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UNDERSTANDING OURSELVES BY STUDYING THE ANIMAL KINGDOM

Researchers look to armadillos, fruit flies, nematodes, and other species to understand human brain function and vision loss

SAN DIEGO — Research released today reveals a new model for a genetic eye disease, and shows how animal models — from fruit flies to armadillos and monkeys — can yield valuable information about the human brain. The findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Animal models have long been central in how we understand the human brain, behavior, and nervous system due to similarities in many brain areas and functions across species. Almost every major medical advance in the last century was made possible by carefully regulated, humane animal research. Today's findings build on this rich history and demonstrate what animals can teach us about ourselves.

Today's new findings show that:

- The nine-banded armadillo may serve as a model for certain types of progressive blindness. The animal's poor eyesight mimics many human disorders and may shed light on new treatment approaches for such diseases (Christopher Emerling, BS, abstract 150.06, see attached summary).
- Analysis of a baboon population reveals particular genes that may be involved in creating the "folds" in the structure of the brain. These findings provide information on how human genes may have evolved to create the brain's shape and function (Elizabeth Atkinson, BA, abstract 195.13, see attached summary).
- Monkeys and humans use similar brain pathways while processing decisions. Detailed analyses of similarities and differences in brain wiring could provide new insights into decision-making in humans (Franz-Xaver Neubert, abstract 18.03, see attached summary).

Other recent findings discussed show that:

- Use of powerful genetic tools in fruit flies is helping to reveal the basic building blocks of brain circuitry and function. This work is furthering our understanding of the human brain and may be helpful in developing medical diagnostic devices (Rachel Wilson, PhD, presentation 302, see attached speaker summary).
- Research in a tiny worm (*C. elegans*) has allowed scientists to map all of the connections between neurons in the species, including the pathways for movement, sex, and more. The findings offer new insights into how the human nervous system functions (Scott Emmons, PhD, presentation 009, see attached speaker summary).

"Neuroscience has always relied on responsible animal research to better understand how our brains and bodies develop, function, and break down," said press conference moderator Leslie Tolbert, of the University of Arizona, whose work in insects provides insights into brain development. "Today's studies reveal new ways that research on unlikely-seeming animals, such as armadillos, fruit flies, and worms, could have real impact on our understanding of the human brain and what can go wrong in disease."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find more information on animal models at *BrainFacts.org*.

– more –

Related Neuroscience 2013 Presentation:

Presidential Special Lecture: **A Molecular Geneticist's Approach to Understanding the Fly Brain**
Sunday, Nov. 10, 5:15—6:25 p.m., Ballroom 20
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Abstract 150.06 Summary

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Through an Armadillo's Eyes: A New Model for Eye Disorders

The nine-banded armadillo offers a new model for genetic colorblindness and loss of vision

Researchers are proposing the nine-banded armadillo as a new model for research on vision diseases in humans, because its very poor eyesight mimics certain human vision disorders. Christopher Emerling of the University of California, Riverside, presented the findings at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"The many mutations that have given the armadillo poor eyesight could allow it to serve as an excellent model for vision problems that arise in humans," said Emerling. "Armadillos could give us better insights into which genes and mutations might lead to debilitating vision problems in humans, and could help us understand how this impaired vision develops and how we might treat it."

One in 30,000 people suffers from diseases such as achromatopsia and progressive cone dystrophy, both genetic forms of near blindness. These disorders cause colorblindness, extreme sensitivity to light, blind spots, poor vision, and severe impairments that leave individuals functionally blind for most aspects of daily life. Symptoms are thought to be due to the loss of cones, receptor cells located in the retina and the source of the sharp, colorful pictures typically thought of as "sight."

Previous models for cone-related diseases have focused on other animal models, such as knockout mice, where a single gene is "knocked out" of the genome to recreate the disorder. However, cone diseases occurring naturally can stem from a number of genes. Since the armadillo has several of these genetic mutations, it allows for more robust research into a variety of genes and potential causes of related eye diseases.

The scientists hope that future research of the armadillo (*Dasypus novemcinctus*) genome could lead to better understanding of how various genetic mutations that affect the visual system arise, and how the effects of those mutations may be addressed.

Research was supported with funds from the University of California, Riverside.

