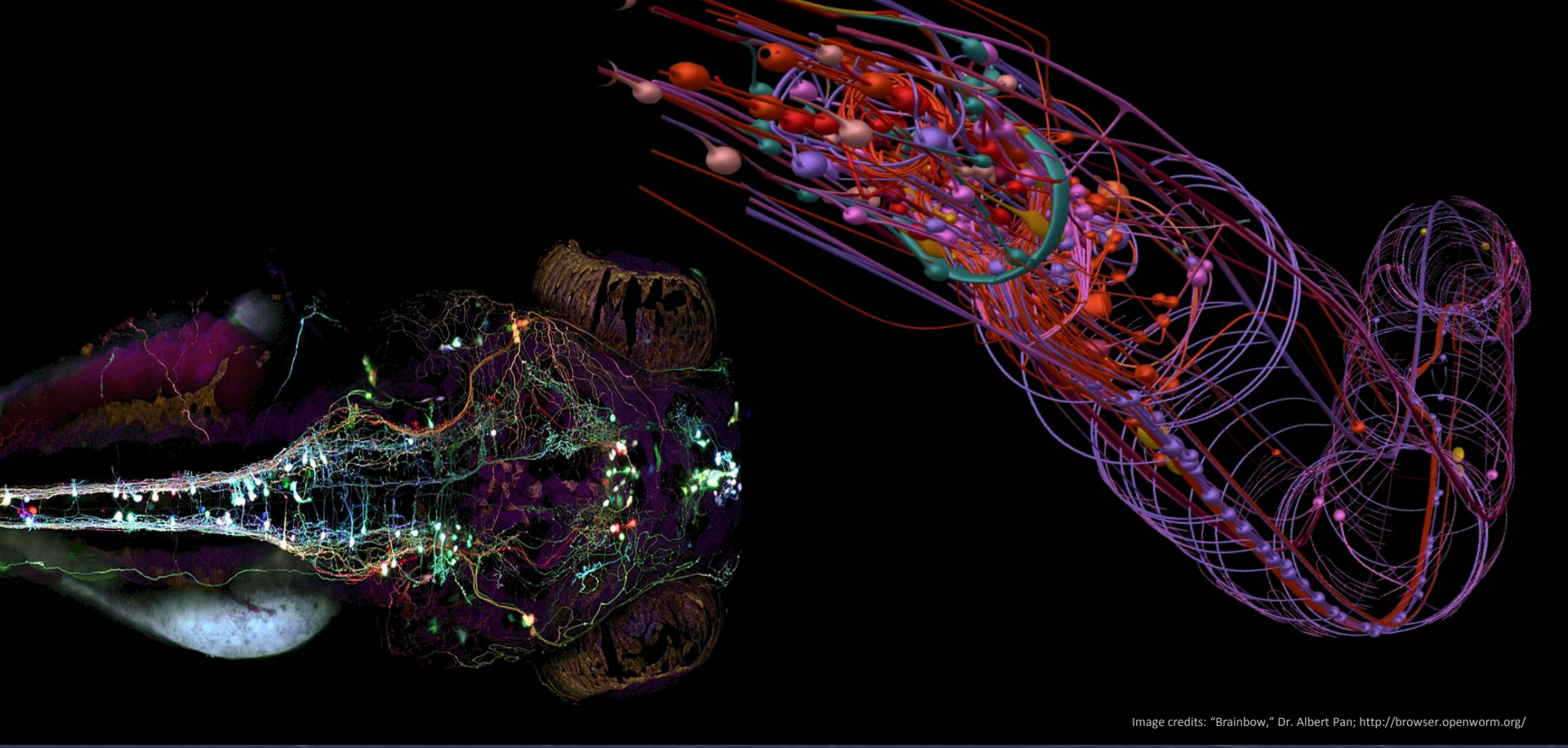
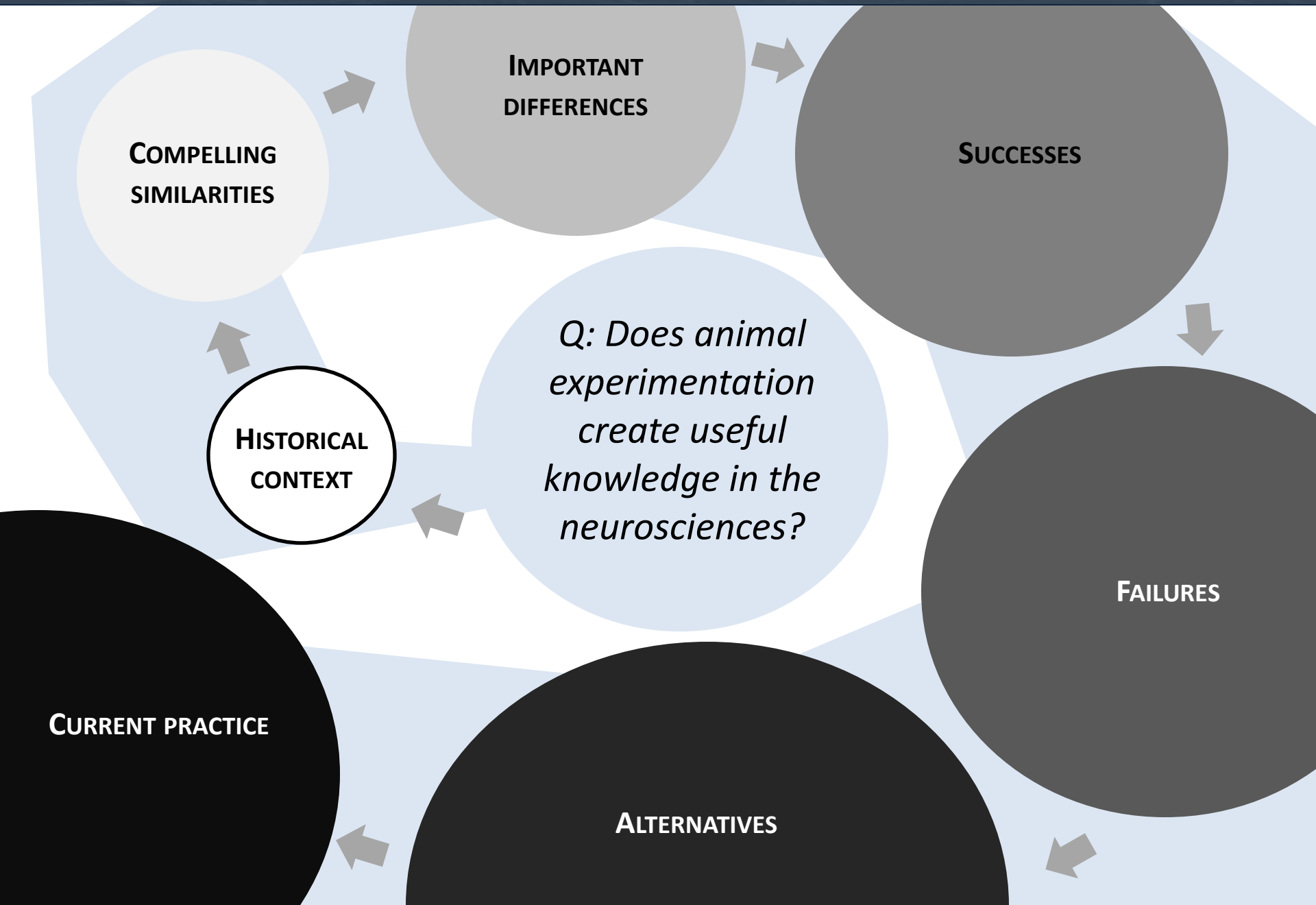


