2005. B: Professor Lee at the Homecoming Day of the Department of Neurology, Seoul National University Hospital in 2009. C: Professor Lee at Café Hakrim in Daehak-ro, Seoul in 2012. D: Professor Lee speaking at the Religion and Posthuman Forum at Kyungdong Church, Seoul in 2017. E: Professor Lee giving a lecture titled ‘Posthuman and Cognitive Science’ at Kyungdong Church in 2017. F: Professor Lee at Seoul National University Hospital in 2017. G: Professor Lee with his wife and two sons in Giethoorn, the Netherlands in 2019. H: Professor Lee at the Seoul National University campus in 2019.
Hicks's law describes that the latency of a behavioral response increases logarithmically with the number of alternative choices.\textsuperscript{10,11} Professor Lee and colleagues confirmed that Hicks's law is also valid for the saccade response.\textsuperscript{12} They used a saccade paradigm that required a stimulus–response transformation similar to that used by Hick, with the results showing a logarithmetic relationship for the saccade response time. These results were replicated in research on monkeys, which also yielded behavioral evidence that spatially distributed regions are generated during training for the sensory-to-motor associations that are subsequently used to make choice decisions.\textsuperscript{13} Professor Lee also examined Hicks's law in a functional magnetic resonance imaging (fMRI) study with a choice-based saccade task.\textsuperscript{14} The results suggested that the cognitive steps involved in making choice decisions occur in different networks of the subregions of the FEF and intraparietal sulcus, which showed distinct activations according to the number of alternatives. Another fMRI study of the finger-movement task also supported Hicks's law, suggesting the involvement of the posterior cingulate, left superior frontal gyri, and bilateral inferior parietal lobules.\textsuperscript{15} Drs. Lee and Keller further advanced these theories in the FEF neurons: the visual responses of the FEF decreased as the number of alternative potential targets increased, whereas the perisaccadic activity increased with the number of alternatives.\textsuperscript{16} These observations suggest two novel findings of FEF neuronal behavior: 1) "phasic visual" cells, which do not discharge during the perisaccade interval in a delayed-saccade paradigm, show such activity in a choice-response task at the time of the saccade; and 2) FEF visuomotor cells display an inverse relationship between perisaccadic activity and the time of saccade triggering, with higher levels of activity leading to longer saccade reaction times. Drs. Lee and Keller developed two tasks to elucidate the function of the FEF: 1) in the extended memory-guided saccade task, the visual stimulus and the saccade response were dissociated in space; and 2) in four-alternatives delayed saccade task, bottom-up attention shift and saccade target selection were independent.\textsuperscript{17} These novel task paradigms revealed that reversible inactivation of the FEF in rhesus monkeys disrupted memory-guided saccades, while visual detection was demonstrated to be intact in the same field. These findings underscore the motor aspect of the area's functions, especially when saccades are generated by internal cognitive processes including visual short-term memory and long-term associative memory. Another important functional aspect of the FEF discovered by Professor Lee through a series of visual short-term memory and attention experiments is the critical role that the FEF plays during information entry into visual short-term memory by allowing attention deployment on targets to be remembered.\textsuperscript{18}
Cognitive Science with Neurophysiological Methods

