ΔΗΜΟΣΙΑ ΣΥΝΕΔΡΙΑ ΤΗΣ 31ΗΣ ΜΑΪΟΥ 2005

ΥΠΟΔΟΧΗ
ΤΟΥ ΞΕΝΟΥ ΕΤΑΙΡΟΥ
κ. ERIC RICHARD KANDEL

ΠΡΟΣΦΩΝΗΣΗ ΥΠΟ ΤΟΥ ΠΡΟΕΔΡΟΥ κ. ΕΜΜΑΝΟΥΗΛ ΡΟΥΚΟΥΝΑ

Μὲ ἰδιαίτερη χαρὰ ἡ Ἀκαδημία Ἀθηνῶν ὑποδέχεται σήμερα τὸν διακεκριμένο καθηγητὴ Eric Richard Kandel, τοῦ Πανεπιστημίου Kolumbia τῆς Νέας Υόρκης.

Ὁ καθηγητὴς Kandel γεννήθηκε στὴ Βιέννη, εἶναι πολίτης τῶν Ἡνωμένων Πολιτειῶν τῆς Ἀμερικῆς καὶ σπούδασε στὸ Harvard College καὶ στὸ Πανεπιστήμιο τῆς Νέας Υόρκης.

Ἀπὸ τὸ 1956 ἕως τὸ 1965 ὑπηρέτησε στὴν Ἰατρικὴ Σχολὴ τοῦ Πανεπιστημίου Harvard καὶ τὸ 1965 ἐξελέγη στὴν Ἰατρικὴ Σχολὴ τοῦ Πανεπιστημίου τῆς Νέας Υόρκης, ὅπου συνέστησε τὴν πρώτη στὶς Ἡνωμένες Πολιτεῖες μονάδα ποὺ ἀσχολήθηκε ἀποκλειστικὰ μὲ τὴ νευροφυσιολογία τῆς συμπεριφορᾶς.

Τὸ 1974 ἵδρυσε καὶ ἔκτοτε διευθύνει τὸ Κέντρο Νευροφυσιολογίας καὶ Συμπεριφορᾶς τοῦ Πανεπιστημίου Columbia τῆς Νέας Υόρκης. Εἶναι πρωτοπόρος στοὺς τομεῖς κατανοήσεως τῆς βασικῆς δομῆς τῆς συμπεριφορᾶς καθὼς καὶ στὴ θεμελίωση ἀρχῶν, οἱ ὁποῖες σήμερα χρησιμοποιοῦνται εὐρύτατα γιὰ τὴ σύνδεση τῶν μοριακῶν καὶ τῶν κυτταρικῶν μηχανισμῶν ποὺ ἐπιδροῦν στὴ δράση τῶν ὀργανισμῶν. Βοήθησε στὴν ἐξήγηση τοῦ θείου δώρου τῆς μνήμης στὸν ἄνθρωπο. Τὰ σπουδαῖα ἐπιστημονικά του ἐπιτεύγματα καὶ ἡ ἐξαιρετικὴ καὶ καρποφόρα ἐρευνητική του προσπάθεια ἀνταμείφθηκαν τὸ 2000 μὲ τὸ βραβεῖο Nobel.

Dear colleague,

The Academy of Athens is honouring your outstanding scholarship and contribution to the enhancement and the dissemination of science. The Academy has elected you as a foreign member and I am pleased to offer you the testimonials of this distinction. I am wishing you all the best in the continuation of your great achievements.

Ἀπόψε, γιὰ λόγους ἀνεξαρτήτους τῆς θελήσεώς του, δὲν θὰ εἶναι μαζί μας ὁ λίαν ἀγαπητὸς ἀντιπρόεδρος τῆς Ἀκαδημίας, ἀκαδημαϊκὸς κ. Κωνσταντῖνος Στεφανῆς.

Ἡ Σύγκλητος ἀνέθεσε στὸν Γενικὸ Γραμματέα ἀκαδημαϊκὸ κ. Νικόλαο Ματσανιώτη νὰ παρουσιάσει τὸν τιμώμενο Ξένο Ἑταῖρο.

ΠΑΡΟΥΣΙΑΣΗ ΥΠΟ ΤΟΥ ΑΚΑΔΗΜΑΪΚΟΥ κ. ΝΙΚΟΛΑΟΥ ΜΑΤΣΑΝΙΩΤΗ

Ἡ Ἀκαδημία Ἀθηνῶν εἶναι εὐτυχὴς ποὺ σήμερα ὑποδέχεται ὡς Ξένο Ἑταῖρο τὸν καθηγητὴ κ. Kandel, τὸν ὁποῖο ἐξέλεξε, μετὰ ἀπὸ πρόταση τοῦ συναδέλφου κ. Κώστα Στεφανῆ, στὶς 22 Φεβρουαρίου τοῦ 2001. Ὁ κ. Στεφανῆς ἀπουσιάζει στὸ Λονδίνο γιὰ λόγους ὑγείας, σύντομα ὅμως θὰ βρίσκεται καὶ πάλι μαζί μας. Ἱκανοποιῶν τὴν ἐπιθυμία του, ἔχω τὴν τιμὴ νὰ προσφωνῶ ἀντ' αὐτοῦ τὸ νέο Ξένο Ἑταῖρο μας.

Ὁ Eric Richard Kandel γεννήθηκε στὴ Βιέννη στὶς 7 Νοεμβρίου 1929. Δέκα χρόνια ἀργότερα, τὸ 1939 ἡ οἰκογένειά του μετανάστευσε στὶς Η.Π.Α. Σπούδασε στὸ Harvard College μὲ κορμὸ τὴν ἱστορία καὶ τὴ λογοτεχνία (cum laude). Συνέχισε τὶς σπουδές του στὴν Ἰατρικὴ Σχολὴ τοῦ Πανεπιστημίου τῆς Ν. Ὑόρκης καὶ ἔλαβε τὸ πτυχίο Ἰατρικῆς τὸ 1956. Ἀκολούθησαν τὰ πρῶτα χρόνια κλινικῆς δραστηριότητας ὡς ἐσωτερικὸς βοηθὸς στὸ Montefiore Hospital, ΝΥ, ὡς εἰδικευόμενος στὸ Κέντρο Ψυχικῆς Ὑγείας Μασαχουσέτης στὴν Ἰατρικὴ Σχολὴ Harvard, στὴν ὁποία καὶ συνέχισε ἐργαζόμενος ὡς στέλεχος τῆς Ψυχιατρικῆς Κλινικῆς (1964-1965).

Ἡ ἐρευνητική του δραστηριότητα ἀρχίζει τὸ 1957 καὶ συνεχίζεται ἕως καὶ σήμερα, καλύπτοντας μεγάλο φάσμα ἐπιστημῶν (ἀρχικὰ κλινικὴ ψυχιατρική, στὴ συνέχεια νευροβιολογία, νευροφυσιολογία, φυσιολογία, ἐπιστῆμες συμπερι-

φορᾶς, βιοχημεία καὶ τέλος μοριακὴ βιοφυσική) σὲ διακεκριμένα Πανεπιστήμια καὶ Ἐρευνητικὰ Κέντρα τῆς Ἀμερικῆς, ἀλλὰ καὶ τῆς Γαλλίας (NIMH, Harvard Medical School, Massachusetts Mental Health Center, NYU School of Medicine, College of Physicians and Surgeons of Columbia University, USPHS College de France, Ladislav Tauc, Paris-France).

Ἔχει τιμηθεῖ μὲ πολυάριθμες διακρίσεις τόσο στὶς Η.Π.Α. ὅσο καὶ στὴν Εὐρώπη. Ἔχει βραβευθεῖ μὲ 8 τιμητικοὺς τίτλους (Honorary degrees) ἀπὸ Πανεπιστήμια καὶ Ἰατρικὰ Κέντρα, εἶναι ἐπίτιμο μέλος 9 Ἐπιστημονικῶν Κέντρων τῶν Η.Π.Α. καὶ ἐπίτιμος διδάκτωρ ἢ μέλος 12 διεθνῶν Ἐπιστημονικῶν Ἑνώσεων καὶ Ἀκαδημιῶν, μεταξὺ τῶν ὁποίων ἡ Γαλλικὴ Ἀκαδημία Ἐπιστημῶν, ἡ Γερμανικὴ Ἀκαδημία Ἐπιστημῶν, ἡ Ἀκαδημία Ἐπιστημῶν τοῦ Βρανδεμβούργου, ἡ Ἀμερικανικὴ Ἀκαδημία Τεχνῶν καὶ Ἐπιστημῶν, τὸ Βρετανικὸ Κέντρο Νευροεπιστημῶν, ἡ Ἀμερικανικὴ Ἀκαδημία Ἐπιστημῶν καὶ τὸ Ἐθνικὸ Ἰνστιτοῦτο Ἰατρικῆς τῶν Η.Π.Α.

Ἔχει διατελέσει μέλος ἢ πρόεδρος 22 διεθνῶν, κυβερνητικῶν, κοινωνικῶν συμβουλευτικῶν ἐπιτροπῶν καὶ ὁμάδων ἐργασίας.

Εἶναι ἐκδότης ἢ συνεκδότης ἢ μέλος ἐκδοτικοῦ συμβουλίου 8 ἔγκυρων ἐπιστημονικῶν περιοδικῶν.

Ἔχει ἐκδώσει 9 βιβλία, ἐκ τῶν ὁποίων τὰ 6 εἶναι προσωπικὰ συγγράμματα. Γνωστὸ παγκοσμίως - μεταφρασμένο καὶ στὴν Ἑλλάδα - εἶναι τὸ κλασσικὸ ἐπίτομο βιβλίο τῶν Kandel and Schwartz "Principles of Neural Science".

Ὁ καθηγητὴς Kandel ἔχει δημοσιεύσει 430 πρωτότυπες ἐρευνητικὲς ἐργασίες στὰ πιὸ ἔγκυρα διεθνῆ ἐπιστημονικὰ περιοδικά (*Nature*, *Science*, *Cell* κ.ἄ.). Ἡ ἔρευνά του ἔχει ἐπικεντρωθεῖ στὴ διερεύνηση τῶν μηχανισμῶν τῆς μνήμης καὶ τῆς μάθησης σὲ μοριακὸ ἐπίπεδο. Οἱ πρωτοποριακές του ἐργασίες τὸν ἔχουν καθιερώσει ὡς τὸν πρωταγωνιστὴ στὸν ἐρευνητικὸ αὐτὸ τομέα, τὸν σημαντικότερο ἴσως ἀπὸ κάθε ἄλλο, ἀφοῦ ἀναφέρεται στὴν προσπάθεια ἑρμηνείας τῶν γνωστικῶν λειτουργιῶν τοῦ ἐγκεφάλου μὲ τὶς πιὸ προχωρημένες μεθόδους τῆς μοριακῆς νευροβιολογίας.

Ἀπέδειξε μὲ τοὺς συνεργάτες του τὶς πολλαπλὲς βιοχημικὲς μεταβολὲς ποὺ συνοδεύουν τὴ δημιουργία τῆς μνήμης, καὶ εἶναι ἴδιες στὸ πειραματικὸ μοντέλο τῆς aplysia, ἕνα μικρὸ θαλάσσιο σαλιγκάρι, καὶ σὲ θηλαστικά, ἐνδεχομένως ἴδιες καὶ στὸν ἄνθρωπο. Ἔδειξε ὅτι ἡ μνήμη, βραχείας διάρκειας, συνδέεται μὲ ἁπλὴ τροποποίηση τῶν συνάψεων, ἐνῶ ἡ μνήμη, μακρᾶς διάρκειας, ἀπαιτεῖ μεταβολὴ τῆς συναπτικῆς δομῆς καὶ τὴ δημιουργία νέων συνάψεων.

Ἐπίσης ἀπέδειξε τοὺς βασικοὺς μηχανισμοὺς μὲ τοὺς ὁποίους τὰ νευρικὰ κύτταρα μεταβάλλουν τὴν ἀνταπόκρισή τους σὲ χημικὰ ἐρεθίσματα, ἔτσι ὥστε νὰ ἐπιτυγχάνεται συντονισμένη μεταβολὴ τῆς συμπεριφορᾶς.

Ὁ καθηγητὴς Kandel κατορθώνει συνεχῶς νὰ ἀξιοποιεῖ κάθε νέα τεχνική, πρόσφορη νὰ ὑπηρετήσει τὰ ἐρευνητικά του ἐνδιαφέροντα, δηλαδὴ νὰ ἐμβαθύνει στὴ λειτουργία τῆς μάθησης τῆς μνήμης καὶ τῆς συμπεριφορᾶς.

Ἡ ἔρευνά του ἔθεσε παράλληλα καὶ τὶς βάσεις γιὰ νὰ κατανοηθοῦν οἱ μοριακοὶ μηχανισμοί, οἱ ὑπεύθυνοι γιὰ ἐγκεφαλικὲς δυσλειτουργίες τοῦ ἀνθρώπου, ὅπως ἡ σχιζοφρένεια καὶ οἱ νόσοι Parkinson καὶ Alzheimer.

Ἔχει τιμηθεῖ μὲ 35 ἀπὸ τὰ πιὸ σημαντικὰ βραβεῖα ἐπιστημονικῶν φορέων καὶ ὀργανώσεων τῶν Η.Π.Α. καὶ πολλῶν ἄλλων χωρῶν. Μεταξὺ αὐτῶν τὸ Βραβεῖο τῆς Ἀμερικανικῆς Ἀκαδημίας Ἐπιστημῶν, τὸ Βραβεῖο Lasker, τὸ βραβεῖο R. V. Cajal καὶ πολλὰ ἄλλα.

Ἡ πιὸ πρόσφατη διάκρισή του εἶναι τὸ Βραβεῖο Nobel 2000, τὸ ὁποῖο τοῦ ἀπονεμήθηκε γιὰ τὴ γενικότερη προσφορά του στὴ Φυσιολογία καὶ τὴν Ἰατρική.

Σᾶς καλωσορίζω καὶ σᾶς εὔχομαι νὰ συνεχίσετε τὸ λαμπρὸ ἔργο σας γιὰ τὸ καλὸ τῆς ἐπιστήμης καὶ τοῦ ἀνθρώπου.

Dear Dr. Kandel

It is an honor and a pleasure to welcome you to this Institution. The proposal for your election as foreign member of the Academy of Athens, put forward by our colleague Kostas Stefanis, was unanimously approved on the 22nd February, 2001.

Unfortunately Kostas Stefanis is not with us this evening, since he is recovering from a serious surgical operation in London. Fortunately enough he is convalescing successfully and we all hope that he will be back with us soon.

In his absence I have tried to outline your tremendous contributions to science which have deepened our understanding of the function of the Brain and may have far reaching applications in the treatment of major neurologic and psychiatric human disorders.

Your contributions to science have been acknowledged by numerous prestigious institutions around the world, culminating in the award of the Nobel Prize in Medicine or Physiology in the year 2000.

We all wish you to continue your marvelous scientific work for the benefit of mankind.

ERIC RICHARD KANDEL

WE ARE WHAT WE REMEMBER: MEMORY AND THE BIOLOGICAL BASIS OF INDIVIDUALITY

TOWARD A MOLECULAR BIOLOGY OF MEMORY AND AGE-RELATED MEMORY DISORDERS

In my talk today I will focus on Memory Storage and Disorders of Memory Storage. Since this may be the first time that some of you are exposed to research in higher mental functioning, I also want to use this opportunity to give you a sense of how neuroscientists go about relating mental functions to brain function and, having done so, go on to analyze brain function on a molecular level so as to develop therapies that can reverse the mental disorder.

