

# The life and career of Paul MacLean: A journey toward neurobiological and social harmony

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Received 4 April 2003; accepted 17 April 2003

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## Abstract

Working as a physician, Paul MacLean's interests moved in the direction of the brain when he realized that most of his patients suffered from symptoms (e.g. anxiety, sleeping problems) that could not be traced to a known physiological cause. His curiosity about the neurological origins of these psychological symptoms led him to the laboratories of Stanley Cobb and James Papez, both of whom were influential in guiding MacLean's interests toward the temporal lobe. His neurobiological interest was not contained, however, to the temporal lobe. As his own family grew to include a wife and five children, his scholarly pursuits extended to social and familial relations and their accompanying underlying neuroanatomical circuits (i.e. the thalamocingulate system). Viewing the brain and behavior from an evolutionary perspective, MacLean introduced the concept of the "triune brain" to describe the evolutionarily distinct components of the mammalian brain and reintroduced Broca's term "limbic" to describe a neuroanatomical system involved in emotional functions. MacLean wrote that the development of social behaviors, such as mother–infant audiovocal communication and the separation cry of the offspring, served as the driving force in the evolution of the neocortex. MacLean's neuroevolutionary perspective and appreciation of the complexity and evolutionary significance of social systems offer valuable insights into the contemporary fields of behavioral neuroscience and biological psychiatry.

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*Keywords:* Triune brain; Limbic system; Paul MacLean; Neuroethology; Thalamocingulate division; Social neuroscience

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## 1. Introduction

According to Paul MacLean, social separation is one of the most stressful events a mammal encounters in its lifetime. Although other environmental events such as pain or starvation offer more severe immediate risks to the survival of an individual, MacLean perceives that the removal of a conspecific results in an even larger emotional response than these more obvious threats to survival. In fact, MacLean places so much value on social and family relations that he proposed that they played an integral role in the direction of mammalian evolution. In the following article, we will discuss the scholarly and personal journey that eventually led MacLean to his pioneering work in the area of social neuroscience. Notable career milestones such as the evolution of the *limbic system* and *triune brain* concepts will also be discussed. Finally, the legacy of Paul

MacLean's career will be considered as we review the impact of his work in the fields of behavioral neuroscience and biological psychiatry.

## 2. Early life and career

Paul MacLean was born on May 1, 1913 in Phelps, NY. He attended prep school for the sole purpose of attending Yale University—following in his brother's footsteps. Following graduation from Yale, he decided to study philosophy with A.E. Taylor, a scholar of Plato, at New College, Edinburgh. However, soon after making this bold decision, MacLean started having second thoughts about his ability to contribute to the body of philosophical knowledge that had existed for centuries. Additionally, his mother became seriously ill around this time. It was originally suspected that she had a cardiovascular condition, but her physician helped to discern that the actual problem was gallstones. MacLean was fascinated with the physician's diagnostic skills and his mother's subsequent recovery, so much so that

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he decided medicine would be a rewarding career. In 1936, he commenced his medical training at Yale University School of Medicine [1]. Interestingly, MacLean's personal maternal relationship played a pivotal role in directing his career toward medicine; as will be discussed later, this interest in the maternal–offspring relationship would later influence him as he theorized about the evolution of mammalian species.

MacLean was initially exposed to psychiatry when he volunteered to be part of the Yale Unit during World War II and was given a hospital assignment in Auckland, New Zealand. When the resident psychiatrist disappeared, MacLean was promptly assigned to Psychiatry where he encountered interesting interactions such as a patient attempting to strangle him with his own necktie. These experiences prompted MacLean to start thinking about the origins of normal and abnormal behavior; however, this early experience with psychiatry was not enough to motivate him to alter his career path toward the field of psychiatry [1].

Following the war, MacLean and his wife moved to the state of Washington where he opened a private practice. MacLean became increasingly frustrated in this practice as he realized that the majority of his patients' symptoms were psychological in nature, leaving him with a feeling of incompetency because he had no idea where in the brain these symptoms were generated. In an attempt to relieve this frustration, MacLean reviewed the writings of Dr. Stanly Cobb at Massachusetts General Hospital in Boston, contacted him, and was subsequently invited for a fellowship [1,3].

