

Profile of Lynn Nadel

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Lynn Nadel says childhood curiosity sparked his fascination with psychology and the brain. Influenced by the fact that his father was an industrial chemist, Nadel initially thought he might study chemistry. So, he decided to attend McGill University for undergraduate studies based on the renown of its chemistry department. "Within about 3 months, I decided chemistry was not for me," he says.

As he explored other courses, Nadel attended a class taught by psychologist Donald Hebb. "I happened to take an introductory course from maybe one of the most famous psychologists of his time," says Nadel. "That course piqued my interest in the kind of psychology Hebb was famous for." During the 1960s, Nadel says, most American psychologists were less focused on neuroscience, compared with their Canadian counterparts. "I got sucked into psychology that was neuroscience-oriented even before the term neuroscience was really in the common usage," he says.

So, Nadel joined McGill University's psychology department. "Just by chance, I was at a place where there was enormous strength in research on human neuroscience, and particularly on memory, so I got pulled into the memory field," he says.

Nadel continues to study memory and has contributed greatly to the scientific understanding of the role of the hippocampus in memory and spatial cognition. His research has also shown how stress and sleep influence memory, and his studies of hippocampal development carry clinical implications, particularly in understanding Down syndrome. In his Inaugural Article, Nadel describes his latest thinking on the hippocampus and memory (1). Nadel is currently a Regents' Professor Emeritus at the University of Arizona and was elected to the National Academy of Sciences in 2021.

Introduction to Memory

After finishing his undergraduate studies in 1963, Nadel applied to medical school but was not admitted. The rejection proved fortuitous; instead, he got a job working as a technician in the laboratory of McGill psychology professor Dalbir Bindra. With Bindra's support, Nadel joined McGill's graduate program in psychology, examining memory mechanisms in both the cortex and hippocampus of rats. "It was a spectacular environment, especially rich in people studying memory," he says.

While Nadel was finishing his doctorate, he received a National Institute of Mental Health-sponsored postdoctoral fellowship, which enabled him to go to the Czech Academy of Sciences in Prague in 1967. There, he worked with neurophysiologists Jan Bures and Olga Buresova. Bures had invented a technique for making temporary reversible lesions in the rat brain, one that Nadel had used in his Master's thesis research, and Nadel was interested



Lynn Nadel. Image credit: Lynn Nadel (University of Arizona, Tucson, AZ).

in learning more about the technique. "It was a leap into the unknown and ended up being a life-changing experience," says Nadel. "Jan and Olga were phenomenal people and had an enormous impact on me, both scientifically and personally."

Nadel's postdoctoral stint was interrupted by sociopolitical events, including the Prague Spring of 1968 and the Russian invasion of Czechoslovakia. He was advised to leave the country and drove across Europe to London, where he joined a friend from McGill, John O'Keefe, who was working in the anatomy department at University College London at the time. Nadel returned to Prague to complete his postdoctoral work after 8 months in London, but his meeting with O'Keefe eventually led to a job offer at University College London in 1970 and launched the next phase of Nadel's career.

Cognitive Map Theory

Around the time that Nadel started working at University College London, O'Keefe discovered place cells in the hippocampus, a groundbreaking discovery that led to a share of the Nobel Prize in Physiology or Medicine for O'Keefe in 2014. "When he discovered the place cells in the hippocampus, he came down and showed them to me early on,

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and it was clear this was something pretty important," says Nadel. "It was luck that I ended up in London just down the hall from O'Keefe's Nobel Prize discovery," he says.

Nadel's work with O'Keefe influenced the rest of his scientific career. "I dropped what I was working on, which was the visual system, and jumped back into studying the hippocampus and joined forces with him," he says. Nadel and O'Keefe's collaboration led to a coauthored book and a new theory called the Cognitive Map Theory (2). "The major emphasis of the book and the original discovery was about the role of the hippocampus in spatial cognition, but it was very clear to us that this was a spatial memory system," says Nadel.

Nadel says the theory was described in some detail in a paper he and O'Keefe had contributed in 1974 (3). "We laid out what we thought a theory of the brain and behavior should look like," he says. "It required multiple levels of explanation and convergent operations."

"We assumed that the brain is compartmentalized, with different ways of getting things done," says Nadel. "We adopted the idea that there are multiple systems, each dealing with a different kind of memory and argued that this approach is important for understanding how memory works, and this notion of multiple memory systems guided much of my work going forward," he says.

Development and Stress

Nadel returned to the United States in 1976, and after stints at the University of California, San Diego, Dalhousie University, Canada, and the University of California, Irvine, he was hired in 1985 by the University of Arizona. He helped start a new cognitive science program there to bridge psychology and cognitive science and became the head of the psychology department within a few years.