Let me begin by putting some of this progress into perspective for you. As you know, in the last five decades, we have witnessed a remarkable increase in the explanatory power and range of biology that is likely to have a broad impact on all aspects of modern thought including how we think about the mind and therefore how we think about ourselves. As a result, when intellectual historians look back on this period, they are likely to acknowledge that the deepest insights into the nature of mental processes will not have come from the disciplines traditionally concerned with mind. They will not have come from philosophy, from the arts, or even from psychology or psychoanalysis, but from biology. This is because in the last two decades, biology has participated not simply in one but in two major unifications of thought which bear on our understanding of mind.

First, there has been a remarkable unification within biology itself. This has brought together into a common molecular science the various sub-disciplines of biology: cell biology, biochemistry, developmental biology, immunology, the biology of cancer and even the biology of nerve cells, the building blocks of the brain. Second, there has been a parallel unification between neural science, the science of the brain, and cognitive psychology, the science of the mind. This

second unification is far less mature than that brought about by molecular biology, but it is potentially equally profound, for it has already provided us with a new framework for understanding perception, action and memory storage.

These two independent unifications stand at the extremes of the biological sciences and raise the questions: To what degree can these two disparate strands be brought together? Can molecular biology, which provided the driving force for the unification of the biological sciences, enlighten the study of mental processes? Can we anticipate an even broader synthesis in the 21st century, a synthesis ranging from molecules to mind, a synthesis that would open up a new molecular therapeutics? In my talk this morning, I would like to outline the possibility of a new science of the mind, a *molecular biology of cognition*, and suggest that it will occupy center stage in the early part of the 21st century, much as the biology of the gene occupied center stage in the last half of the 20th century.

Let me begin by putting the study of memory into a bit of a context for you. It is convenient to divide the study of memory into two parts: the **systems problem of memory and the molecular problem** of memory. In the *systems problem* of memory we ask the question: Where in the brain is memory stored? In the molecular problem of memory we ask: How is memory stored at each site? What are the molecules that are important for storage?

All of the early work on memory focused on the systems problem and on the question: "Where is memory stored?" So let me place this question into historical context.

The question of where memories are stored is part of a long tradition of brain research that has attempted to address the more general question: Can any mental process be localized to a specific region or combination of regions in the brain? One of the great intellectual accomplishments of brain science in the 19th century was the discovery that all mental functions derive from the brain and that these mental functions are mediated by combinations of identifiable, localized regions.

The first modern effort to locate brain function began in Vienna in the first part of the nineteenth century with Franz Joseph Gall (1758-1828), a physician and neuroanatomist who worked and taught for many years at the

University of Vienna. Gall made two remarkable and enduring contributions to our understanding of brain. First, he appreciated that all mental processes are biological and arise from the brain. He therefore opposed the Cartesian mind-brain dualism of his day and argued for a materialist view of the mind. This view later led the authorities in Vienna to accuse him of having offended moral and religious principles, an accusation that led to his leaving Vienna for Paris in 1805. Second, he posited that different mental functions were localized to different regions within the brain. He argued that the brain (and specifically the cerebral cortex) does not act as a single organ. It is not homogeneous but is subdivided into functionally distinct regions, each of which serves as the organ for one or another of the 35 mental functions defined by contemporary academic psychology. Gall assigned to the front of the brain intellectual processes such as the ability to evaluate causality, to calculate, to sense order. He assigned to the back of the brain instinctive characteristics such as amativeness (romantic love), combativeness, parental love. He assigned to the middle of the brain sentiments such as hope, reverence, benevolence. Thus, Gall argued that even the most abstract and complex of human behaviors, such as cautiousness, secretiveness, hope, sublimity, and parental love, were mediated by different, individual cortical regions. Gall therefore was the first strong proponent of the localization of function within the cortex, and he thereby initiated a debate that persisted for the next century.

While Gall's theory of localization was prescient, Gall's specific localizations per se were deeply flawed because they were not based on evidence. Rather than test his idea empirically, by looking into the brain and correlating lesions in specific regions of the brain following tumor or stroke with resulting defects in mental attributes, Gall distrusted clinical findings and therefore ignored the consequences of brain lesions following tumors or strokes. Rather, he was guided instead by a theory he developed at the beginning of his career according to which the size of a given area of the brain is related to usage of that area by the mental faculty it represents. Exercise of a given mental faculty causes the corresponding critical brain region to grow. This growth would in turn cause the overlying skull to protrude. By examining the bumps and ridges on the skulls of people well endowed with specific faculties, Gall sought to identify the centers for those faculties. This led to "phrenology," a discipline concerned with determining personality and char-

acter based on the detailed shape of the skull.

Gall developed this idea based on his experiences as an attending physician at an asylum for the mentally ill in Vienna. At the asylum Gall began to study patients suffering from *monomania*, a disorder characterized by a deep urge to commit one specific form of behavior often of an aberrant or socially deviant type: theft, hyper-religiosity, murder, romantic excess, etc. By examining the skulls of these patients and subsequently other subjects with particular passions, such as criminals, priests, composers, athletes and artists—all of whom excelled in some specific way or another, Gall assigned each attribute to a specific brain region based on his theory that excessive use leads to increase in size and ultimately distorts the skull. Based on these findings Gall drew diagrams (such as those of fig. 1). Although now we think of these as completely fanciful, Gall thought of them as rigorously empirical. He thought that even the most abstract of human behaviors, such as motherly love, generosity and secretiveness, occur in discrete areas of the brain.

Toward the end of Gall's life in the late 1820s, Gall's ideas were subjected to experimental analysis by the French experimental neurologist Pierre Flou-

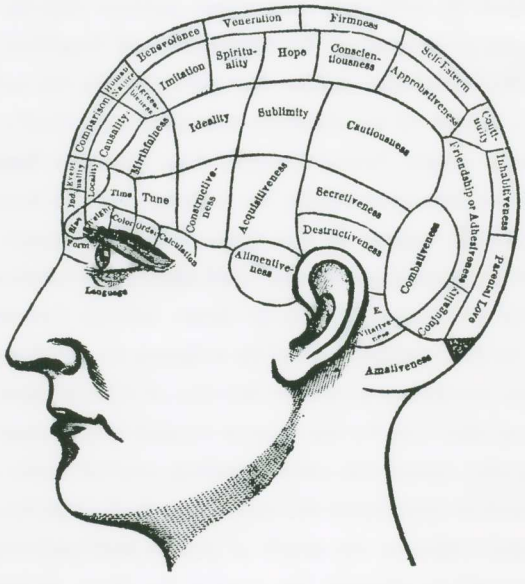


Fig. 1

Franz Joseph Gall (1758–1828).

Marie-Jean-Pierre Flourens (1794–1867).

Pierre-Paul Broca (1824–1880).

rens, who readily showed that the bumps on a person's skull bear little relation to the shape of the brain underneath. Flourens removed cortical areas in experimental animals corresponding to certain of the functional areas defined by Gall and failed to find any of the deficits that Gall's theories predicted. In fact, Flourens was unable to identify any specific deficits in behavior, which were associated with specific lesions of the neocortex. He thus concluded that the nervous system in general and the cerebral hemispheres in particular, are equipotential: any part of the cerebral cortex participates in and is able to perform all the functions of the whole. Injury to any part would, according to this theory, not affect any one capacity more than others. Flourens wrote (1823): *All perceptions, all volitions, occupy the same seat in these [cerebral] organs; the faculty of perceiving, of conceiving, of willing, merely constitutes thereby a faculty which is essentially one.*

The rapid acceptance of this belief (later called the aggregate-field view of the brain was based partly on Flourens' experimental work. It also represented a cultural reaction against the reductionist view that the human mind has a biological basis, the notion that there is no soul, that all mental processes could be reduced to actions within different regions of the brain.

Here the situation stood until 1861, when language—the highest human function—became analyzable through the study of aphasia—a set of disorders of language. Before we consider the relevant clinical and anatomical studies concerned with the localization of language, let us briefly survey the structure of the brain.

Much of what we know about the localization of normal language has come from the study of aphasia, a disorder of language. Many of the really important discoveries in the study of aphasia occurred in rapid succession during the last half of the 19th century, and formed one of the most exciting chapters in the intellectual history of human psychology. The initial advance occurred in 1861 with the publication of a paper by the French neurologist, Pierre Paul Broca a person much influenced by Gall and by the idea that functions could be localized. He argued the location should be based on examining damage to the brain by clinical lesions—it should be a phrenology of convolutions in the cortex not bumps on the skull. Moreover, Broca went on to say: "I had thought that if there were a phrenological science, it would be

phrenology of convolution (in the cortex) and not phrenology of bumps (on the head)." In this way, Broca founded what we *now* call neuropsychology.

Broca described the case of a patient named **Leborgne** who could understand language and could follow commands but who had lost the ability both to speak fluently and to write sentences (Fig 2). He could only speak an occasional word. This language disorder was not a motor disorder in a conventional sense; Leborgne could form some words, hum a melody without words fluently. Moreover, he showed disorder writing, although he could use his hands in other ways—he had a specific disorder of the motor output of language. Post-mortem examination of the brain showed a lesion in the posterior portion of the frontal lobe (an area now called Broca's area). Broca next collected 8 cases, all of which showed a lesion at this site and, in all cases the lesion existed in the left half of the brain. This led Broca to announce in 1885 one of the most famous principles of brain function:

"Nous parlons avec l'hemisphere gauche!" We speak with our left hemisphere (left-right hemiparesis).

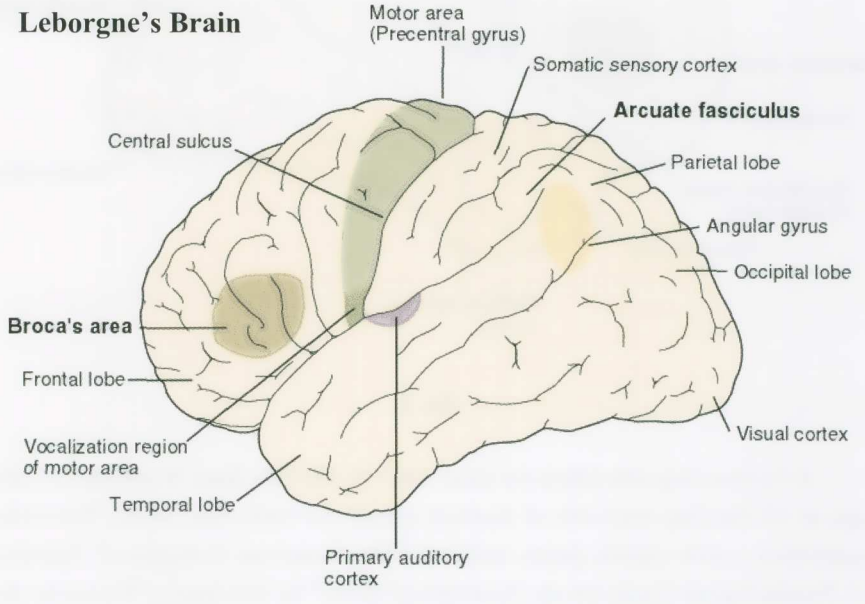


Fig. 2

Broca's discovery stimulated a wider search for the cortical loci of behavioral function, a search that was soon rewarded. In 1870, nine years after Broca's initial discovery, Gustav Theodor Fritsch and Eduard Hitzig galvanized the scientific community with their discovery that characteristic movements of the limbs can be produced in dogs by stimulating electrically the precentral gyrus in front of the central sulcus. Moreover, Fritsch and Hitzig found that there was a cortical representation for the individual muscle groups and that the region of the cortex devoted to different muscle groups was relatively small and discrete (Fig 3).

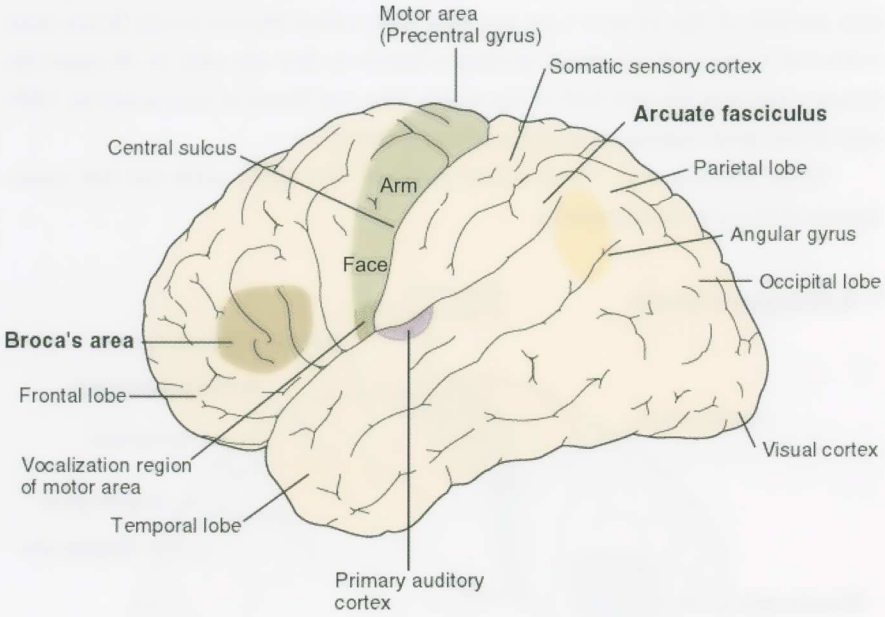


Fig. 3.

A further step was taken six years later in 1876 by Karl Wernicke. At the age of 26 (having been out of medical school for only four years) Wernicke published a now classic paper, entitled "The Symptom Complex of Aphasia: A Psychological Study on an Anatomical Basis." In this paper, Wernicke described a new kind of aphasia—an impairment of comprehension, a sensory,

as opposed to a motor, malfunction. Whereas Broca's patient could understand but could not speak, Wernicke's patient could speak but could not fully comprehend. The patient uses words, the sentences may even be grammatically correct, but there is very little meaning to them, much like a presidential press conference. Wernicke's new type of aphasia also had a different locus from that described by Broca: it was located in the posterior part of the temporal lobe (Fig. 4).

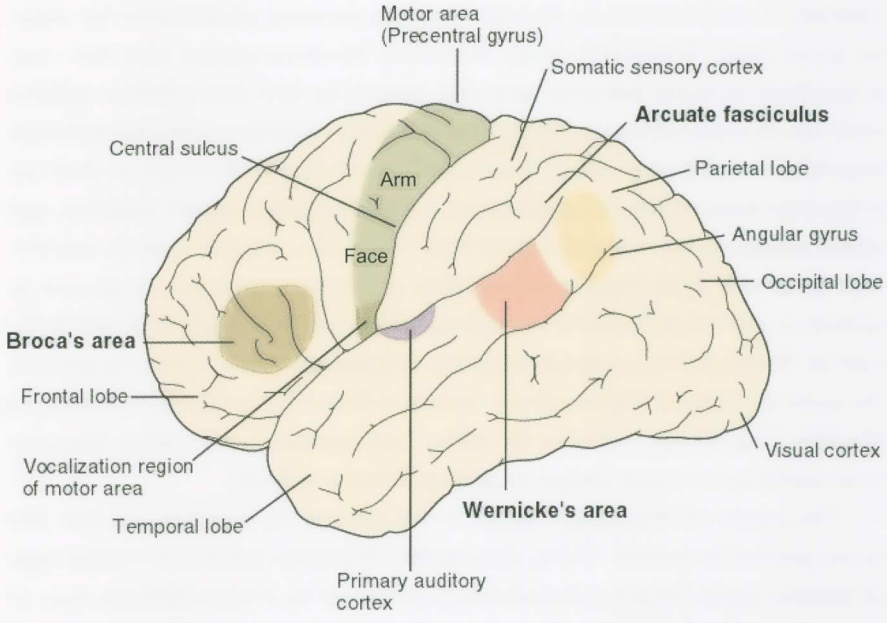


Fig. 4.