### 3. The evolution of the limbic system concept

After moving his three young boys to Boston, MacLean embarked on a research project assessing the bioelectrical activity of certain structures at the base of the brain. Because of its reported role in emotions, MacLean was initially interested in the hypothalamus. His first contact with the brain tissue itself came when he designed nasopharyngeal electrodes that could be slipped up the sides of the nose. Working with patients suffering from psychomotor epilepsy, MacLean noted the relationship between the structures of the temporal lobe, especially the area around the hippocampal formation, and emotional experiences reported by the patients. But why was this structure involved in emotions? Again, MacLean consulted the literature and was intrigued by an article he discovered entitled *A Proposed Mechanism of Emotion* written by James W. Papez in 1937 [4].

As MacLean read Papez's description of an emotional circuit, in which the hippocampal formation connected with the hypothalamus, he knew that he was on the right track toward understanding the neuroanatomy of emotions. MacLean remained puzzled, however, about the relationships between exterosensory information and the emotional

activation that he had observed in his epileptic patients. Cobb suggested that MacLean visit Papez to discuss these matters and, during the spring break of 1948, MacLean traveled to Cornell to experience an intense 3-day tutorial in comparative neuroanatomy with Papez [1]. This visit was a life-changing experience for MacLean as he was in awe of the neuroanatomical skill of Papez, who pointed out how visual, auditory and somatic sensory information entered the hippocampal formation. Even today, 55 years following his time with Papez, MacLean describes him as *saint-like* and one of the most gifted neuroanatomists of the last century [4]. This work culminated in a publication entitled: *Psychosomatic Disease and the 'Visceral Brain'* in 1949 [5]. MacLean avoided referring to the circuit as the rhinencephalon because he wanted to downplay the olfactory function and emphasize the emotional function. He subsequently decided to use the term *visceral* because of its original 16th century definition referring to strong inward feelings. The significant aspect of this paper was MacLean's suggestion that mammalian brains may have a common feature of a rather primitive system responsible for integrating sensory information, suggesting a dichotomy between our intellectual behavior and emotional, nonverbal, behavior [1].

Following his research fellowship in Cobb's laboratory, John Fulton invited MacLean to join the Department of Physiology at Yale Medical School. During his tenure at Yale, MacLean turned to Broca's work and became especially interested in his descriptions of a "great limbic lobe" that surrounded the brainstem [6]. Because Broca emphasized the limbic lobe's role in olfaction, a function thought to be of little importance to humans, this anatomical circuit had become the unwanted child of brain anatomy books and lectures. MacLean wrote that one author conveyed that this area of the brain likely contributed very little to the evolution of the human brain and, consequently, should not be considered further in the text [7]. After reviewing Broca's use of the term *limbic*, he felt that this term was more appropriate than the term *visceral* and he began referring to the emotional circuit as the limbic system because this new term had only descriptive connotations as opposed to the functional connotations associated with the term *visceral* [1].

### 4. The evolution of the triune brain concept

As MacLean was becoming interested in the limbic circuit, he was intrigued by a comment made by Rose suggesting that the mesocortex made its first appearance in mammals and was somewhat transitional between the more primitive archicortex and the more recently evolved neocortex (Ref. [8] reviewed in Ref. [7]). MacLean later conducted a study with rats in which he showed differential uptake of S-labeled L-methionine among the archicortex, mesocortex and neocortex areas—a finding that he felt distinguished the limbic cortex from the neocortex [7].

While at Yale, he continued to conduct research discerning the neuroanatomical boundaries and characteristics of the areas comprising the limbic circuit.

In 1956, MacLean was awarded an NSF senior postdoctoral fellowship at the Institute of Physiology at the University of Zurich. Upon returning, he was invited to join a new lab section at the National Institute of Health that was subsequently named *The Section on Limbic Integration and Behavior*. He joined the NIH in 1957 embarking on a career that he would cherish until his current state of semi-retirement (he continues to visit a modest lab and office at NIMH). The primary purpose of this laboratory was to investigate the electrophysiological and anatomical aspects of the limbic cortex and its multiple associated sensory systems. In order to do this, MacLean turned to a squirrel monkey model and employed the help of the German psychiatrist Detlev Ploog, who had specialized interests in ethology, to help establish an ethogram for these animals [1,9].