Scientific Presentation: Sunday, Nov. 10, 9–10 a.m., Halls B-H

150.06, The nine-banded armadillo: A proposed model organism for achromatopsia and progressive cone dystrophies
***C. A. EMERLING**, M. S. SPRINGER; Univ. of California, Riverside, Riverside, CA

TECHNICAL ABSTRACT: Achromatopsia and progressive cone dystrophies are inherited retinal diseases that are characterized by nonfunctional cone photoreceptors, resulting in an inability to discriminate colors, photophobia and reduced visual acuity. With such a major impairment in visual capabilities impacting day to day living in afflicted individuals, and an estimated prevalence of 1:30,000, these disorders are an important avenue for further medical research. Animal models for these conditions exist that involve gene-knockout mutants lacking one of the genes necessary for cone phototransduction. The problem is that multiple genes are known to be necessary for cone function, and many undiscovered loci may prove to be crucial as well. Instead, a mammal that has naturally lacked cones for millions of years of its evolutionary history would be an optimal model. The visual capabilities of the nine-banded armadillo (Dasypus novemcinctus), already a model organism for leprosy research, have been reported to be extremely poor, in a manner seemingly consistent with rod-only vision. However, this has generally only been described in field observations. We tested this hypothesis by examining the genomic basis for cone phototransduction in the armadillo, predicting that related genes would be found to be nonfunctional. We downloaded mRNA sequences of these genes from GenBank and BLASTed them against NCBI's whole genome shotgun contig database. Armadillos belong to one of four superorders of placental mammals, so for comparison we gathered genes from representatives of the other superorders that are known to have functional cones. We assembled the gene sequences for all pertinent species, aligned them manually, and searched for inactivating mutations. For genes that were found to be nonfunctional, we estimated their dates of pseudogenization using a previously published method. We discovered that Dasypus naturally lacks cones, with multiple genes related to cone phototransduction estimated to have been nonfunctional for tens of millions of years. In contrast, mammals that possess cones have retained functional copies of these genes. Given these results, we propose that the nine-banded armadillo be considered as a model for achromatopsia and progressive cone dystrophies. Due to the ancient history of cone loss in this organism, it's probable that other genes related to cone function have also become nonfunctional. This makes the genome of this species a useful tool to search for candidate loci related to these disorders. Additionally, live armadillos can be used to study the development of these conditions, and would be excellent candidates for gene therapy to restore sight.

Abstract 195.13 Summary

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The Genetic Basis of Our Lumpy, Bumpy Brains

Studies of baboon brains show a genetic basis for the connections and cognitive function of humans

Researchers are beginning to uncover a relationship between genes and the foldings of the brain in baboons, yielding initial information that may tell us how our brains evolved. The findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"The evolution of the human brain over time is a very complex process," said Elizabeth Atkinson, of Washington University in St. Louis. "Our study connects the folding of the brain with the underlying genetics, and provides unique insight into how the evolution of our genes has driven the shape, and ultimately the function, of our brains."

During the evolution of the highly-functioning human brain, the number of brain cells and connections increased dramatically. However, this growth is constrained by the size of the skull in relation to the birth canal. The size limitations suggest that, as the human brain grows, it increasingly folds into ridges and valleys, known as gyri and sulci, respectively. The growth that these wrinkles can accommodate determines cognitive capacity. Human brains have 30 percent more folds than chimpanzee brains, our nearest evolutionary relative.

As humans evolved and developed more brain cells, the genetic controls of the brain shaping mechanism have remained unknown. To begin to understand this process, researchers looked to the baboon as a model to examine how the folds of the brain relate to underlying genes. Using nearly 1,000 baboon brain scans, they were able to pinpoint a handful of chromosome segments and genes that affect the way the brain is folded. The results will have important implications for understanding the evolution of both the shape and the function of the human brain, and may help to explain the evolutionary mechanisms that affect neurological differences among primates.

Research was supported with funds from the National Science Foundation.

Scientific Presentation: Sunday, Nov. 10, 8–9 a.m., Halls B-H

195.13, The genetic architecture and evolution of brain cortical gyrification in a pedigreed primate population
***E. G. ATKINSON**[1], J. ROGERS[2], M. C. MAHANEY[3], L. A. COX[3], J. M. CHEVERUD[1]; [1]Anat. and Neurobio., Washington Univ. in St. Louis, MO; [2]Dept. of Mol. and Human Genet., Baylor Col. of Med., Houston, TX; [3]Dept. of Genet., Texas Biomed. Res. Inst., San Antonio, TX

TECHNICAL ABSTRACT: Elevated cognition is a hallmark of the primate clade. Cognitive capacity is determined both by number of neurons in the brain and the network of information exchange between brain regions. Increased folding (gyrification) of cerebral cortex allows more neurons to fit within the skull with minimal overall volume increase. The arrangement of folds (sulci) across cerebral cortex indicates the connectivity network; due to selection for the most efficient information-processing strategy, regions experiencing the highest level of crosstalk tend to be anatomically co-located along a gyrus and those least connected functionally tend to be separated anatomically by a sulcus. Despite its importance, the genetic and evolutionary underpinnings of primate brain gyrification remain unknown.
In this project, we answer pivotal questions about the genetic architecture of baboon cortical gyrification, differing cognitive strategies across the primate clade, and the evolutionary mechanisms responsible for their formation. We use a pedigreed baboon population (N=980) to assess the genetic basis, modularity, and morphological integration of cortical folding in primates and identify the chromosomal regions and candidate genes affecting these traits. Heritability of 25 brain traits has been quantified (average h2= 31.1%) in the population, asymmetry assessed (Pearson's T-test p=0.0345) and phenotypic variation mapped to the genome using QTL analysis (highest peak: trait Left acruate rectus spur; baboon chromosome 4, 628Mb-707Mb). Four genes of interest are present in this region, including brain-specific angiogenesis inhibitor 3.