Wernicke immediately saw the implication of his work in relation to that of Broca and used his findings and Broca's to formulate a theory of language. He realized that a complex behavior, like language, is not localized to a single brain region but is distributed and involves the interconnections between the discrete regions. He therefore postulated that speech involves at least two regions, a motor region and a sensory region, and he ascribed the motor component to Broca's area. He realized that Fritsch and Hitzig had found that stimulating the lower end of the precentral gyrus, the area near Broca's area,

led to bilateral movements of the vocal apparatus, the mouth, tongue, palate and vocal cords. Wernicke therefore argued that, Broca's area, which lies immediately in front of this part of the motor area, incorporates the neuronal programs for coordinating the muscles of the vocal apparatus into coherent speech. Wernicke then assigned the sensory component to the area in the temporal cortex that he had discovered. Wernicke was struck by the fact that this area was located near both the auditory and visual association cortex. The Viennese psychiatrist Theodor Meynert (the teacher of both Wernicke and Sigmund Freud) had found that the auditory pathway projected to the angular gyrus (near Wernicke's area). Wernicke therefore argued that this zone is involved in word selection and that lesions in this area produce aphasia with loss of comprehension. Thus, Wernicke put together a coherent although somewhat simplified model of speech that is still useful, although we shall see it has now been modified importantly. According to this model, auditory and visual sensation are conveyed from their respective sensory areas to association areas and from there to Wernicke's area where they are recognized as spoken or written expressions of language. Without the recognition, which occurs in Wernicke's area, comprehension of language is lost. Once recognized, the auditory forms of the words are relayed to Broca's area which, according to Norman Geschwind, contains the rules, "the grammar", for coding language from auditory or visual images to spoken or written form.

The power of Wernicke's model is not only in its completeness but also in its predictive powers. Using this model, Wernicke predicted a third type of aphasia (later discovered clinically), produced by a very different type of lesion than that involved in Broca's and Wernicke's aphasia. This new type of aphasia spared the receptive and motor speech zones, but destroyed the pathways connecting them. Wernicke predicted that this disconnection syndrome, later called conduction aphasia, should lead to incorrect word usage (paraphasia). Although comprehension is good, speech is fluent but meaningless. Patients with paraphasia omit parts of words, substitute incorrect sounds in the word, or use correct words incorrectly. As Wernicke correctly predicted, this lesion interrupts the arcuate fasciculus of the lower parietal region (Fig. 5).

Thus, by the beginning of the 20th century it was well established that language, movement, touch, hearing and vision, as well as other functions can be localized to particular regions. Once this was accomplished, it was only

Karl Wernicke (1848-1905)

Karl Lashley (1890-1950)

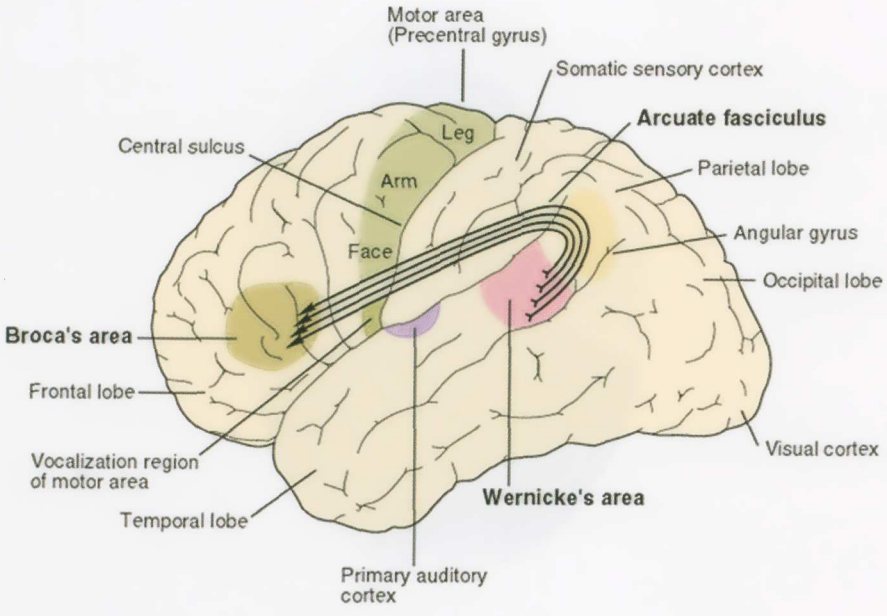
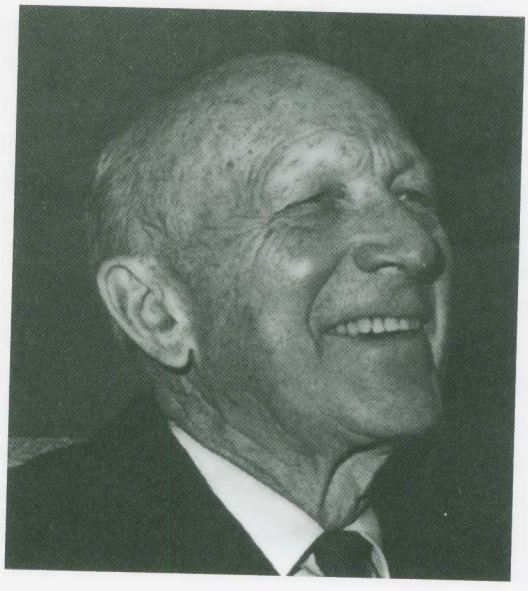


Fig. 5.

a matter of time before efforts to localize cognitive function would turn to memory. Memory posed a unique problem. Was it in fact an independent faculty of mind? Indeed, the initial attempts to localize memory by Karl Lashley, Professor of Psychology at Harvard in the 1940s failed to find it localized to any specific region.

Lashley began the experimental search for the locus of memory storage by training rats on specific memory tasks, systematically removing portions of cortex, and then testing them for recall. In so doing, he repeatedly failed to find any particular brain region that was special to or necessary for the storage of memory. On the basis of these findings, Lashley formulated the law of equipotentiality and *mass action*, according to which, memory is diffusely distributed in the brain and the extent of a memory deficit is correlated with the amount of cerebral cortex removed but not with the specific site of that lesion.



Wilder Penfield (1891-1976)

Brenda Milner 1918-

The first suggestion that aspects of memory might be stored in a specific site of the human brain came in the 1940s from the work of an innovative neurosurgeon trained at Columbia, Wilder Penfield. Working at the Montreal Neurological Institute, Penfield pioneered the neurosurgical treatment of focal epilepsy. This form of epilepsy produces brain seizures that are restricted to limited regions of cortex. Penfield developed a technique, still used, to remove the epileptic tissue while minimizing damage to the patient's mental functions. To assure that he did not damage areas critical for language during surgery, he applied weak electrical stimulation to various sites in the cortex of his patients and determined its effects on their ability to speak and comprehend language. Because the brain contains no pain receptors, patients received only a local anesthetic; they remained fully conscious during surgery and were able to report their experiences. Through these responses, Penfield could identify specific brain sites important for language in the individual patient and then try to avoid these sites when removing epileptic tissue.

In this way, Penfield explored much of the cortical surface in more than 1000 patients. On occasion, he found that in response to electrical stimulation the patients would describe coherent perceptions or experiences. For example, one patient stated, "It sounded like a voice saying words, but it was so faint that I couldn't get it." Another patient said, "I am seeing a picture of a dog and cat...the dog is chasing the cat." These responses were rare but they were invariably elicited only from one region of the brain, the temporal lobes, never from other areas, and even within the temporal lobes, stimulation evoked coherent experiences only rarely, in about 8 percent of cases. Penfield concluded that portions of the temporal lobe were specifically concerned with memory (Fig. 6).

More conclusive evidence for the involvement of temporal lobe structures in memory came in 1957, when William Scoville, a neurosurgeon influenced by Penfield, and Brenda Milner, a psychologist and long-term collaborator of Penfield's, reported the now famous case of H.M. At age 9, H.M. was hit by a bicycle and knocked down, and sustained a head injury. By the age of 27, he was severely incapacitated. Because H.M.'s epilepsy was thought to have its origin within the brain's temporal lobe, Scoville decided, as a last resort, to remove the inner surface of the temporal lobe on both sides of the brain, including a structure called the hippocampus, in an attempt to treat his epilepsy.

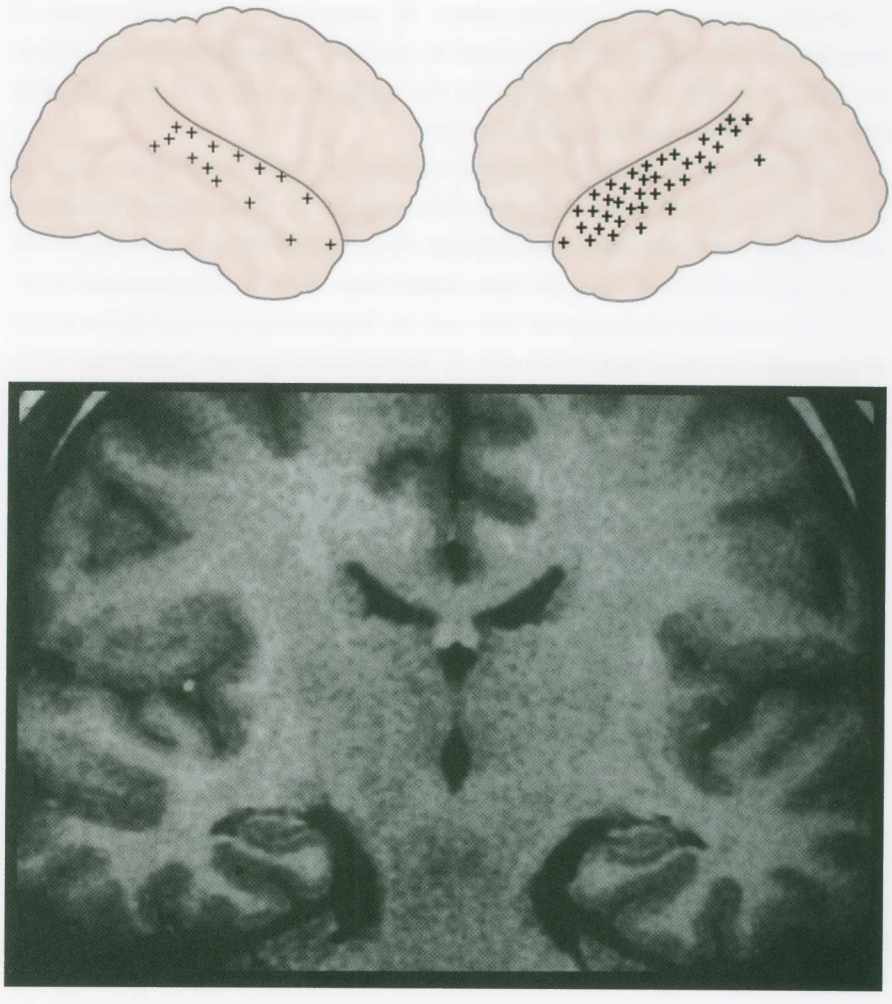


Fig. 6.

Although this surgery greatly improved his epilepsy, it left H.M. with a highly specific but nonetheless devastating memory loss from which he has never recovered. From the time of his operation in 1953 until the present day, H.M. has been unable to convert a new short-term memory into a new permanent long-term memory.

What was astonishing about this memory loss was that it proved to be

amazingly selective. H.M.'s surgery only interfered with certain components of memory storage but not with others. By characterizing which aspects of memory function H.M. lost and which he retained, Milner was able to delineate three features, which characterize the specific role of the temporal lobes and the hippocampus in memory storage.

First, Milner found that H.M. had a perfectly good long-term memory for events prior to his operation. He was able to maintain his overall intelligence and to speak coherent and fluent English. He remembered vividly many of the events of his childhood and his later experiences at work. These several findings indicated that the temporal lobe and the hippocampus is not the ultimate storage site for long-term memories of *previously* acquired knowledge. (We now have reason to believe that these are stored in other regions, most likely the cerebral cortex.)

Second, H.M. had a perfectly good short-term memory. He could repeat a name or a telephone number, for example 884-5447, as accurately as an intact person, and he could carry on a normal conversation, providing it did not last too long or move among too many topics. Thus, the temporal lobes were also not required for short-term memory.

Third, what H.M. did lack, and lacked to the most extraordinary degree, was the capability to put new short-term information into new long-term storage. As a result of this one striking defect, he appeared to forget events as soon as they happened. Less than an hour after eating, he could not remember anything that he had eaten or even the fact that he had had a meal. He would read the same magazine over and over without knowing what he had read. When told to remember the number 884-5447, he could repeat the number immediately. If he was distracted, however, even briefly, he completely forgot the number. He was able to retain new information only as long as his attention was not diverted from it. Yet, only a minute or two later, after his attention had been directed to another task, he could not remember the number or any of his trains of thought about the number.

As a result of this difficulty in translating information from short- to long-term memory, H.M. did not recognize new people, even when he met them repeatedly. He met with Brenda Milner monthly for over a 20-year period. Each encounter was like the first. As the years passed, he could not

recognize himself in a photograph of himself 20 years earlier because he had no memory of his changed appearance. Other patients with lesions of the hippocampus show similar learning deficits. So do experimental animals with lesions of the hippocampus.

Milner's three discoveries revealed two important principles. First, Milner completely disproved Lashley's idea of mass action and equipotentiality. She had found that memory was a discrete mental faculty that was localized. Restricted lesions of the temporal lobes, a lesion that had no effect on perception and intellectual functions, seriously interfered with the ability to lay down in memory the records that ordinarily result from engaging in perceptual and intellectual work. Second, she showed that lesions of the temporal lobe and hippocampus led to a dissociation of short-term memory from long-term memory, thereby validating, on a biological level, the fundamental distinction between short- and long-term memory formulated by William James.

Originally, Brenda Milner thought that the memory deficit following hippocampal lesions was global and applied to all forms of new learning and long-term memory. But it has since become clear that this is not the case. In 1962, Milner unearthed evidence that even though patients with hippocampal lesions have profound deficits, they can accomplish certain types of learning tasks quite well, and retain the memory of these tasks for long periods.

She found that there were, in fact, certain types of knowledge that H.M. could learn and remember perfectly well! Specifically, he retained the ability to learn new hand-eye coordination skills. He could trace the outline of a star in a mirror and his performance improved daily as would that of a normal subject (Fig. 7).