MacLean first publicly discussed his idea of the triune brain in 1969 when he delivered a series of lectures at Queens University in Kingston, Ontario (Ref. [10] reviewed in Ref. [11]). He explained that the formidable cortex of humans evolved while retaining three basic formations delineating its ancestral relationship with reptiles, as well as early and more recent mammals. He argued that one may perceive humans as having three different brains in one with each “brain” having a distinctive set of capabilities. He later wrote:

Man, it appears, has inherited essentially three brains. Frugal Nature in developing her paragon threw nothing away. The oldest of his brains is basically reptilian; the second has been inherited from lower mammals; and the third and newest brain is a late mammalian development which reaches a pinnacle in man and gives him his unique power of symbolic language. This can be said with some assurance, because the big brain which sits on top has been more thoroughly investigated than the other two. ([11], p. 96)

Much to MacLean’s surprise, the notion of this multifaceted brain became wildly popular in the press. The media, however, overemphasized MacLean’s suggestion that we are under the control of three very different brains, failing to convey his ideas that these components contribute to a single, functioning brain. This confusion led him to search once again for a more defining term to use. Because triune literally means *three-in-one*, he chose that term for his new evolutionary brain theory [1]. Considering that MacLean’s father was a Presbyterian minister, this term seemed perfect for his theory at the time, but he later regretted this choice due to its religious connotations [3].

MacLean expanded his neurobehavioral investigation of the triune brain to a larger repertoire of species when NIH completed a satellite field laboratory just south of Poolesville, MD in 1971 [1,3]. It was here that MacLean began his

studies with reptiles, namely, the Komodo dragon, and discovered that mammals and reptiles share a common base of basic behaviors consisting of behaviors such as daily routines and subroutines and the displays associated with social communication [12]. These studies convinced MacLean that, whereas the mammalian brain was more advanced than the reptilian brain, the mammalian brain retained the primitive aspects of the reptilian brain. Human cases, in which a relentless murderer stalks his/her next victim, convinced MacLean that the reptile was at work in the human brain [13]. MacLean’s work also directed him to the “basal ganglia and company” (as he described them in an interview [14]) as the neuroanatomical site for this ancient reptilian neuroanatomical complex (also known as the R-complex). More advanced behaviors associated with both self-preservation and survival of the species (e.g. the addition of *affect* associated with basic survival behaviors and decreased tendency to cannibalize offspring) appeared along with the appearance of the limbic structures [12]. The most recent mammalian brain is characterized by the thalamocingulate division with numerous connections between the cingulate mesocortical areas and the anterior thalamic nuclei (among other thalamic areas [1]). There appears to be no neuroanatomical corollary to the thalamocingulate division in the reptilian brain—making it uniquely mammalian. As discussed in the next section, this brain area is involved in more advanced social behaviors such as communication (see Fig. 1 for illustration of MacLean’s triune brain).



Fig. 1. A recent interpretation of MacLean’s triune brain emphasizing the reptilian brain (hindbrain), the paleomammalian brain (limbic system) and neomammalian brain (neocortex). Because MacLean emphasized the role of the maternal–infant relationship, the brain is situated inside a maternal squirrel monkey, a species that MacLean used extensively in his neuroethological research (artwork by Jacqueline Berry, design by Kelly Lambert).

## 5. A mother's hand rocks the evolutionary cradle

With the discovery of the uniquely mammalian neuro-anatomical circuit, namely, the thalamocingulate system, MacLean once again allowed his interest in the maternal–offspring relationship to direct his scholarly and professional interests. According to MacLean, the three behaviors that separate mammals from other vertebrates include (1) *nursing, conjoined with maternal care*; (2) *audiovocal communication for maintaining mother–offspring contact*; and (3) *play behavior* ([1], p. 269). In fact, MacLean included an entire chapter on this circuit and family-related functions in his book (*The Triune Brain In Evolution: Role in Paleocerebral Functions* [7]) entitled *Participation of thalamocingulate division in family-related behavior*. In this chapter, MacLean emphasizes the profound importance of social relations in the evolution of the brain by arguing that the prolonged separation of the offspring from its nursing mother results in fatal consequences for the developing mammal. He proposed that the separation cry that enables the mother to locate her lost offspring might have been one of the first examples of mammalian vocalization [1]. Corroborating this theory of the separation cries being associated with the limbic circuit, MacLean, working with John Newman (Child Health Laboratory of Comparative Ethology), found that the ablation of parts of the medial frontal cortex in squirrel monkeys, specifically a portion of the pregenual cingulate cortex and its extension to the subcallosal cingulate cortex, resulted in an elimination of the spontaneous separation cry [7].