Abstract 18.03 Summary

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The Decision-Making Process: Do Monkeys and Humans Differ?

New research sheds light on what can be learned from monkey models of decision making

Humans and monkeys make complex decisions in very similar ways, with some small, potentially important, differences. Recent findings by Franz-Xaver Neubert of the University of Oxford help clarify those differences, and were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Making poor decisions can have critical impacts on our lives, and our findings give us increased understanding of how we can better study decision-making," said Neubert. "Knowing both the similarities and differences in how humans and monkeys make decisions can help us understand more about the human decision making process."

Human decision-making is a complex mental process, taking into account many variables, including the present situation, potential future considerations, available resources, likelihood of success, and other concerns. In making these decisions, humans often employ a large group of brain areas, including: the lateral orbitofrontal, ventromedial prefrontal, anterior cingulate, and frontal polar cortex.

Although monkeys also make complex decisions in the wild, they may not do so in exactly the same way. In order to learn more about the complex decision-making process, researchers used magnetic resonance imaging data (MRI) from 25 humans and 25 monkeys to examine the connections between their decision-making brain areas.

The findings suggest that the decision-making brain areas of humans and monkeys are largely the same, but with some slight differences that may be interesting. Humans have some interactions between decision-making and social processing areas, for example, suggesting that humans may use social information differently than monkeys. Additionally, one brain region in humans, the lateral frontal pole, appears to have no analogue in the monkey brain.

"Despite these differences, human decision-making capitalizes on a brain cell network similar to the one that supports monkeys when foraging in the wild," said Neubert. "These results could be used to weigh differences when studying monkeys, and to link differences in decision making to differences in brain wiring."

Research was supported with funds from the Medical Research Council (United Kingdom), and the University of Oxford.

Scientific Presentation: Saturday, Nov. 9, 1–4:30 p.m., Room 4

18.03, Connectivity profiles reveal the relationship between brain areas for reward-guided learning and decision making in human and monkey frontal cortex
***F.-X. NEUBERT**, R. B. MARS, J. SALLET, M. F. S. RUSHWORTH; Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

TECHNICAL ABSTRACT: Reward-guided decision-making depends on a network of brain regions. Among these are (1) lateral orbitofrontal (lOFC), (2) ventromedial prefrontal (vmPFC) (3) anterior cingulate (ACC) and (4) frontopolar (FP) cortex. Studies in both monkeys and humans suggest these areas play a role in reward learning and decision making. However it is less clear (I) if these areas constitute anatomical and functional unities, (II) if and how these areas correspond between monkeys and humans. Looking at the connectivity of these areas in both species can address these questions. (I) For example several important aspects of decision making such as error detection, conflict resolution, reward and effort learning, uncertainty representation or cost-benefit evaluation have been attributed to the ACC. It is not clear, however, if this region is a single functional unit or if these ascriptions refer to different ACC sub-regions. (II) Another example is that fMRI-studies on humans have emphasized the role of vmPFC in value-representation whereas neuro-physiological studies in monkeys have shown value-related neuronal activity particularly in lOFC. Therefore these areas have been treated as homologous. Comparing the connectivity profiles of these areas in both species can test if this is indeed the case.
We used a combination of structural and functional neuroimaging methods to identify key components of the human reward-guided decision making network in ACC, lOFC, vmPFC and FP. We compared how these core-components interacted with other brain areas in 25 humans and 25 macaques using the same methods. We were able to dissociate several regions in the human ACC, vmPFC, lOFC and FP based on their structural connectivity profile with the rest of the brain. We then looked at their functional connectivity and established regions in the macaque ACC, vmPFC, lOFC and medial FP that showed similar functional connectivity profiles. We also delineated a region in the human lateral FP whose functional connectivity pattern could not easily be matched to any area in the macaque frontal cortex.

Speaker Summary (302)

Speaker: Rachel Wilson, PhD (617) 432-5571
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Boston

Special Lecture: **Sensory Processing in Drosophila: Synapses, Circuits, and Computations**
Monday, Nov. 11, 11:30 a.m.–12:40 p.m., Ballroom 20

Our research illustrates how fruit flies can be used to discover basic building blocks of brain circuitry.