When H.M. is asked what he remembers of this particular task, he will deny learning the task even when his response reveals good learning and memory. As Weiskrantz comments, the patient "convincingly reveals his amnesia in his answer to the question." The memory of amnesic patients, moreover, is not limited to the learning of procedures and skills. For example, patients with bilateral lesions in the hippocampal system learn new motor skills normally, and they acquire and retain simple forms of reflexive learning like habituation, sensitization, and classical conditioning. The learning tasks that amnesic patients are capable of remembering all have several things in common. They

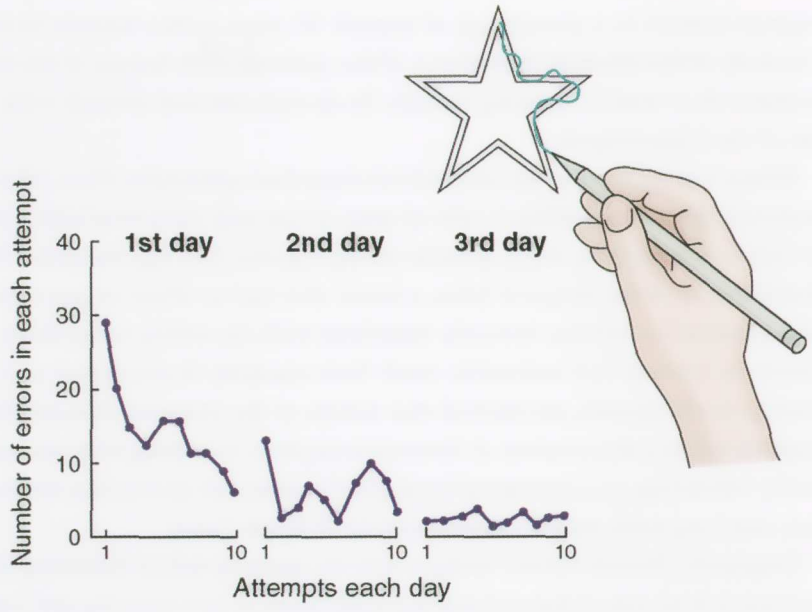


Fig. 7.

have an automatic quality and their formation of expression is not dependent on awareness or cognitive processes such as comparison and evaluation. This type of memory accumulates slowly through repetition over many trials and is expressed primarily by improved performance on certain tasks. Many of these learning skills are, as the psychologist Lawrence Weiskrantz has remarked, reflexive rather than reflective. The patient need only produce a physical response to a stimulus or a cue. In none does the patient have to reflect—to recall or think about what is to be remembered. Thus, if the patient is given a highly complex mechanical puzzle to solve, the patient may learn it as quickly as a normal person, but on questioning will not remember seeing the puzzle or having worked on it.

MEMORY IS NOT A UNITARY FUNCTION OF MIND

It thus became clear that memory is not a unitary faculty of mind but has at least two forms: Explicit or Declarative ("knowing that") and Implicit or Procedural ("knowing how") (Fig. 8).

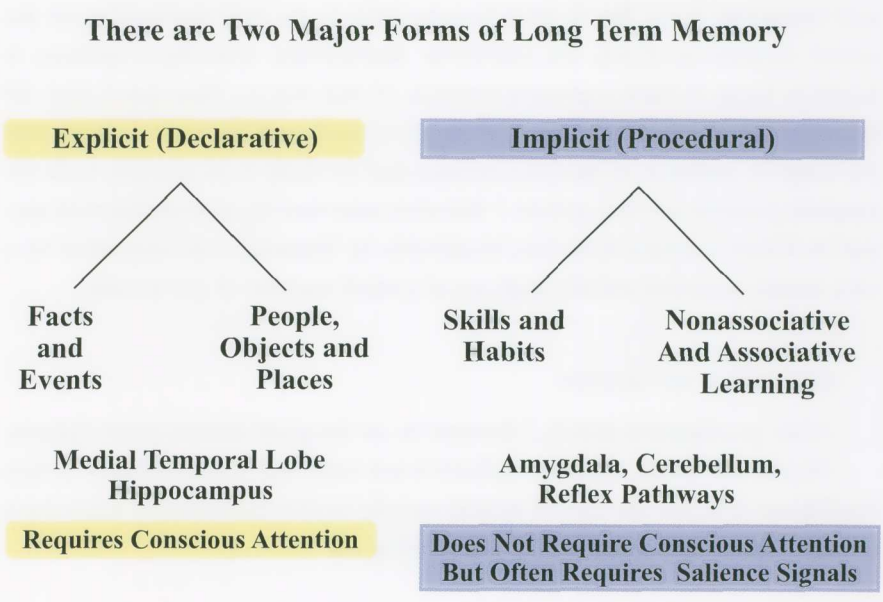


Fig. 8.

Explicit memory is what one usually thinks of as memory. It is the *conscious* recall of facts or events. It is a conscious memory for people, places, objects and events, and it requires attention for both storage and recall. This form of memory is mediated by the medial temporal lobe and a structure deep to it: the hippocampus.

Implicit memory is an unconscious memory for perceptual skills and motor procedures as well as for associative and non-associative learning; its recall does not require attention or conscious effort and it does not require the medial temporal lobe system. Rather, it is mediated by three distinct subcortical structures: the striatum, the amygdala, and the cerebellum, and in the simplest cases, by the reflex pathways themselves.

THE *MOLECULAR* PROBLEM OF MEMORY: HOW IS MEMORY STORED AT EACH SITE?

Since I came to the biology of memory from an interest in psychoanalysis, I therefore was initially tempted to tackle this problem in its most complex

and intriguing form. But it soon became clear to me that irrespective of the neural systems involved, the molecular mechanisms whereby a memory is stored is likely to have a general solution. If that was so, then one is best off taking a reductionist approach. One needs to study not the most complex but the simplest instance of memory storage, and to study it in animals with the simplest possible nervous system. I therefore searched for an experimental animal in which a simple behavior, modifiable by learning, was controlled by a very simple neuronal circuit made up of a small number of nerve cells.

PICTURE OF AN *APLYSIA*

After an extensive search, I focused in on the giant marine snail *Aplysia*.

As you can tell at a glance, *Aplysia* is not only highly attractive, it is very intelligent. It is just the sort of animal anyone would immediately select for a radical reductionist analysis of learning (Fig. 9).

COMPARISON OF THE HUMAN BRAIN TO THE BRAIN OF *APLYSIA*

But what is most remarkable about the animal is that it has mastered all of its behavior with a very simple nervous system made up only of a few nerve cells. While your brain and mine has a million-million cells, *Aplysia* has only 20 thousand. As a result, simple behaviors that can be modified by learning may involve only about 100 cells. This enormous simplification in numerical complexity makes possible precise identification of the contribution of individual cells to the behavior in which they participate (Fig. 10).

THE GILL-WITHDRAWAL REFLEX

In this simple animal we delineated the simplest possible behavior capable of being modified by learning: the simple reflex withdrawal of the gill — the respiratory organ of the animal — to stimulation of the siphon. This defensive withdrawal is much like the withdrawal of a hand from a hot object (Fig. 11).

THE NEURAL CIRCUIT OF THE GILL-WITHDRAWAL REFLEX

We next defined the neural circuit of this behavior in cellular detail. The

Fig. 9.

The Human Brain
is complex
10^{12} Neurons

The *Aplysia* Brain
is simple:
2×10^{4} Neurons

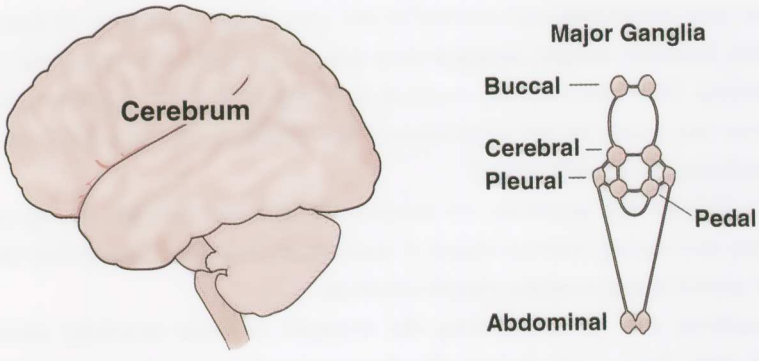


Fig. 10.

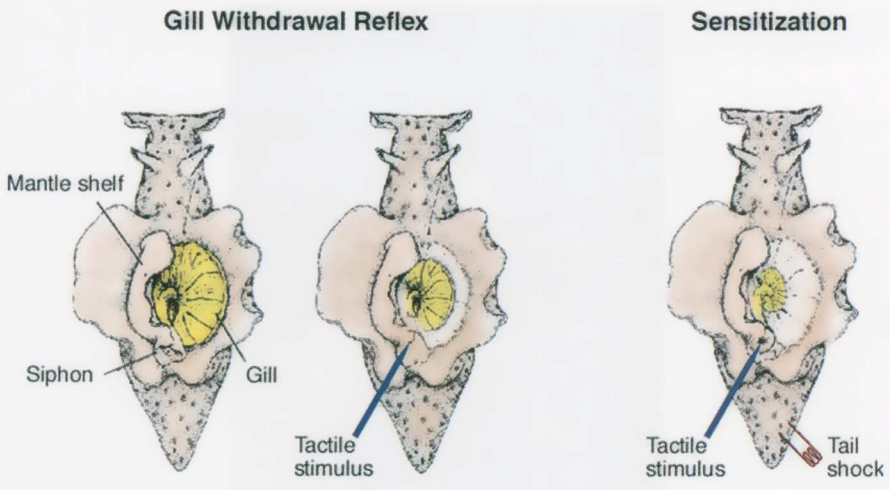


Fig. 11.

reflex has both direct connections made by 24 sensory neurons to six motor neurons, and indirect connections through interneurons (Fig. 12).

In examining the neural circuit, we noticed a remarkable invariance of behavior. Not only the cells of the neural circuit are invariant, but all the interconnections are invariant. In every animal we examined, a given sensory cell or interneuron only connects to a particular target cell and not others.

This invariance has been found for other behaviors and gave us the first insight into the nature of Kantian *pre-knowledge. Built into the brain under genetic and developmental control is the very basic capability of behavior.* But this Kantian insight raised a deep question in the cell biological study of learning: How can learning occur in such a precisely wired neural circuit? How can one reconcile the invariance of the neural circuit of a behavior with its capability for modification?

To address this question, we examined these connections during actual learning and during various stages of memory storage, and found that the apparent paradox had a rather simple solution:

Learning acts by modulating the strength of these precisely interconnected cells. Thus, even though the developmental program assures that the connections between cells are invariant and correctly specified, it does not

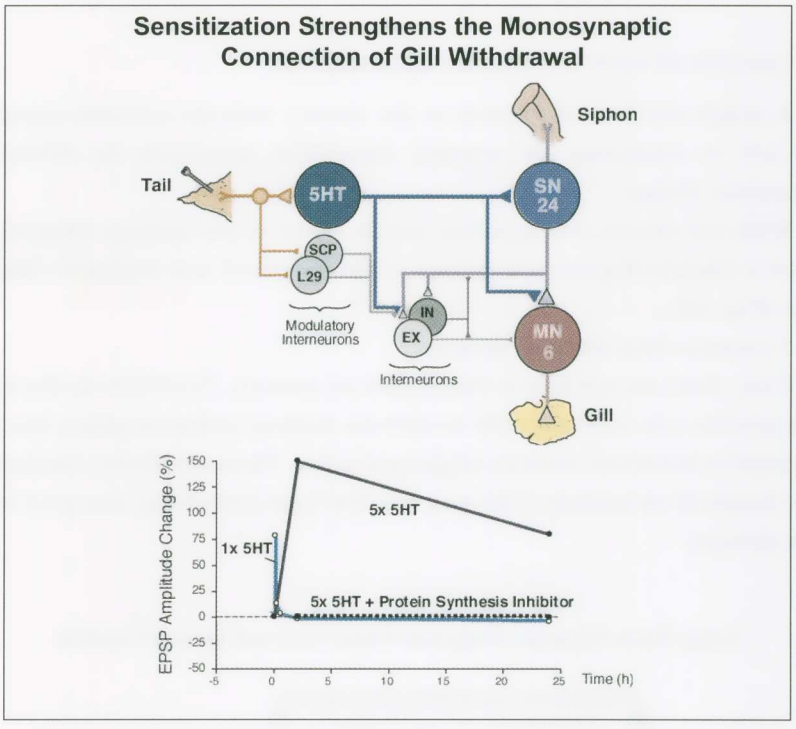


Fig. 12.

specify the precise, absolute strength of the connections. It is learning that plays upon these connections to alter their strength.

Moreover, the persistence of this change is the mechanism whereby memory is stored.

Let me illustrate this in more detail. The tail stimuli that produce sensitization strengthen the reflex by activating a modulatory system of which the most important component is serotonergic. These serotonergic cells act on the sensory neuron, including its terminals, to enhance the strength of its connections. A single stimulus produces a transient strengthening of this connection. Repeated stimuli produce a persistent strengthening.

How is the short-term process set up with one pulse of 5-HT, and how is it converted to the long-term process with five pulses of 5-HT? The next slide shows a blow-up of the sensory neuron, which summarizes how the long-term process is set up.

CARTOON OF SHORT- AND LONG-TERM MEMORY

A single shock to tail system in the sensory neurons activates signaling that acts to strengthen the synaptic connection transiently by enhancing transmitter release.

With tail shocks, the signaling system moves to the nucleus where it activates a cascade of genes which leads to the growth of new neuronal connections (Fig. 13).

I comment here on three features.

First, *there are inhibitory constraints on memory.* To switch on the long-term process, you need not only to activate memory enhancer genes, but you also need to inactivate memory suppressor genes. These inhibitory constraints set a threshold on memory. This way you don't put everything into your long-term memory.

Long-Term Memory Requires Gene Activation and Growth

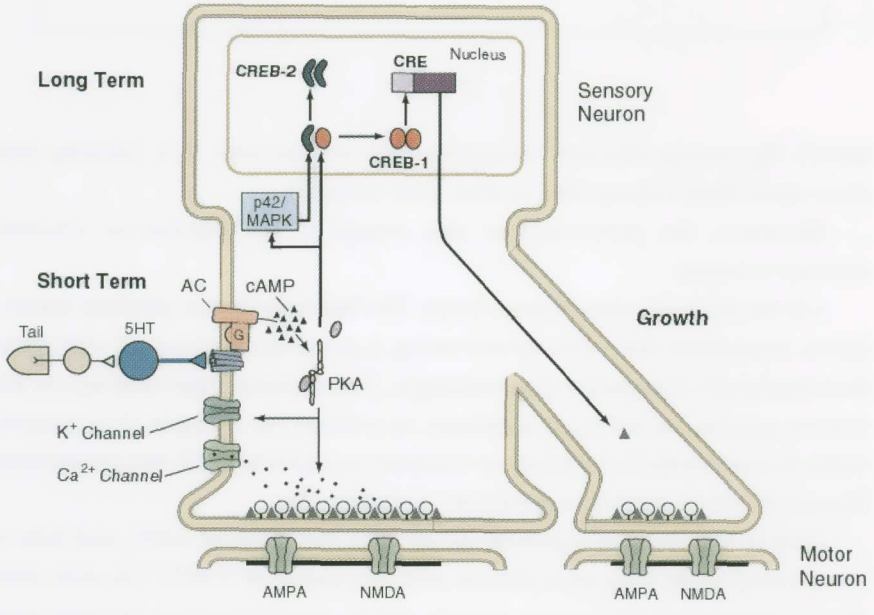


Fig. 13.