At the University of California, Irvine and later at the University of Arizona Nadel worked on brain development. The hippocampus develops relatively late after birth in most animals, including humans. For example, the hippocampus takes 3 to 4 weeks in rats and 18 to 24 months in humans to become functional. "Given the importance of this structure in memory, this is really fascinating," says Nadel. "It helps understand why we have no memories from early in life, because the brain system responsible for our episodic, autobiographical memories is really not functional at the start of life," he says.

The hippocampus may also be particularly susceptible to disruption during this developmental phase. "Many of the early developmental disorders, such as autism, Down syndrome, Williams syndrome, Fragile X, lead poisoning, involve the hippocampus," says Nadel. Of Down syndrome, Nadel says, "It became fairly clear that there was a hippocampus problem, which I then pursued, trying to figure out what was going wrong in early hippocampal development that contributed to the cognitive problems in Down syndrome." Nadel spent the next two decades exploring the mechanisms underlying the cognitive problems and seeking ways to ameliorate them.

Nadel also started studying the effects of stress on memory, prompted by neuroscientist Bruce McEwen's discovery of stress receptors in the hippocampus. "It's one of

the structures in the brain that has the highest density of stress receptors," says Nadel. Among other things, Nadel investigated how developing animals might respond to stress. "If you stress animals early in life, you can alter hippocampal development," he says. "We, and many others, have now shown that early life stress can disrupt brain development," says Nadel.

The clinical implications of his research were not lost on Nadel. He collaborated with W. Jake Jacobs at the University of Arizona on the implications of delayed hippocampal development for certain clinical syndromes, including panic and other anxiety-based disorders (4). "We proposed a theory about the role of early developmental changes in the emergence of certain kinds of clinical anxiety and depression," he says. "So, there's a whole clinical side to my work that emerged out of the developmental work in the 1980s and 1990s," says Nadel.

Memory and Consolidation

In 1996, Nadel began to collaborate with neuropsychologist Morris Moscovitch, during the latter's sabbatical at the University of Arizona. "We ended up proposing a new theory of memory and memory consolidation that took hold in the field," says Nadel (5). "It built upon the notion that retrieving a memory from prior experience opens that memory up to being updated, and then reconsolidated back into long-term memory," he says.

Among other things, the work led Nadel to collaborate on a theory for how psychotherapy works (6). "Our approach is predicated on the notion that during therapy people can be led to reevaluate a prior experience with the help of a psychiatrist, bringing up and reconsolidating old memories with new and more positive framing," says Nadel. He is currently working with psychiatrists and brain-imaging researchers to examine how the brain changes during such therapy.

Nadel's work on the hippocampus and memory form the core of his Inaugural Article (1). "In the field of hippocampal research, one of the major conundrums is trying to figure out why this structure that is critically important for spatial cognition is simultaneously involved with memory in general," he says. In the article, Nadel describes a framework for thinking about the hippocampus as a structure that helps bridge gaps in space and time. "The claim I'm making is that this brain system is set up to solve this problem of having to act with respect to goals that are distant and not locally detectable," says Nadel. "It would account for the fact that the hippocampus is crucial for space, for time, and for memory, all three things in some interwoven way," he explains.

Nadel says he owes many of his contributions to the fields of psychology and neuroscience to close collaborations with other researchers. "I'm not somebody who wants to do it all on my own, and the most fun and most productive times I've had have been in really deep collaborations," he says. During his long career, these collaborations have allowed Nadel to focus on the big picture. "I've always believed you have to pay attention to the brain but, in the end, what I'm interested in is cognition, not just pictures of brains lit up."

1. L. Nadel, The hippocampal formation and action at a distance. *Proc. Natl. Acad. Sci. U.S.A.* **118**, 10.1073/pnas.2119670118 (2021).
2. J. O'Keefe, L. Nadel, *The Hippocampus as a Cognitive Map* (Clarendon Press, Oxford, 1978).
3. L. Nadel, J. O'Keefe, "The hippocampus in pieces and patches: An essay on modes of explanation in physiological psychology" in *Essays on the Nervous System. A Festschrift for J. Z. Young*, R. Bellairs, E. G. Gray, Eds. (The Clarendon Press, Oxford, 1974), pp. 367-390.
4. W. J. Jacobs, L. Nadel, Stress-induced recovery of fears and phobias. *Psychol. Rev.* **92**, 512-531 (1985).
5. L. Nadel, M. Moscovitch, Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* **7**, 217-227 (1997).
6. R. D. Lane, L. Ryan, L. Nadel, L. Greenberg, Memory reconsolidation, emotional arousal, and the process of change in psychotherapy: New insights from brain science. *Behav. Brain Sci.* **38**, e1 (2015).