Professor Lee made outstanding contributions to cognitive science by employing neurophysiological techniques such as electroencephalography (EEG) and transcranial magnetic stimulation (TMS), functional near-infrared spectroscopy (fNIRS), and electrocorticography (ECoG), in addition to basic electrophysiological studies involving nonhuman primates. Professor Lee and colleagues used fMRI and TMS to investigate the orchestrated reorganization of the sensorimotor and temporal association cortices that contribute to skilled fingering and musical processing resulting from practicing the playing of stringed instruments. Taking advantage of the transient interference effect of TMS on cerebral processing, Professor Lee and colleagues also found that the right posterior parietal cortex (rPPC) plays an important role in temporal order judgment, at about 50–100 ms after the first target onset. These results show that the rPPC plays an essential role in timely detecting a target appearing in the left visual field, especially in competition with another target simultaneously appearing in the opposite field. In another study, Professor Lee and colleagues looked into whether the timing and spatial distribution of the EEG oscillations are associated with the aberrant phase of the visual short-term memory in change blindness; that is, the failure to notice a large change in the visual scene when the change occurs while the view is briefly interrupted. They suggested that poor initial image encoding is responsible for subsequent failure of change detection, and that anomalous processing in later stages of visual short-term memory is a consequence of the poor initial encoding and also contributes to change blindness. An fNIRS study performed by Professor Lee’s group also suggested that both speech and nonspeech sounds are processed and maintained by a neural mechanism for achieving sensorimotor integration using articularatory codes in the left inferior frontal gyrus. In 2018 Professor Lee and colleagues made ECoG recordings in nonhuman primates during a simple visual guided reaching task, and observed that right lateralization in long-range phase synchrony in the 10–20 Hz low beta band is involved in the motor preparation stage, irrespective of the side of the upcoming effector.

Functional Neuroimaging Studies

Professor Lee’s initial research into functional neuroimaging was conducted during his clinical training at Cornell University Medical College and Memorial Sloan-Kettering Cancer Center. He and colleagues reported intriguing fMRI findings of distinct cortical areas associated with native and second languages in 12 bilingual subjects at various stages of second-language acquisition. They concluded that the processing of two languages tends to occur in spatially distinct regions of Broca’s area when the second language was acquired late in life rather than during early childhood, whereas Wernicke’s area showed little or no separation of activity regardless of the age of acquisition. These observations significantly advanced the understanding of the cortical processing of multiple languages.

Professor Lee focused on collaborative functional neuroimaging studies with a multidisciplinary approach from diverse research fields after moving to Seoul National University, including in the fields of neurology, radiology, nuclear medicine, ophthalmology, and cognitive science. His early work mainly focused on the functions of the visual cortex. His research group produced several papers on fMRI and positron emission tomography (PET) that provided novel insight into the dynamic responses of the human visual cortex to external visual stimuli, which contributed to the understanding of the mechanisms of developmental visual impairment. He also performed fMRI investigations of many different areas of the human brain associated with various functions, such as attention, language, memory, motor, and sensory functions. One of his early fMRI studies revealed that the human supplemental motor area (SMA) can be separated into the pre-SMA and SMA proper based on their different functions: the former involving motor preparation and the latter involving motor execution. Professor Lee subsequently used fMRI to examine psycholinguistic differences between phonographic (Hangul) and ideographic (Hanja) characters by taking advantage of the two-script system of the Korean language, which was followed by more extensive fMRI studies on language and other brain functions.

Translational Research in Behavioral Neurology

Professor Lee led multiple collaborative neuroimaging studies with the Neuroscience Research Institute of Gachon University and the Korean National Primate Research Center into neurodegenerative diseases and animal models of dementia. He developed a nonhuman primate model of Alzheimer’s disease (AD) by performing intracerebroventricular injections of streptozotocin in cynomolgus monkeys. The AD nonhuman primate model was subsequently validated based on the cortical distribution of glucose hypometabolism and gene expression analysis using [18F]fluorodeoxyglucose (FDG) PET and the reverse-transcription quantitative polymerase chain reaction, respectively. Professor Lee and colleagues also showed that the antioxidant vitamin C reduced AD pa-
thologies such as the amyloid plaque burden, blood–brain barrier disruption, and mitochondrial alteration in animal models of AD.9,30 In an FDG PET study his group found that the neural activity of the basal forebrain is initially increased in patients with mild cognitive impairment, which suggested the existence of brain reserve against functional impairment during the incipient stages of dementia.41 His group subsequently investigated the topographical distribution of tau brain binding in patients with semantic variant primary progressive aphasia using [18F]THK5351 PET.32