Second, once the inhibitory constraints are removed, the switch for long-term memory is triggered and activates a cascade of genes. *So genes are not simply the automatic controllers of behavior – genes also are the servants of our environment.* They respond to social and environmental stimulation. This symposium, for example, will cause genetic fireworks in your brain.

Third, what gives the memory its long-term persistence is the growth of new synaptic connections. Thus, if you remember anything of this lecture. In fact, the function of a great university is to alter your brain. It actually does so!!!

This set of mechanisms has proven to be very general. It applies to invertebrate as well as vertebrate, to explicit as well as implicit memory.

Let me illustrate this with growth.

THE SOMATOTOPIC MAP IN THE BRAIN IS MODIFIABLE BY EXPERIENCE

How important is growth in determining the functional architecture of *your* brain? This is you (Fig. 14). This how you look to yourself. When no one else is looking. I was taught this was fixed. But we now know that this is not so.

The cortical maps of an adult are subject to constant modification on the basis of use or activity of the peripheral sensory pathways. Since all of us are brought up in somewhat different environments, are exposed to different combinations of stimuli, and are likely to exercise our motor skills in different ways, the architecture of each brain will be modified in special ways. This distinctive modification of brain architecture, along with a distinctive genetic make up, constitutes the biological basis for the expression of individuality.

SKILLS, TALENTS, AND THE DEVELOPING BRAIN

Given the shared evolutionary history of monkeys and humans, it would be surprising if the lessons learned from monkeys did not apply to humans as well. The emergence of functional neuroimaging in the 1990s made it possible to confirm the link directly.

**Every person in the audience will have a slightly different brain, because they have different life experiences.* Even identical twins with identical genes will have different experiences and different brains. Explains the issue of qualia: Is the red you see the same as the red I see?

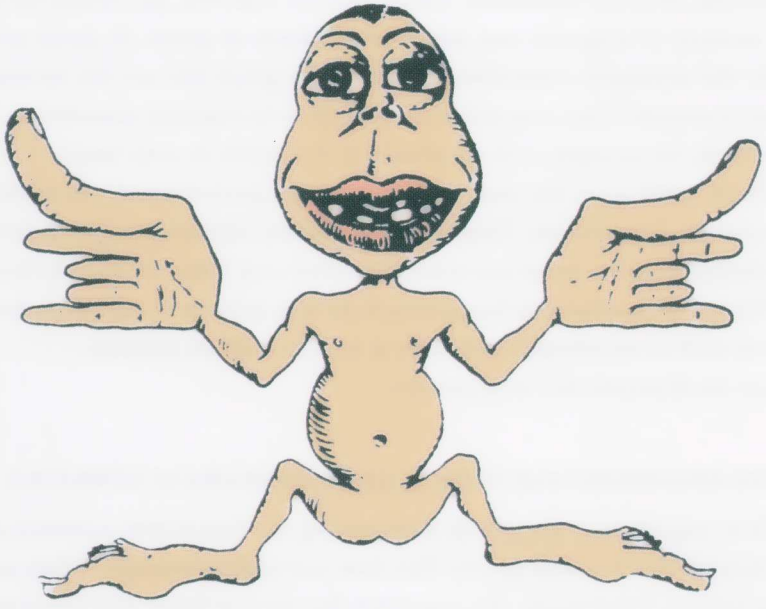


Fig. 14.

In one study, Thomas Ebert at the University of Konstanz in Germany, and his colleagues, studied the brains of violinists and other string players in comparison to the brains of nonmusicians. String players are an interesting group for studies of how experience affects the brain because during performance the second to fifth fingers of the left hand are manipulated individually and are continuously engaged in skillful behavior. In contrast, the fingers of the right hand, which move the bow, do not express as much patterned, differentiated movement. Brain imaging studies of these musicians revealed that their brains were different from the brains of nonmusicians. Specifically, the cortical representation of the fingers of the left hand, but not of the right, was larger in the musicians. These results dramatically confirm in humans what animal studies had already revealed in more detail. The representation of body parts in the cortex depends on use and on the particular experiences of the individual (Fig. 15).

These structural changes are more readily achieved in the early years of life. Thus Wolfgang Amadeus Mozart is Mozart and Michael Jordan is Jor-

Cortical Representation of Fingers

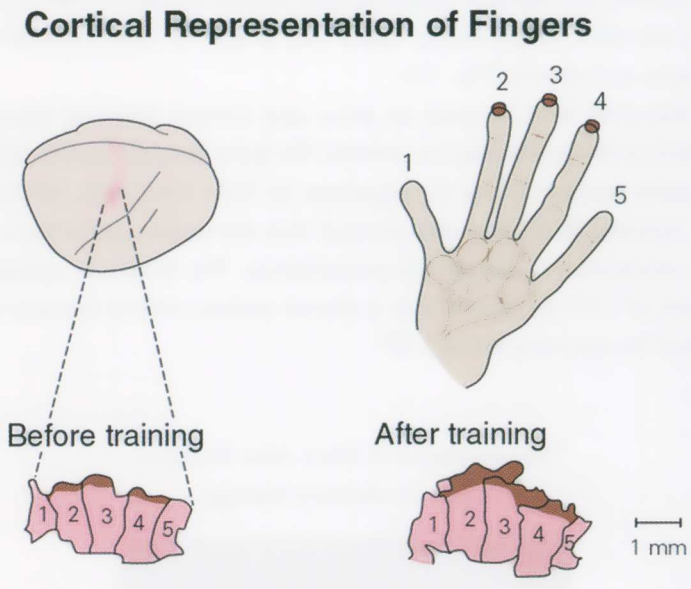


Fig. 15.

dan, not simply because they have the right genes (although genes help) but also because they began practicing the skills they became famous for at a time when their brains were most sensitive to being modified by experience.

WHAT ABOUT EXPLICIT MEMORY STORAGE?

To remind you, explicit memory storage is the memory stage we associate with our own fondest memories – for people, places, and objects – this requires a mammalian brain, and specifically the hippocampus and the medial temporal lobe system.

This system is of further interest in that it is particularly affected with age, a topic I want to turn to later in my lecture.

Ten years ago, it became possible to change genes in the brains of mice. This made it clear that, in the long run, mice offer a superb genetic system for relating individual genes to synaptic plasticity on the one hand, and to complex memory storage on the other.

Although mice *are relatively simple mammals*, they have a medial temporal lobe system, including a hippocampus, which resembles that of humans, and they use their hippocampus much like people to store explicit memory about places and objects (Fig. 16).

We therefore have focused on place and context learning because it is particularly well documented in rodents. We have focused specifically on the hippocampus because it was so important in H.M. Moreover, following the work in *Aplysia*, Bliss and Lømo showed that the hippocampus has a cellular learning mechanism — long-term potentiation. We therefore examined the mechanism of LTP and found that it shared certain critical features with the facilitation we encountered in LTP.

Hippocampus of Mice Also Encodes
Explicit Memory Storage

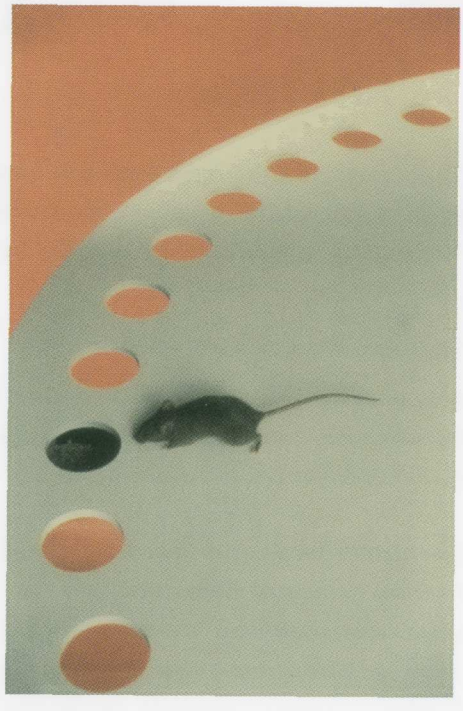


Fig. 16.

We therefore were interested in examining the relation between LTP and spatial learning in a ***new*** *way, by interfering not with the induction and early maintenance of LTP, but by looking specifically, as we did in Aplysia, at the transition of short-term to long-term LTP and thereby to examine the switch to long-term memory, but now with the opportunity of exploring long-term memory for complex spatial and contextual tasks* (Fig. 17).

With these questions in mind, we examined each of the three major pathways in the hippocampus

(1) Medial perforant pathway.

(2) Mossy fiber.

(3) Schaffer collateral.

We found that LTP in each of these pathways has phases. In each case, the late phase requires repeated training trials, in each case the late phase requires

Late LTP Requires PKA and Transcription

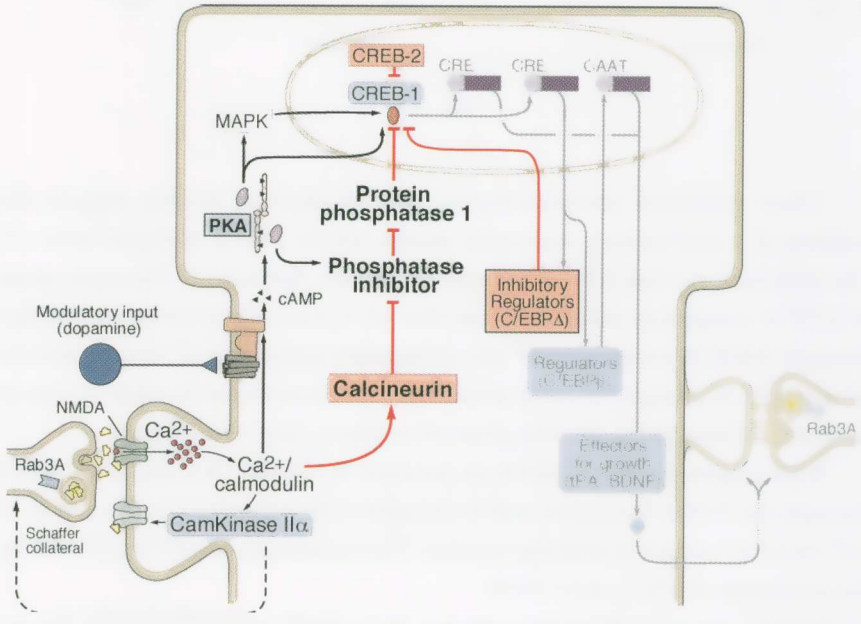


Fig. 17.

translation and transcription, and in each case the late phase requires PKA. *In two of these cases, Schaffer collateral and mossy fiber, Alcino Silva and we have shown that CREB is involved in the late phase* (Fig. 18).

Expression of R(AB) Transgenic Construct Leads to a Defect in Late LTP

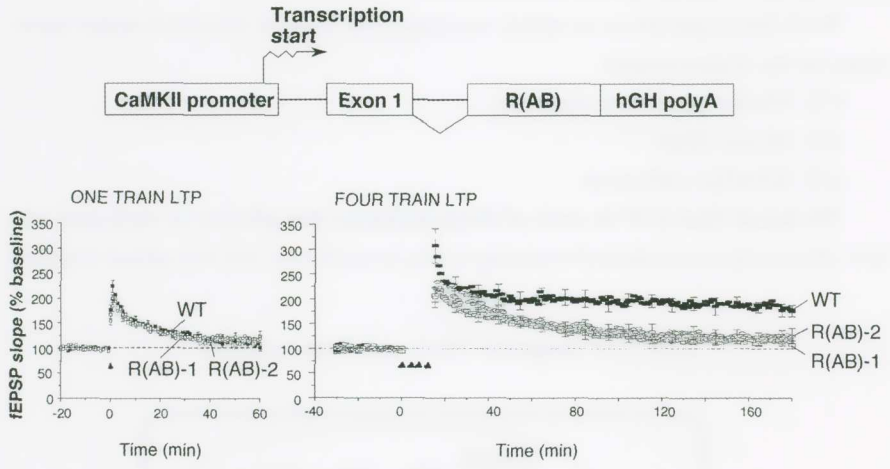


Fig. 18.

These combined pharmacological and biophysical studies suggest the outlines of a preliminary molecular model, which I have sketched here: *(1) Our data indicate that LTP has phases, much like Aplysia. (2) The early phase of LTP is completely different from that of Aplysia. It involves* Ca^{2+} *influx through NMDA receptors and the subsequent activation of several protein kinases. (3) Although this early phase bears no resemblance to what we saw in Aplysia or Drosophila, the late phase does bear a clear resemblance.*

With repeated trains, there is an increase in cAMP. This also is mediated through the NMDA receptor and is thought to be secondary to the action of Ca^{2+} on a Ca^{2+}-sensitive adenylyl cyclase. The increase in cAMP is followed by the activation of PKA and CREB.

In turn, we and others have shown that cAMP and LTP lead to the activation of immediate-early genes, only two of which I have indicated here because they have been particularly well studied: (1) tPA which has been

shown to stimulate process outgrowth, and (2) C/EBPβ, a homolog of *Aplysia* C/EBP. Both of these have CRE upstream.

To test this model genetically, we have turned to genetically modified animals. Here they have attempted to create more subtle lesions than with earlier transgenic studies. Earlier studies with ablation of fyn and CaM kinase were designed to eliminate the early phase of LTP. In the present studies we specifically did not want to interfere with the early phase of LTP but wanted to restrict our phenotypes to the late phase. By this means we should not in any way affect LTP to a single train and use that as a control for both the physiology and the learning and memory systems.

Toward that end, Ted Abel has expressed REVAB (the subunit has to dissociate to free catalytic subunits) under CAM kinase promoter. We have cloned out this promoter and used it before because it has a very interesting pattern of expression: (1) it is limited in expression to forebrain structures; (2) it has a high level of expression; and (3) it begins to be expressed only late in development. REVAB selectively affects the late phase. We have obtained similar results with ablation of one of the isoforms of the catalytic subunits (Fig. 19).

These animals have an interesting defect in LTP—normal early phase, normal synaptic transmission, selective defect in late phase thus providing independent genetic evidence for the late phase. From this, one might make a stringent prediction: normal short-term memory; defective long-term memory, *a la Aplysia and Drosophila.*

These animals show a memory defect in the Morris and Barnes Mazes. But the Morris and Barnes Mazes allow poor time resolution because they require training over days. What is needed is a test with training over a period of minutes, which would allow good temporal resolution that allows one to follow a memory over time. For this purpose, we have turned to *context conditioning* developed by Fanselow. Three training trials occur over a brief time period: Explain. Animals freeze. Measure freezing (Fig 20).

Two tests: *context: tests for hippocampal-based memory; cued: amygdala-based.*

These tests are nice: They allow us to distinguish – short from long – term memory amygdala from hippocampus.