In an article entitled *Women: A More Balanced Brain* [2], MacLean continues with his scholarly interest in the mother's role in evolution. He wrote, “For more than 180 million years, the female has played the central role in mammalian evolution” ([2], p. 422). Additionally, MacLean proposed that it was mothers who directed our species toward right-hand dominance as they held their babies near their hearts so that their heart rates would calm the baby—and subsequently relied on their right hands to manipulate environmental surroundings. He felt that carrying infants might have also influenced the anatomical and functional expansion of the right hemisphere in women. Such evolutionary expansion might have led to a more balanced brain, prepared for the multitasking demands of caring for offspring [2]. Related to this observation, MacLean wrote:

... I will draw upon findings of continuing research that provide both anatomical and functional evidence that the minds of women sail in a vessel less tilted to the left than do those of men. ([2], p. 422)

MacLean also noted subsequent neuroimaging research documenting more interhemispheric activity in women compared to men who exhibited more prevalent intrahemispheric activity [15]. Other supporting research comes from an analysis of the planum temporale (PT), a brain area hidden in the Sylvian fissure that is thought to be involved

in verbal associations related to hearing. Although original reports suggested that the PT was larger in the left hemisphere [16], upon a more specific analysis of gender differences, it was discovered that the left hemisphere dominance was only apparent in the male brains—the PT was most often larger in women's right hemisphere [17].

Additionally, MacLean hypothesized that maternal communication with her offspring, complete with fundamental mammalian vowel and consonant sounds, served as the originating point of speech [1]. Although it was once thought that a baby's babbling was a mere exercise of the mouth's muscles, it is interesting to note that recent research suggests that babbling responses are indeed generated in the left hemisphere, as is language [18].

Thus, as vertebrates evolved from the nonmaternal, sometimes cannibalistic, reptiles—that rarely offered more directive maternal care than merely laying eggs—to mammals such as squirrel monkeys that carry their offspring almost continuously for months to years, the thalamocingulate portion of the brain expanded in accordance with this family-centered neurobehavioral transition [1]. The fact that this thalamocingulate division is not apparent in the reptilian brain reinforces its role in the mammalian family-related behaviors [7]. Additionally, with the observations that the rostral cingulate cortex has been implicated in the offspring's production of the separation cry, MacLean established a link between the evolutionary significant separation cry, a behavior important in maintaining maternal–offspring relations, and the mammalian thalamocingulate division. With such a valuable evolutionary investment depending on the effective processing of this vocalization, it is likely that subsequently evolved mammals became increasingly prepared to respond to both the separation cry and emerging, more specific vocalizations. Hence, the genesis of more complex communication processes [3,9,12].

## 6. The neuroscience of social harmony

As mentioned above, MacLean also noted the emergence of play in the behavioral repertoire of mammals. Reinforcing the notion that this behavior is mediated by the cingulate portion of the limbic system, hamsters with cingulate lesions appeared normal on every account except for the fact that they did not engage in play behavior with their littermates. Speculating on the function of play, MacLean has written that it might have evolved to promote social harmony in the nest and, as the animal matures, social affiliation [12].

Ironically, the evolutionary predisposition to maintain social harmony, or even a family way of life, comes with the cost of drastic repercussions when the social harmony is interrupted by social separation. As discussed in the opening statements of this article, MacLean conveyed that nothing brings more pain to a mammal than being separated from its own kind. MacLean suggested that this is the case because the cortical area underlying the separation cry is partially

innervated by the thalamic nuclei that are involved in pain perception. Accordingly, small doses of morphine have been found to eliminate the cry [1]. Thus, when mammals became family oriented, they became a target for one of the most distressing forms of suffering—social separation and isolation [12]. Because, according to MacLean, this social dependence evolved in synchrony with the mammalian female's maternal responses, the female brain may be more empathetic than the male's brain. Further, the social responsibility toward her offspring seemed to be a step up the ladder to humanity as the maternal animals extended care to nonfamily members and began to develop a sense of *social conscience*. This highly evolved thalamocingulate division is also responsible for humans being the first species to not only care if our own species lives or dies, but to extend that concern to other species [1,3].