Professor Lee’s clinical research interests ranged from imaging and pathological findings of neurodegenerative diseases to multiple aspects of cognitive function associated with various brain conditions. He was involved in collaborative research into the utility of a test for examining early cognitive function in predicting the prognosis of glioblastoma,43 the effect of deep brain stimulation of the subthalamic nucleus in patients with Parkinson’s disease,44 and the association between cognitive dysfunction and decreased vital capacity in patients with amyotrophic lateral sclerosis.45 His research group found that poor performance of patients with ischemic stroke in the Korean Syntactic Comprehension Test was significantly associated with lesions in the left perisylvian area and anterior temporal lobe.46 In one of their studies of patients with mild cognitive impairment, they found that the sound naming test was more sensitive than the picture naming test, which was attributed to early AD-related pathology in the temporal cortex.47

Professor Lee also collaborated on many other studies involving novel topics of behavioral neurology, such as the neuroanatomical mechanisms of apraxia,48 hemispatial neglect,49 and the alteration of functional neuroanatomy in epilepsy.50

His group also reported that arithmetic function is related to working memory in a subsystem-specific manner, with multiplication and subtraction being more closely linked to the phonological loop and the visuospatial sketchpad, respectively.51 In a more recent study, his group investigated the iconic memory decay of different stimulus attributes comprising an object and suggested that the various visual attributes of an object are lost over time at differing rates.52 In another recent study, his research group investigated the ability to inhibit eye movements when a subject has to process a peripheral target while maintaining strict fixation, and concluded that the inhibitory process controlling eye movement competes with other cognitive resources.53

Unfinished Projects

The research performed by Professor Lee in behavioral neurology and cognitive science deepened and widened his insight into humanity. In 2016 he recognized the increasing role of cognitive science in the advent of artificial intelligence (AI), which prompted him to critically consider the ethical problems in AI and perform academic investigations of their countermeasures by combining science, humanities, and religion. He analyzed the ontological influence of AI on modern society from the perspective of posthumanism. In particular, he helped to further our understanding of the characteristics of human intelligence, criticized the meaning and limitations of AI from the perspective of modern human theory, and highlighted the important research results of cognitive science in relation to ethics. This work is particularly significant in the aspect that the philosophical and religious “sensitivity” and the scientifically explained “identification” were combined to explore the possibilities of an ontological turn of intelligence and human being in the age of AI.44

Professor Lee also explored different possibilities for expanding human experiences outside of the constrained real world by taking advantage of the latest advanced technologies. To this end, he conducted various scientific investigations of cognitive processes in virtual environments and video games.55 To establish a scientific perspective and evidence for video games, he hosted seminars and forums and wrote a book in Korean titled Game Sapiens to communicate with experts from different fields and the public.56 Professor Lee further established the “Game-n-Science Institute” to understand the cognitive mechanisms underlying participation in games. His research group classified the cognitive characteristics of games into six dimensions: cooperativity, cognitive processing depth, perspectivity, multitasking, and reward time span. These concepts are being used to develop new methods and tools for predicting the aptitudes of game users. This work will be useful in diverse applications, such as improving the cognitive function of the elderly, conducting psychological experiments, selecting promising esports players, and developing rehabilitation treatments.

As a physician and devout Christian, Professor Lee lived a life devoted to the advancement of medicine and service to the weak. Professor Lee led an Official Development Assistant project through Korea International Cooperation Agency to train community health workers in Bulacan, the Philippines from 2016 to 2018. To solve the shortage of medical personnel in developing countries and establish a sustainable community-based healthcare system, emphasis was placed on developing a training curriculum aimed at increasing the number of community health educators in the Philippines.

Unfortunately, Professor Lee’s activities encompassing science, medicine, humanities, and religion stopped in July 2022. This is especially sad since we are sure that he would have made even more contributions in the future. We pay tribute to all that he has achieved, and wish that he may rest in peace.
Availability of Data and Material
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest
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