R(AB) Mice show a Hippocampal-Dependent Loss of Spatial Memory

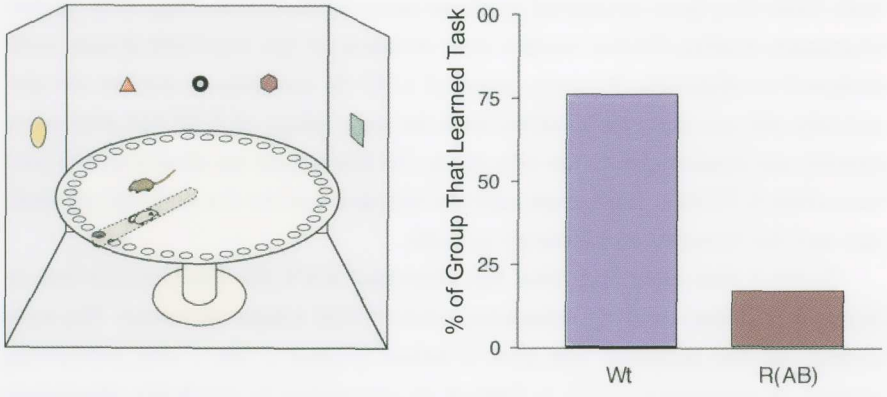


Fig. 19.

Both Explicit and Implicit Memory Storage Use Modulatory Transmitters as a Salience Signal and a CREB-Mediated Transcriptional Switch for Converting Short-term to Long-term Memory

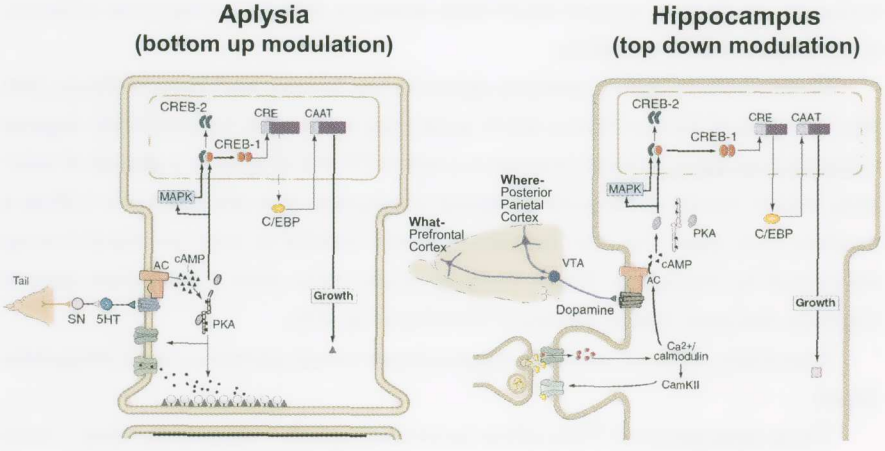


Fig. 20.

To summarize, the requirement of a cascade of gene activation involving PKA and CREB in both explicit and implicit memory explained two features: (1) Why the switch from short- to long-term memory requires new protein synthesis? (2) Moreover, these experiments illustrate that despite the fundamental behavioral differences between implicit and explicit memory, the molecular mechanisms for storage are conserved. Indeed, even modulation is similar and gives us an insight into where attentional processes come in.

AGE-RELATED MEMORY LOSS

With this as background in understanding a core signal transduction pathway required for stabilizing long-term memory, we have tried to use mice as animal models of human memory deficits, focusing on age-related memory loss. Let me put age-related memory loss into an epidemiological perspective (Fig 21).

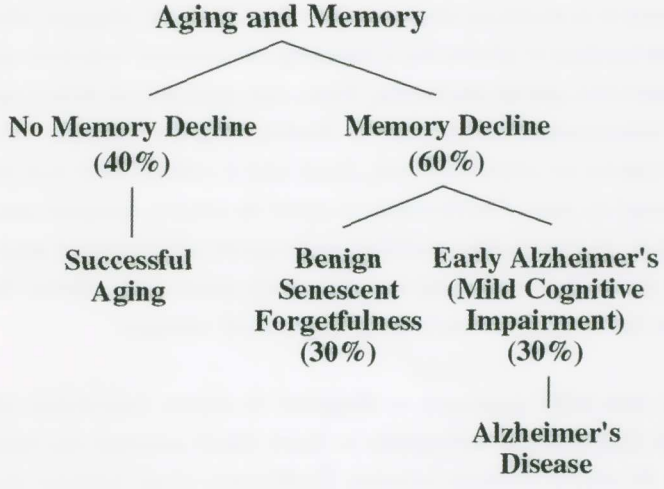


Fig. 21.

Epidemiological studies have shown that if you follow a normal healthy population of people 70 years old over time and exclude all cases of dementia, Parkinson's disease, depression, or stroke, about 40% of this population shows good retention of memory — successful aging. The remaining 60% show a modest decline in memory loss, as evident in such tasks as the delayed recall

component of a word list memory task: The Selective Reading Task. *This correlation is selective for memory performance; it was not found between signal and performance scores on* other cognitive measures of abstract reasoning, language, or visuospatial ability. In the early stage, these two forms cannot be distinguished clinically based on their cognitive performance, *but with time, half of the 60% (or 30% of the total population) will stabilize into a benign senescent forgetfulness. The remaining half (the other 30%) will go on to progressive Alzheimer's disease.*

Scott Small and his colleagues at Columbia have recently developed a variant of functional magnetic resonance imaging (fMRI) in humans, which is not task-oriented but is designed to be sensitive to static *neuronal function. This method is* based on resting or static, instead of dynamic, changes in oxygen-dependent signal (resting T2* signal). *The idea of using resting T2* signal derived from the consideration that most causes of brain dysfunction produce changes not only in the* active *but also in the* resting *function of neurons.* Because it is based on resting rather than dynamic changes, this method has two advantages: it allows for a mapping of neuronal function and it does so with improved spatial resolution. Thus, this method can detect signal from different hippocampal subregions in human subjects. *Because this method does not require an activation task, Scott and I collaborated and found that it can be used in mice. Furthermore it could be used to compare anesthetized normal mice, to genetically-modified and cognitively-impaired mice. In mice we could show that the signal is sufficiently sensitive to detect functional changes in the absence of underlying anatomical changes.*

Using this MRI approach — designed to detect functional changes in individual hippocampal subregions — Scott Small assessed the hippocampal circuit in 30 elderly subjects between 70-88 years of age without dementia to determine whether one could delineate, in a preclinical way, two populations that are indistinguishable on cognitive tests: those that develop benign senescent forgetfulness and those that go on to Alzheimer's disease. Forty percent (12) had stable hippocampal signal; 60% had diminished signal. Single-subject analysis revealed that hippocampal dysfunction, found in 60% of elderly people, was selectively correlated with memory decline. The 60% group with reduced memory function fell into two groups: in one group (30%), all hip-

pocampal subregions declined normally with age. This decline was particularly evident in the subiculum. In fact, in these elderly individuals, signal intensity from the subiculum correlated selectively *with age.*

In the second group — the other 30% — there were two disorders. First, there was an overall decline also particularly evident in the subiculum but in addition there was a second hit that affected selectively and dramatically the entorhinal cortex.

The entorhinal cortex is the first hippocampal subregion targeted by Alzheimer's pathology, and the pathological decline observed in the signal of the entorhinal cortex likely reflects elderly people with the earliest manifestations of Alzheimer's pathology. If so, individuals with entorhinal dysfunction are at increased risk to progress to Alzheimer's dementia, and Scott is currently testing this prediction by following subjects prospectively.

These results show that memory decline is caused by at least two different mechanisms: (1) subicular disease, and (2) entorhinal disease superimposed upon subicular disease.

To obtain a better understanding of these two processes, Scott and I have collaborated in the study of animal models, and I want to focus primarily on age-related memory loss. Can it be demonstrated in the mouse? Does it involve the subiculum?

BUT FIRST LET ME SAY MORE ABOUT CLINICAL CHARACTERISTICS OF BENIGN SENESCENT FORGETFULNESS

Benign senescent forgetfulness is neither completely benign nor does it necessarily begin in senescence. This disorder first becomes evident in some people when they reach their mid-40s and it typically becomes more prevalent and pronounced with time. So that by age 60 it affects at least 25% of the population to some degree. This memory loss is probably the most bothersome and frequently mentioned complaint of the elderly.

Age-related memory deficits are not limited to humans. We have recently developed a mouse model to study the effects of normal aging on explicit forms of memory.

The task we used is particularly good because it allows one to dissect the

strategies used by the mouse: random, serial, spatial. The first two are nonhippocampal. *Only* spatial requires the hippocampus. To reach criterion animal must make three errors or less on seven consecutive days (Fig. 22).

Mice Show a Hippocampal Dependent Age Related
Loss of Spatial Memory

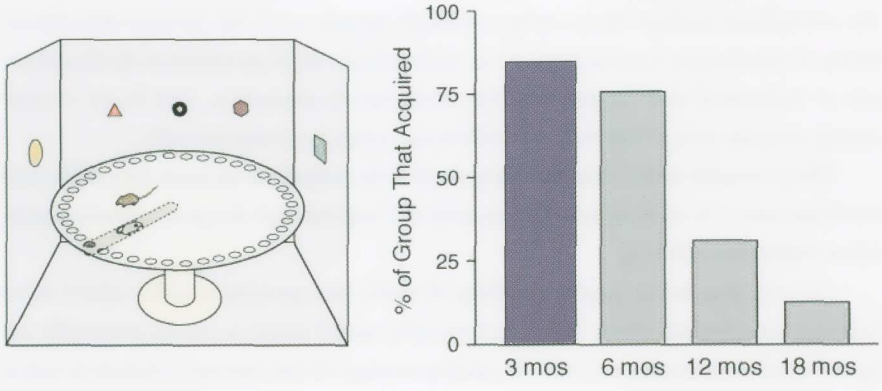


Fig. 22.

As is the case with aging humans, rodents show a marked loss of explicit memory storage with age that has two properties: (1) it affects in particular the ability to consolidate long-term memory, and (2) it begins to be manifest early in middle life.

Methods for primate imaging have recently been developed by Logothetis and his colleagues (Logothetis et al., 1999). Scott Small and I have applied to the mouse the MRI methodology he developed for humans because of the unique experimental advantage that mice afford for genetic studies. In addition, in looking at age-related memory loss in the mouse, there is no confusion with Alzheimer's Disease. This disease does not occur spontaneously in the mouse. We can, therefore, ask: Does the mouse develop a pure subicular defect? What is its mechanism? A clue came from comparing it to R(AB). The R(AB) mice have a reduction in basal PKA and an impairment in long-term synaptic plasticity

in the CA1 region. We found that ROXY-dependent imaging was able to map this molecular lesion and to detect a reduced signal in the CA1 region of the transgenic mice compared to wild-type littermates. By carrying out cell counts and other histological analyses, we could document that the reduced signal did not result from obvious structural changes in CA1 neurons. Thus, the ROXY-dependent imaging is sensitive to alterations in physiologic dysfunction.

These findings constitute the first demonstration that an MRI technique can detect a pure physiologic lesion. This is important because many causes of brain dysfunction are likely to cause physiological deficits without changes in neuronal structure. This is true for many causes of hippocampal dysfunction; and is even true for the earliest stages of Alzheimer's disease, where physiological deficits antedate cell loss. These physiological lesions cannot be detected microscopically by analyzing brain tissue accessed by biopsy or at autopsy. Together with its anatomical resolution, ROXY-dependent imaging provides a physiological biopsy of the hippocampal subregions.

Since age-related memory loss in the mouse resembles R(AB) both in its behavioral defect and in its functional abnormality with MRI imaging, we wondered whether there were corresponding changes in synaptic plasticity in the hippocampus.

We therefore turned to the hippocampus itself and looked for how the cellular representation of consolidation changes as a function of age. We found that LTP in the hippocampus (1) declines with age and (2) that this decline selectively affects the late protein synthesis dependent phase of LTP (Fig. 23).

This decline parallels the memory loss.

We therefore searched for natural modulators. It was natural to think that dopamine might be a key modulatory input important for the late phase(Fig. 24).

D1 AGONISTS ENHANCE THE LATE PHASE AND REVERSE AGE-ASSOCIATED MEMORY DEFICIT

Two specific agonists of the dopamine 1 (D1) receptor, a receptor coupled with adenylyl cyclase, stimulate a slowly developing long-lasting potentiation of field EPSP in the CA1 region of hippocampus lasting more than 6 hours.

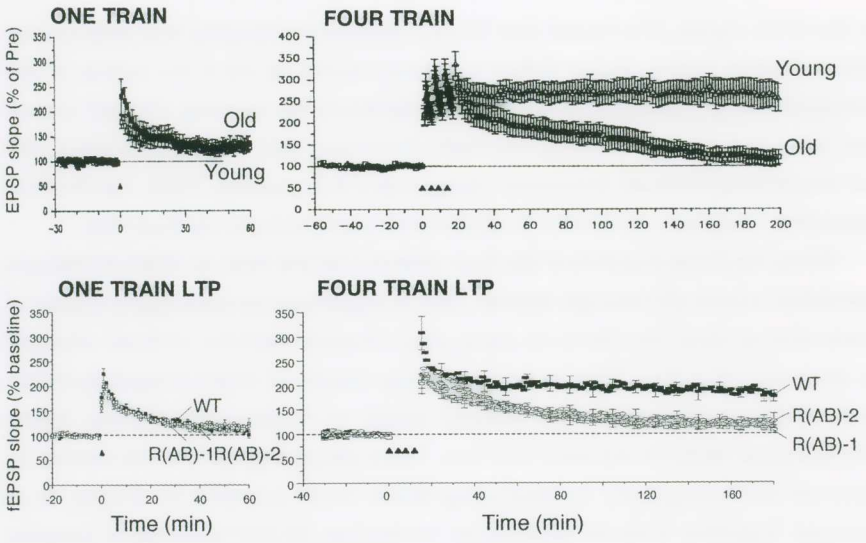


Fig. 23.

Late LTP Requires PKA and Transcription

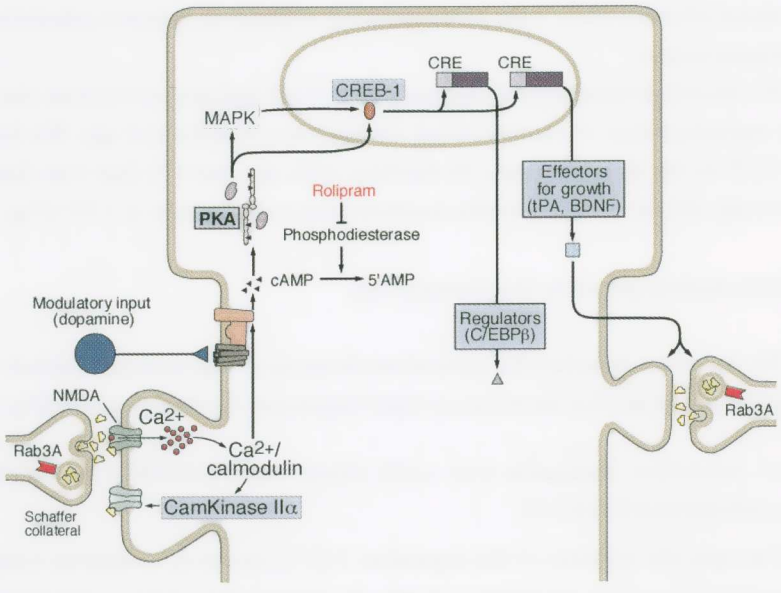


Fig. 24.