In an interview with Constance Holden for *Science* in 1979 [13], MacLean was quite optimistic about the harmony of the human race—especially if we could maximize the use of one of the destinations of the limbic system's thalamocingulate circuit, namely, the prefrontal cortex. Unique to humans, abilities such as foresight and insight merge to create empathy and altruism, where the boundaries between the well-being of self and others start to fade and become dependent on one another. In a recent interview [9], MacLean's optimism had waned after the horrific tragedies occurring in the United States on September 11, 2001—a tragedy designed by the uniquely human cortex. However, as separation cries were heard across the country as loved ones were declared missing, and eventually deceased, the tendency of U.S. citizens to reach out to each other instead of running to safety in isolation was striking—and predictive from MacLean's writings about the familial tendencies of the thalamocingulate division of the limbic system.

## 7. The legacy of Paul MacLean ... and lessons learned?

### 7.1. Reaction to *The Triune Brain in Evolution*

It is difficult to imagine a scientist who has embarked on more groundbreaking topics of such profound importance to the human species than Paul MacLean. His work culminated in his publication of *The Triune Brain in Evolution: Role in Paleocerebral Functions* in 1990 [7]. After spending 30 years writing this comprehensive volume, it was finally out for the public to read and review. Considering the attention MacLean's work attracted from outside the mainstream science venues, such as Carl Sagan's utilization of the triune brain concept in his book entitled *The Dragons of Eden* [19], the fields of neuroscience, psychiatry and psychology have been a bit more cautious about embracing his theories. As described by Gerald Cory [20], MacLean received critical reviews in two prominent scientific journals, *Science* [21] and *American*

*Scientist* [22]. Focusing on the *Science* review [21], Anton Reiner, a recent graduate in the field of neuroscience at the time, was critical about several basic premises of the book. For example, he criticized MacLean's *triune brain* concept for being outdated and his *limbic system* concept for being out of step with the current evidence (current as of 1990) that the hippocampus seemed to play a sole function in memory. Cory [20] subsequently defended the scholarship of MacLean by systematically addressing the criticisms raised in the *Science* review. The *American Scientist* review [22] was a briefer account but resembled the issues raised by Reiner. Unfortunately, because readers usually prefer reading a brief review as opposed to an entire book, the negative reviews had a sizeable impact on the scientific community's reluctance to embrace MacLean's meticulously documented book.

In spite of MacLean's misfortune with book reviews, his ideas remain valued by many in the field today [23]. The notion of the limbic system remains a popular classification of the cluster of brain areas involved in emotional processing. His ideas concerning the importance of social bonds have shed light on possible mechanisms of mental disorders such as autism, a disorder of social functioning. Specifically, neuroanatomical studies of individuals diagnosed with autism point to inappropriately developed limbic structures, namely, the amygdala and hippocampus [24,25].

### 7.2. Neuroethological approach to the mind

MacLean's interest in the development of a neuroethological approach to understanding mental experiences is slowly growing acceptance as a legitimate and informative perspective in several mental health disciplines such as psychiatry, psychology, neuroscience and neurology. Along these lines, a book entitled *Darwinian Psychiatry* [26] was recently published documenting the value of understanding the evolutionary context and function of certain behaviors. Although his neuroethological approach to the "mind" has been slow to gain mainstream acceptance, MacLean's theories explain many puzzling human behaviors ... such as why the President of the United States might risk his career by engaging in the more familiar behaviors of the R-complex; or why certain individuals with no violent history seem to "snap" and commit uncharacteristic acts of crime (perhaps due to an epileptic–limbic type of seizure [27]); or why surgeries interrupting the communication between the striatum and cingulate cortex relieve some of the compulsive behaviors (or R-complex master routines) observed in Obsessive–Compulsive Disorder [28]; or why infants deprived of their mother's nurturing care and forced to live in neglectful orphanages sometimes develop subsequent social dysfunction [29]; or, finally, why, as children's worlds become more dominated by socially isolated endeavors such as viewing television or interacting with a computer, and more traditional social play becomes a fading compo-

ment of elementary school curricula, that an increasing number of children are suffering from cognitive and behavioral disorders (e.g. ADHD) [30].