One of the revolutionary discoveries of modern biology was the finding that many genes are conserved in animals as evolutionarily distant as flies, worms, mice, and humans. Moreover, many genes are actually composed of smaller building blocks that have been shuffled and combined in different ways during evolution. Insight into these basic building blocks began with work on simple organisms, and has led to a deep understanding of how genes function within living cells.

In a similar vein, we hypothesize that many elements of brain circuits are also conserved in flies and humans. In addition, we hypothesize that many brain circuits are composed of smaller building blocks ("microcircuits") which are combined in different ways in different organisms and brain regions. We think that understanding these building blocks in simple organisms will help us understand the complex functions of the human brain.

Motivated by this, we have been investigating microcircuits in the brain of the fruit fly Drosophila melanogaster. Many powerful genetic tools have been developed in Drosophila. We use these tools to make precise manipulations of neural circuits, and to examine the impact of these manipulations on neural activity and behavior.

Of course, the fly brain is much smaller than the human brain and actually smaller than a poppy seed. It is also simpler than the human brain, and thus easier to understand. Nevertheless, the work of our laboratory and others has already provided evidence that we can learn some fundamental principles about brain function from this tiny insect. For example, research into the fly brain has already revealed much about the structure and function of brain circuits that detect and discriminate between odors. This reflects the strong resemblance between the anatomy of the fly's odor-processing brain regions and the odor-processing brain regions of mammals. Ultimately, we expect that this research will be useful in helping to design artificial odor analysis devices for medical diagnostic applications. It should also help us understand what features of brain circuits are conserved across organisms.

Funding for this research was provided by the National Institutes of Health and the Howard Hughes Medical Institute.

Speaker Summary (009)

Speaker: Scott W. Emmons, PhD 718-430-3130
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Featured Lecture: **The Mind of a Worm: Learning From the C. Elegans Connectome**
Saturday, Nov. 9, 5:15–6:25 p.m., Ballroom 20

Our brains contain billions of electrical circuits formed by trillions of connections between nerve cells. In order to understand how such circuits function, scientists turn their attention to much simpler animals. We have deciphered the neural circuits governing the sexual behavior of a tiny nematode worm.

This work reveals the synapses — the sites where one nerve cell communicates with another cell or with a muscle — in the part of the male worm nervous system that is situated in the tail region and controls copulation, thus yielding a wiring diagram. The results make it possible to trace the potential flow of information from sensory input to muscle output as the male attempts to inseminate its mating partner.

Such a detailed view of the nervous system underlying behavior is a longstanding goal of neuroscience. Combined with a similar study of the nervous system in the male head — also carried out as part of this work — it is now possible for the first time to compare the complete map of the male nervous system to that of the opposite sex, which for the worm has been available for a number of years.

The two sexes in the worm, Caenorhabditis elegans or C. elegans for short, are a modified female with her own sperm, hence a hermaphrodite, and a male. Using electron microscopy for detailed anatomical study, we found that copulation of the male with the hermaphrodite is controlled by 144 neurons (nerve cells) and 64 muscles. Most of these neurons and muscles are specialized for mating and are found only in the male. Intriguingly, many of these are also in the hermaphrodite, where they serve different functions, such as response to touch. Among the shared neurons are many that differ between the sexes in both branching structure and connectivity, indicating that the sex of the animal affects the development of its neurons.

The 144 neurons form a complex neural network resulting from some 8,000 synapses and neuromuscular junctions. The neural pathways are surprisingly short — in many instances, sensory neurons form synapses directly onto muscles. Short synaptic pathways are consistent with the quick, reflexive actions of the male. But the sensory neurons are also interconnected to one another and to interneurons, neurons that relay information from one neuron to another. The complexity of the network necessitated methods from the mathematical field of graph theory. These methods were used to identify groups of neurons involved in particular steps of copulatory behavior and connectivity motifs that suggest how the network functions. Importantly, we determined the size of each synapse, allowing us to estimate the functional strength of connections, information essential for attempts to reverse engineer the network.

This is one of the first new results in the field of connectomics. C. elegans was selected for study in the late 1960s by Nobel laureate Sydney Brenner precisely because its tiny size, 1mm, and limited number of neurons made it possible to construct a complete map of its nervous system by serial section electron microscopy. Additional experimental characteristics of the worm — its rapid growth on petri plates, transparency, and ability to be stored frozen — has made it a powerful model organism for wide-ranging biological research. The field has garnered three Nobel Prizes so far.

In early work, the wiring diagram of the C. elegans hermaphrodite was obtained in a heroic effort and published in 1986. It required the advent of modern computers to speed the analysis before researchers again attempted to obtain additional new data. With further improvements in experimental methods, today's connectomics researchers hope one day to obtain a wiring diagram of the human brain, a structure a billion times larger than a worm.

This research was supported by the The G. Harold & Leila Y. Mathers Charitable Foundation and the National Institutes of Health.