This potentiation is blocked by the specific D1 receptor antagonist 23390 and occluded by the potentiation produced by cAMP agonists. Although this slow D1 agonist-induced potentiation is partially independent of NMDA receptors, it seems to share some steps with the late phase of LTP produced by repeated trains applied to the Schaffer collateral pathway, and is occluded by the late phase of LTP produced by tetanization of the Schaffer collateral. Similarly, the D1 antagonist 23390 depressed late expression of tetanization-induced LTP. Moreover, D1 agonist-induced synaptic potentiation could be blocked by the protein synthesis inhibitor anisomycin. These results suggest that the D1 receptor may be involved in the late protein synthesis-dependent component of LTP, either as an ancillary component or as a major mediator of the late phase (Fig. 25).

These effects of D1 agonist at the level of synaptic plasticity were found to correlate with a reversal of age-related memory decline in the age-sensitive task that had developed (Fig. 26).

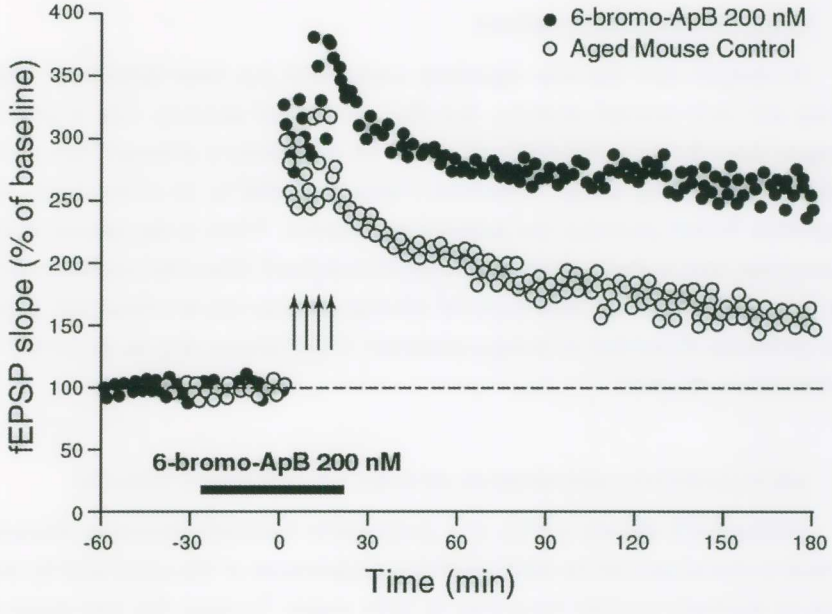


Fig. 25.

Dopamine Agonist (SKF38393) Can Reverse
the Age-Related Memory Deficit

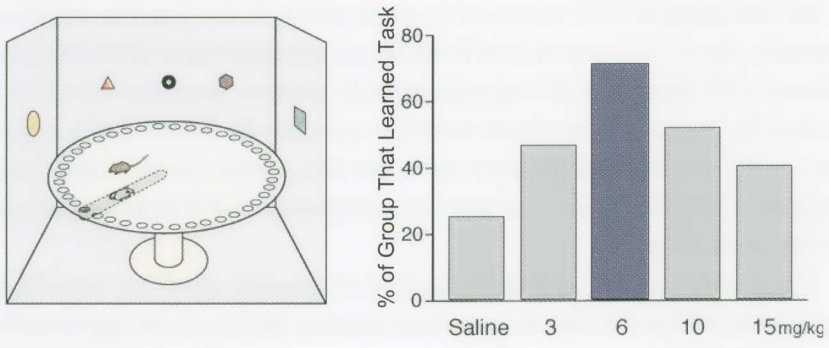


Fig. 26.

EARLY ALZHEIMER'S DISEASE

So insight into the core signaling component has been helpful in clarifying not only normal memory, but also age-related memory. Can it give us insight into the early cognitive disorders of Alzheimer's disease? One of the interesting features about Alzheimer's disease is that in its early stages, the cognitive deficit precedes the pathological disease. What is the nature of the functional deficit that precedes the cognitive deficit? Since the cognitive deficit is so similar and the pathways for storing memory are so conserved, might the pathways disturbed in benign senescent forgetfulness also be disturbed in Alzheimer's disease?

MILD COGNITIVE IMPAIRMENT OF EARLY ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is characterized by mild cognitive impairment at the onset and by deficits in multiple cortical functions in later stages. To date, the vast majority of the symptoms have been attributed to the loss of synapses and to the death

of neurons that occur in the course of the disease. The overproduction and accumulation of the β-amyloid peptide have been shown to play a crucial role in both of these processes in animal models of AD. Although these phenomena can account for the late debilitating stages of the disease, the mechanisms by which *Aβ causes early cognitive* and behavioral changes remain a matter of conjecture. Recent studies on animal models of AD have highlighted the discrepancy between behavioral deficits and neuropathological findings. Electrophysiological studies of mice that overexpress Aβ show impairment of long-term potentiation (LTP) that do not correlate with the extent of amyloid plaques and cell death. In addition, animals without detectable accumulation of aβ have been reported to have behavioral deficits. While examining gene expression in NGF-primed PC12 cells which had been exposed for 3 hours to $A\beta_{1-42}$, the principle and most neurotoxic component of the amyloid plaque, Shelanski and his colleagues soon realized that a group of genes, including CREB2 (ATF4) and ubiquitin c-terminal hydrolase, which have been implicated in the switch from early to late long-term potentiation, were regulated in a manner consistent with inhibition of late LTP. These findings are in agreement with studies reporting that Aβ inhibits LTP both *in vitro* and *in vivo* at concentrations lower than those that are necessary for triggering neuronal apoptosis. The biochemical pathway mediating the switch from early to late LTP has been worked out in *Aplysia* and in mice and depends on the activation of the transcription factor CREB by phosphorylation by protein kinase A (PKA).

When Shelanski assayed the basal PKA phosphorylation activity in whole cell extracts of hippocampal cells treated with 1 μM $A\beta_{1-42}$ for 3, 6, 12, and 24 hours and compared them to untreated cells, they observed that PKA activity fell rapidly in the treated cells reaching 50% of control values in 3 hours and 15% in 24 hours.

To determine whether the loss of PKA activity was due to the persistence of the PKA regulatory subunit, they examined the levels of the IIα regulatory subunit, the predominant neuronal isoform, as a function of exposure to $A\beta_{1-42}$. After 5 days in culture they exposed dissociated hippocampal neurons from rat brain at embryonic day 18 to 1 and 10 μM $A\beta_{1-42}$ for 3, 6, and 12 hours and subjected the protein extracts to Western blotting using an anti-

body against isoform IIα of the PKA regulatory subunit. In the presence of 10 μM $A\beta_{1-42}$ there was a marked increase in the IIα subunit which peaked by 3 hours and fell to basal levels by 12 hours. When treated with 1 μM $A\beta_{1-42}$ there was a marked increase between 3 and 6 hours which was sustained at 12 hours. The higher concentration (10 μM) induced apoptosis in hippocampal neurons and the decrease from 12 to 24 hours could reflect a decreasing number of healthy cells in the culture. Only minimal cell death was seen within 48 hours at 1 μM $A\beta_{1-42}$. Pretreating the cultures with 0.1 mg/ml cycloheximide did not result in a fall in the IIα regulatory subunit (data not shown). The increase in the PKA regulatory subunit suggests that it is responsible for the fall of PKA.

Since CREB phosphorylation depends on PKA activity, they extended their observations by measuring phosphorylated CREB (pCREB) levels in response to a glutamate stimulus (50 μM). Cultures pretreated with 5 μM Aβ showed a 40–45% decrease in CREB phosphorylation in response to treatment with 50 μM glutamate for 15 min. These results are consistent with those previously reported at higher Aβ levels. To test whether the inhibition of CREB phosphorylation was cAMP dependent, they added 5 μM rolipram during the preincubation with Aβ. Rolipram is a type IV-specific phosphodiesterase inhibitor, which has been reported to lead to increased cyclic AMP levels, dissociation of the regulatory and catalytic subunits of PKA, and reinforcement of LTP. Rolipram completely blocked the Aβ decrease in pCREB. Treatment with $A\beta_{1-42}$ for 24 hours irreversibly compromised phosphorylation (Fig. 27).

To validate the physiological importance of the molecular changes detected in cultures, they studied LTP responses in acute mouse hippocampal slices. As expected from previous reports, they found that Aβ strongly inhibited LTP generation in CA1 hippocampal region when slices were exposed to 200 nM Aβ for 20 min prior to tetanic stimulation of the Schaffer collateral pathway (137.54 ± 6.14% of baseline slope at 60 min after tetanus, n=9). The amount of inhibition was statistically significant compared with control tetanized slices treated with vehicle alone. Aβ had no effect on basal synaptic responses both during its application and 60 min after the end of the application in experiments where no tetanic stimulation was applied. Addition

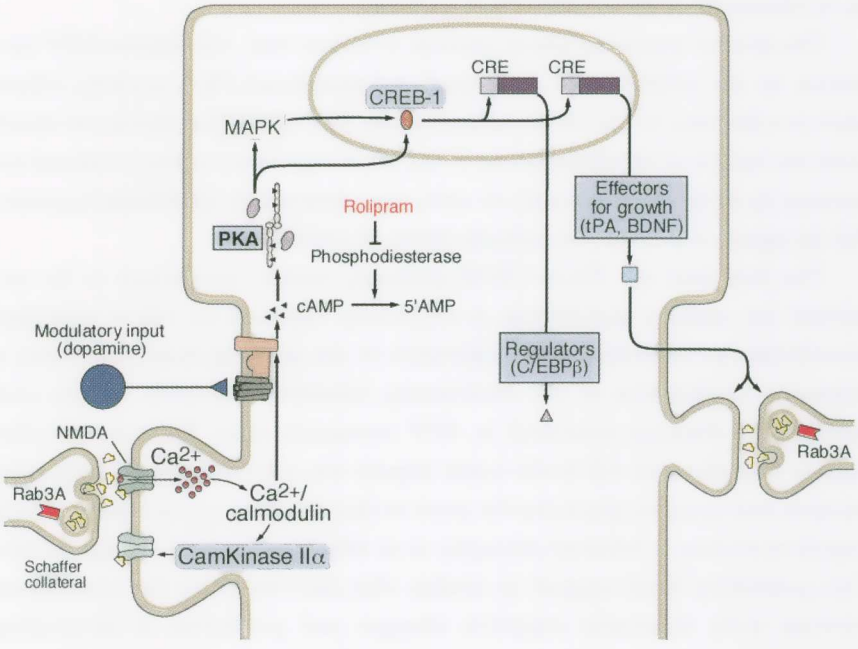


Fig. 27.

of forskolin, a selective activator of adenylate cyclase, at 50 μM, showed a significant protection under the same conditions. The protection was not due to enhancement of LTP that remains in the presence of Aβ because forskolin alone without Aβ did not enhance tetanus-induced LTP, nor to an action of forskolin on baseline transmission. Consistent with these results, lower doses of forskolin (5 μM) showed also protection. Similarly, 1 μM rolipram, added to the incubation medium at the time of the stimulation, completely abolished the Aβ inhibition, while it had no effect on baseline transmission. Moreover, similar to forskolin, rolipram alone did not produce LTP enhancement, suggesting that the drug truly reverses Aβ effect. To confirm that the modulation of LTP was due to PKA activity, 50 μM H89, a cell membrane – permeable PKA inhibitor, was added to the slices. This treatment completely abolished the protective effect of rolipram on Aβ treated slices. These results indicate

that Aβ inhibition of LTP generation in CA1 hippocampal region is due to an involvement of the cAMP/PKA pathway.

The studies presented above provide evidence that Aβ impairs LTP formation by the inhibition of both basal and stimulated PKA activity, which leads to a decrease in CREB phosphorylation. The inhibition appears to result from the failure of the dissociation of the PKA regulatory subunit IIα and an increase in its levels in the cell. At early time points this inhibition is reversible by agents which elevate cellular levels of cAMP.

The fact that the PKA/CREB pathway, widely recognized to be important for memory acquisition, is selectively impaired by Aβ at sublethal concentrations underlines the importance of the pathway itself and offers a molecular explanation of the discrepancy between behavioral deficits and pathological findings described in APP transgenic mice. These results also suggest that elevated Aβ levels could impede the consolidation of long-term memory and synaptic plasticity for years or decades prior to the time at which cognitive decline is detected clinically or at which anatomical damage occurs. This possibility finds support in studies that describe either the correlation between early detectable cognitive changes and prediction of developing dementia late in life or the importance of education as a protective factor. We can hypothesize that the correlation between poorer performance in psycholinguistic tests and the probability of developing Alzheimer's disease later in life might be explained by impaired neuronal plasticity throughout development due to higher Aβ levels in the brain. Since this pathway has been shown to induce functional presynaptic boutons in the hippocampus, it is possible that profound inhibition by very high levels of Aβ, such as are found in Down's syndrome, might result in extensive alterations in synaptic development and mental retardation. Stimuli, such as education, would act to mitigate this effect.

These results also suggest that Aβ may function as a modulator of memory storage, perhaps in response to stress or at times when the brain is confronted with more information than it can process effectively. If this were so, we would expect to see Aβ levels increase as a function of the induction of high levels of neuronal activity. This possibility is supported by the amnestic actions of infused amyloid peptides.

Finally, the results presented here suggest a new avenue, which might be

effective in preventing or delaying the onset of AD. While we failed to rescue LTP in neurons, which had been exposed to 1 μM Aβ for 24 hours, the physiological situation is likely to involve far lower levels of Aβ and a longer time frame. It is possible that long-term treatment of patients at risk for AD with agents which elevate cAMP could reverse the risk associated with higher Aβ levels. They also argue that it might be desirable to institute amyloid-lowering therapies, when they become available, well in advance of any cognitive changes in persons with an elevated risk for the disease.

An Overall View

In my talk today, I have tried to make five points:

(1) Molecular biology has led to the identification of two major signaling pathways shared by both implicit and explicit memory. A memory activating pathway which serves to switch short- to long-term memory and a memory suppressor pathway which acts to increase the threshold for putting information into long-term memory.

(2) In benign age-related memory loss, it is possible to identify a defect in this switch which affects preferentially the output of the CA_1 pyramidal cells – the subiculum, leading to subicular disease.

(3) A similar molecular defect may contribute to the disturbance of function in the entorhinal cortex during early stages of Alzheimer's disease.

(4) One can use the insight into the molecular biology of this switch to delineate drugs that can reverse the defects of benign senescent forgetfulness physiologically and behaviorally.

(5) One can extend this approach to animal modes of mental disorder.

Thus, we are entering a new era in which the insights from the molecular biology of cognition are beginning to open up avenues for therapy. In a larger sense, we are moving from the Decade of the Brain, which marked the last decade of the 20th century and was concerned with unsolving the mysteries of brain function to the Decade of Therapeutics in this first decade of the 21st century. In no area of medicine have therapies been needed as badly as we need them here.