Also important in the development of MacLean's neuroethological approach was the inclusion of several species—a true comparative biopsychological approach. Toward this goal, MacLean worked with humans, peacocks, squirrel monkeys, rats, hamsters, anolis lizards and even komodo dragons, as he disentangled the more primitive common behaviors shared by all vertebrates. In keeping with MacLean's neuroevolutionary perspective, contributions in this special edition consist of research conducted on humans, nonhuman primates, rats, mice, lizards, prairie voles and tree shrews. As species such as the tree shrew are being viewed as living fossils for more recent neomammals, it is likely that future comparative research may provide additional evolutionary insights into the origins, maintenance and functions of various behaviors.

### 7.3. *Maintaining an appropriate neurobiological perspective*

One of MacLean's most consistently reinforced themes included his desire to consider both the “big picture” of neurobiological functions as well as the more fine-tuned cellular approaches when investigating the neurobiological foundations of certain behaviors and mental functions. In fact, MacLean recently claimed that the most unfortunate event that ever occurred in the history of biological psychiatry was Camillo Golgi's discovery of a new technique to stain neurons because neuroscientists tackled the microstructure questions and abandoned their curiosity concerning the systems of the brain [9]. Although MacLean remains passionate about neuroanatomy, likening viewing the brain through the microscope to “walking in a cathedral,” he adamantly proclaims that structures are located in the brain to build circuits and scientists should also be interested in learning more about these circuits and the behaviors they control [3]. Accordingly, he wrote:

...starting with the subjective self as its province (its territory), the domain of evolutionary psychiatry encompasses both the microscopic and macroscopic aspects of all the underlying phenomena as they seem to unfold in past–present–future and relate to the cosmos. ([31], p. 219)

Corroborating MacLean's value of the more encompassing evolutionary perspective, Jaak Panksepp recently conveyed his concern for a neuropsychiatry that emphasizes molecular interactions while ignoring evolutionary issues, claiming that this approach represents a *scientific shortsightedness*—often missing the functional forests for the more molecular undergrowth. In spite of MacLean's attempt to emphasize the importance of investigating both the functional forests and the molecular details in order to arrive

at a more thorough understanding of the nervous system, a more balanced approach is long overdue [23].

### 7.4. *Establishing and maintaining professional and personal harmony*

In sum, Paul MacLean's list of accomplishments throughout his career are quite distinctive . . . ranging from the contributions of important concepts such as the limbic system and the triune brain to his tenure as the Chief of the NIH's *Laboratory of Brain Evolution and Behavior*. As he approaches his 90th birthday (see Fig. 2), he is doing anything but resting on his laurels—continuing to struggle with the big questions such as the meaning of life, the evolutionary origins of tears of grief and tears of laughter, the place of the family in the history of evolution and why humans continue to optimistically bring children into a world filled with uncertainty and violence [1,3]. He continues to frequent a small office at NIH where he works on a project he affectionately calls the “5000 year project” in which he is busy investigating even more connections among the systems of the triune brain, hoping to further delineate the harmonious connections among the many circuits of the brain. He remains fascinated by the relationship between a musical experience and an emotional experience as he frequently uses emotional terms to describe musical ability, claiming that his gifted grandson can make a piano “weep” and musical terms for emotional/



Fig. 2. Paul MacLean in his home in the spring of 2001 (photo by Kelly Lambert).

limbic observations as he likens the lines on a music sheet to layers in the neomammalian cortex, or claims “that the human brain can not be made to dance to any tune by simply delivering a single drug...” [31]. Further, he sometimes finds himself speculating that something akin to the phenomenon of a musical experience—a phenomenon likely rooted in the basic rhythmic patterns of the R-complex yet branches into the advanced thoughts of the neocortex—may serve as an interesting model or analogy for understanding emotional experiences [3,9]. Just as music adds meaning to the rhythmic patterns of the R-complex, stimulation of the prefrontal area ultimately adds relevancy and meaningfulness to more basic emotional stimulation originating in this area. Thus, harmony seems to be a word that captures the life and career of Paul MacLean. He attempted to define harmony among the evolutionarily distinct sections of the mammalian brain as well as establish harmonic relations among the micro and macro circuits of the brain. MacLean’s most valued endeavors, however, comprise the fruits of his own thalamocingulate neuroanatomical division as he enjoys the social harmony provided by his wife, five grown children, eleven grandchildren, and cherished colleagues.

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