ΠΕΡΙΛΗΨΗ

Μνήμη καὶ βιολογικὴ βάση τῆς ἀτομικότητας

Στὴν ὁμιλία μου θὰ ἐστιάσω στὴν ἐναποθήκευση τῆς μνήμης καὶ στὶς διαταραχές της. Θὰ ἤθελα νὰ χρησιμοποιήσω αὐτὴ τὴν εὐκαιρία γιὰ νὰ σᾶς δώσω μιὰ ἰδέα γιὰ τὸν τρόπο μὲ τὸν ὁποῖο οἱ νευροεπιστήμονες συσχετίζουν τὶς νοητικὲς διεργασίες μὲ τὴ λειτουργία τοῦ ἐγκεφάλου καὶ κατόπιν προχωροῦν στὴν ἀνάλυση τῆς λειτουργίας τοῦ ἐγκεφάλου στὸ μοριακὸ ἐπίπεδο, μὲ στόχο τὴν ἀνάπτυξη θεραπειῶν ποὺ μποροῦν νὰ ἀναστρέψουν τὶς νοητικὲς διαταραχές.

Θὰ ἤθελα νὰ ἀρχίσω κάνοντας μιὰ ἐπισκόπηση τῆς προόδου ποὺ ἔχει ἐπιτευχθεῖ στὸν ἐρευνητικὸ αὐτὸ τομέα. Τὶς τελευταῖες 5 δεκαετίες ἔχουμε γίνει μάρτυρες μιᾶς ἐντυπωσιακῆς αὔξησης τῶν δυνατοτήτων καὶ τοῦ εὔρους τῆς βιολογίας, κάτι ποὺ ἀναμένεται νὰ ἐπηρεάσει ὅλες τὶς ἐκφάνσεις τῆς μοντέρνας σκέψης, συμπεριλαμβανομένης καὶ τῆς ἀντίληψης ποὺ ἔχουμε γιὰ τὴ νόηση, καὶ ἐπομένως καὶ γιὰ τὸν ἑαυτό μας. Ὡς ἀποτέλεσμα, ὅταν στὸ μέλλον ἱστορικοὶ τῆς νόησης ἀνατρέχουν στὴν παροῦσα περίοδο, εἶναι πολὺ πιθανὸ νὰ διαπιστώνουν ὅτι ἡ βαθύτερη κατανόηση τῆς φύσης τῶν νοητικῶν λειτουργιῶν δὲ θὰ ἔχει προέλθει ἀπὸ τὰ πεδία, τὰ ὁποῖα παραδοσιακὰ ἀσχολοῦνται μὲ τὴ νόηση. Δὲ θὰ ἔχει προέλθει ἀπὸ τὴ φιλοσοφία, ἀπὸ τὶς τέχνες, ἢ ἀκόμη τὴν ψυχολογία ἢ τὴν ψυχανάλυση, ἀλλὰ ἀπὸ τὴ βιολογία. Καὶ αὐτὸ γιατὶ τὶς δύο τελευταῖες δεκαετίες ἡ βιολογία ἔχει συμμετάσχει ὄχι μόνο σὲ μία, ἀλλὰ σὲ δύο μεῖζονες συγκλίσεις τῆς σκέψης ποὺ σχετίζονται μὲ τὴν κατανόηση τῶν νοητικῶν διεργασιῶν.

Κατ' ἀρχήν, ἔχει πραγματοποιηθεῖ μιὰ ἐντυπωσιακὴ σύγκλιση μέσα στὴν ἴδια τὴ βιολογία. Αὐτὴ ἔχει ὡς ἀποτέλεσμα τὴ δημιουργία μίας κοινῆς μοριακῆς ἐπιστήμης, ποὺ συμπεριλαμβάνει διάφορα πεδία τῆς βιολογίας: κυτταρικὴ βιολογία, ἀναπτυξιακή-ἐξελικτικὴ βιολογία, ἀνοσολογία, βιολογία τῶν καρκινικῶν κυττάρων, καὶ ἀκόμη καὶ βιολογία τῶν νευρικῶν κυττάρων, ποὺ ἀποτελοῦν τὰ συστατικὰ τοῦ ἐγκεφάλου. Αὐτὴ ἡ σύγκλιση ἐκπορεύεται ἀπὸ μεῖζονες ἀνακαλύψεις ποὺ μᾶς ἔχουν ἐπιτρέψει νὰ κατανοήσουμε τὸ γονιδίωμα καὶ νὰ ἀντιληφθοῦμε μὲ ποιὸν τρόπο ἡ δομή του καθορίζει τὴν κληρονομικότητα καὶ ἡ ρύθμισή του τὴν ἀνάπτυξη καὶ λειτουργία τοῦ κυττάρου. Αὐτὲς οἱ σημαντικὲς ἀνακαλύψεις, συνδυαζόμενες μὲ τὴ δυνατότητα νὰ κλωνοποιήσουμε καὶ νὰ ἀποκρυπτογραφήσουμε συγκεκριμένα γονίδια, μᾶς ἔχουν ὁδηγήσει στὴ διαπίστωση

ὅτι ὑπάρχει σημαντικὴ ὁμοιότητα καὶ διαφορετικῶν κυττάρων στὸν ἴδιο ὀργανισμό, ἀλλὰ καὶ μεταξὺ διαφορετικῶν ὀργανισμῶν.

Ἡ δεύτερη μείζων σύγκλιση εἶναι αὐτὴ μεταξὺ τῶν νευροεπιστημῶν, τῶν ἐπιστημῶν ποὺ ἀσχολοῦνται μὲ τὸν ἐγκέφαλο, καὶ τῆς γνωσιακῆς ψυχολογίας, τῆς ἐπιστήμης ποὺ ἀσχολεῖται μὲ τὸν νοῦ. Αὐτὴ ἡ δεύτερη σύγκλιση εἶναι λιγότερο ὥριμη ἀπὸ αὐτὴν ποὺ ἔχει καθιερώσει ἡ μοριακὴ βιολογία, ἀλλὰ εἶναι ἐν δυνάμει ἐξ ἴσου σημαντική, καθὼς μᾶς ἔχει ἤδη προσδώσει ἕνα καινούργιο πλαίσιο γιὰ τὴν κατανόηση τῆς ἀντίληψης, τῆς δράσης καὶ τῆς ἐναποθήκευσης τῆς μνήμης.

Αὐτὲς οἱ δύο ἀνεξάρτητες συγκλίσεις βρίσκονται στὰ δυὸ ἄκρα τῶν βιολογικῶν ἐπιστημῶν καὶ ἐγείρουν τὰ ἀκόλουθα ἐρωτήματα: Σὲ ποιὸ βαθμὸ μποροῦν αὐτὰ τὰ δύο διαφορετικὰ νήματα νὰ συμπορευτοῦν; Μπορεῖ ἡ μοριακὴ βιολογία, ποὺ ἀποτέλεσε τὴν κινητήριο δύναμη γιὰ τὴν ἑνοποίηση τῶν βιολογικῶν ἐπιστημῶν, νὰ διαφωτίσει καὶ τὴ μελέτη τῶν νοητικῶν λειτουργιῶν; Μποροῦμε νὰ περιμένουμε μιὰ ἀκόμη πιὸ εὐρεῖα σύνθεση τὸν 21ο αἰ., μία σύνθεση ποὺ θὰ ἐκτείνεται ἀπὸ τὰ μόρια μέχρι τὸν νοῦ; Στὴν ὁμιλία μου θὰ ἤθελα νὰ ἀναπτύξω τὴν πιθανότητα μιᾶς καινούργιας βιολογίας τοῦ νοῦ, *μίας μοριακῆς βιολογίας τῆς νόησης*, καὶ νὰ προτείνω ὅτι αὐτὴ θὰ ἀποτελέσει τὸ ἐπίκεντρο τῆς ἐπιστημονικῆς ἀναζήτησης κατὰ τὰ πρῶτα χρόνια τοῦ 21ου αἰ., μὲ τὸν ἴδιο τρόπο ποὺ ἡ μοριακὴ βιολογία ἦταν στὸ ἐπίκεντρο τὸ δεύτερο ἥμισυ τοῦ 20οῦ αἰ.

Θὰ ἀναπτύξω αὐτὲς τὶς ἐξελίξεις χρησιμοποιώντας ὡς παράδειγμα τὴ μελέτη τῆς μνήμης. Ἐστιάζομαι στὴ μνήμη γιατὶ αὐτὴ ἀποτελεῖ τὸ γνωστικό μου ἀντικείμενο. Ἡ μελέτη τῆς μνήμης μὲ ἔχει ἀπασχολήσει τὰ τελευταῖα 50 χρόνια. Ὁ στόχος μου ὅλο αὐτὸ τὸ διάστημα ἦταν νὰ ἀναπτύξω μιὰ ἀφαιρετικὴ προσέγγιση γιὰ τὴ μελέτη τῆς μάθησης καὶ τῆς μνήμης, ἡ ὁποία θὰ μοῦ ἐπέτρεπε νὰ ἐξερευνήσω τοὺς ὑποκείμενους μοριακοὺς μηχανισμούς.

Ὅπως γνωρίζετε, ἡ μάθηση εἶναι ἡ διεργασία μέσῳ τῆς ὁποίας προσλαμβάνουμε καινούργια γνώση γιὰ τὸν κόσμο ποὺ μᾶς περιβάλλει, καὶ μνήμη εἶναι ἡ διεργασία μὲ τὴν ὁποία διατηροῦμε αὐτὴ τὴ γνώση διὰ μέσου τοῦ χρόνου. Ἡ μάθηση καὶ ἡ μνήμη ἔχουν ἀποδειχθεῖ σαγηνευτικὲς νοητικὲς διεργασίες ἐπειδὴ σχετίζονται μὲ μία ἀπὸ τὶς πιὸ ἐντυπωσιακὲς πτυχὲς τῆς ἀνθρώπινης συμπεριφορᾶς: τὴ δυνατότητα νὰ γεννήσουμε καινούργιες ἰδέες μέσα ἀπὸ τὴν ἐμπειρία. Οἱ περισσότερες ἀπὸ τὶς ἰδέες ποὺ ἔχουμε γιὰ τὸν κόσμο καὶ γιὰ τὸν πολιτισμό μας εἶναι προϊὸν μάθησης, καὶ ἔτσι σὲ μεγάλο βαθμὸ ἡ ταυτότητά μας εἶναι συνυφασμένη μὲ τὴ μάθηση καὶ τὴ μνήμη.

Ἀπὸ τὴν ἄλλη πλευρά, θεωρεῖται ὅτι πολλὲς ψυχολογικὲς καὶ συναισθηματικὲς διαταραχὲς προέρχονται, τουλάχιστον ἐν μέρει, ἀπὸ τὴν ἐμπειρία, καὶ συγκεκριμένες διαταραχὲς μάθησης ἢ μνήμης καταδυναστεύουν τὸ ἀναπτυσσόμενο παιδί, καθὼς καὶ τὸν ὥριμο ἐνήλικα. Τὸ σύνδρομο Down, ἡ φυσιολογικὴ ἔκπτωση τῆς μνήμης μὲ τὴν πάροδο τῶν ἐτῶν καὶ ἡ νόσος Ἀλτσχάιμερ ἀποτελοῦν μόνο τὰ πιὸ ἁπτὰ παραδείγματα μιᾶς μεγάλης γκάμας ἀσθενειῶν ποὺ ἐπηρεάζουν τὴ μνήμη.

Τὸ ἀρχικό μου ἐνδιαφέρον γιὰ τὴ μελέτη τῆς μνήμης κεντρίστηκε λόγῳ τῆς ψυχανάλυσης, ὅταν ἤμουν ἀκόμη προπτυχιακὸς φοιτητὴς στὸ Harvard College. Καθώς, ὅμως, ἐμβάθυνα στὸν κόσμο τῆς βιολογίας κατὰ τὴ διάρκεια τῶν Ἰατρικῶν σπουδῶν μου, ἄρχισα νὰ θεωρῶ τὴν ψυχαναλυτικὴ προσέγγιση περιοριστική, καθὼς ἔτεινε νὰ διαχειρίζεται τὸν ἐγκέφαλο, τὸ ὄργανο ποὺ δημιουργεῖ τὴ συμπεριφορά, σὰν ἕνα μαῦρο κουτί.

Στὰ μέσα τῆς δεκαετίας τοῦ 1950, ἐνῶ ἤμουν ἀκόμη στὴν Ἰατρικὴ Σχολή, ἄρχισα νὰ συνειδητοποιῶ ὅτι κατὰ τὴ διάρκεια τῆς γενιᾶς μου τὸ μαῦρο κουτὶ τοῦ ἐγκεφάλου θὰ ἄνοιγε καὶ ὅτι σταδιακὰ θὰ ἀπομυθοποιοῦνταν. Συνειδητοποίησα ὅτι τὸ πρόβλημα τῆς ἐναποθήκευσης τῆς μνήμης, ποὺ κάποτε ἦταν ἀποκλειστικὸ προνόμιο ψυχολόγων καὶ ψυχαναλυτῶν, θὰ μποροῦσε νὰ προσεγγιστεῖ μὲ τὶς μεθόδους τῆς μοντέρνας βιολογίας. Τὸ ἀποτέλεσμα ἦταν ὅτι τὸ ἐνδιαφέρον μου γιὰ τὴ μνήμη μετατοπίστηκε ἀπὸ μιὰ ψυχαναλυτικὴ σὲ μιὰ βιολογικὴ προσέγγιση. Εἶχα τὴν ἀσαφῆ ἐλπίδα ὅτι, μὲ τὴν πάροδο τοῦ χρόνου, θὰ μποροῦσα νὰ συνεισφέρω στὴ μετάφραση μερικῶν κεντρικῶν ἀναπάντητων ἐρωτημάτων τῆς ψυχολογίας τῆς μάθησης καὶ τῆς μνήμης στὴν ἐμπειρικὴ γλώσσα τῆς βιολογίας. Ἤθελα νὰ μάθω: Τί εἴδους ἀλλαγὲς προξενεῖ ἡ μάθηση στὰ νευρωνικὰ κυκλώματα τοῦ ἐγκεφάλου; Πῶς ἐναποθηκεύεται ἀρχικὰ ἡ μνήμη; Καί, μιᾶς καὶ ἀποθηκευτεῖ, πῶς διατηρεῖται; Ποιὰ εἶναι τὰ μοριακὰ μονοπάτια μέσῳ τῶν ὁποίων ἡ προσωρινὴ μνήμη βραχείας διαρκείας μετατρέπεται σὲ ἐμπεδωμένη μνήμη μακρᾶς διαρκείας;

Ὁ σκοπὸς αὐτῆς τῆς προσπάθειας μετάφρασης δὲν ἦταν νὰ ἀντικαταστήσω τὴν ψυχολογικὴ ἢ ψυχαναλυτικὴ σκέψη μὲ τὴ λογικὴ τῆς μοριακῆς βιολογίας, ἀλλὰ νὰ συνεισφέρω σὲ μιὰ καινούργια σύνθεση μιὰ νέα ἐπιστήμη τοῦ νοῦ, ποὺ θὰ λάμβανε ὑπ' ὄψη καὶ τὴ νοητικὴ ψυχολογία τῆς ἐναποθήκευσης τῆς μνήμης καὶ τὴ μοριακὴ βιολογία τῆς ἐνδοκυττάριας μεταβίβασης σήματος. Αὐτὴ ἡ σύνθεση πρόσφατα ἔχει ἀρχίσει νὰ σχηματοποιεῖται, καὶ στὴν ὁμιλία μου θὰ προσπαθήσω νὰ ἀναπτύξω αὐτὰ τὰ ἀρχικὰ στάδια.