Image credits: “Brainbow,” Dr. Albert Pan; http://browser.openworm.org/

ANIMAL RESEARCH IN THE NEUROSCIENCES: HELPING US UNDERSTAND OURSELVES?

Kelley M. Swanberg
신경과학
경희대학교 동서의과학과
2015.05.04

Overview


Important differences
Successes
Compelling similarities
Historical context
Q: Does animal experimentation create useful knowledge in the neurosciences?
Failures
Current practice
Alternatives

INTRODUCTION: KELLEY M. SWANBERG (bahamut1243@gmail.com)

Current research interests

- **Maximizing validity of preclinical drug screening procedures in mice**
- **Relationships between telencephalic lesioning and drug addiction using mouse models of TBI**
- **Preclinical development of noninvasive neural activity stimulation using low-intensity ultrasound**

Research advisors

Margaret MacDonnell, Ph.D., Argonne National Laboratory **(organophosphate toxicology)** (2005-2006)
Jack Tsao, M.D., D.Phil, Walter Reed Army Medical Center **(post-amputation neural reorganization)** (2007)
Daniel Schacter, Ph.D., Harvard University Department of Psychology **(aging and reality monitoring)** (2006-2007)
Robert Stickgold, Ph.D., Harvard Medical School Department of Psychiatry **(sleep and declarative memory)** (2007-2009)
Sungho Maeng, M.D., Ph.D., Kyung Hee University Department of East-West Medicine **(preclinical mouse modeling)** (2013-2015)

Academic affiliations

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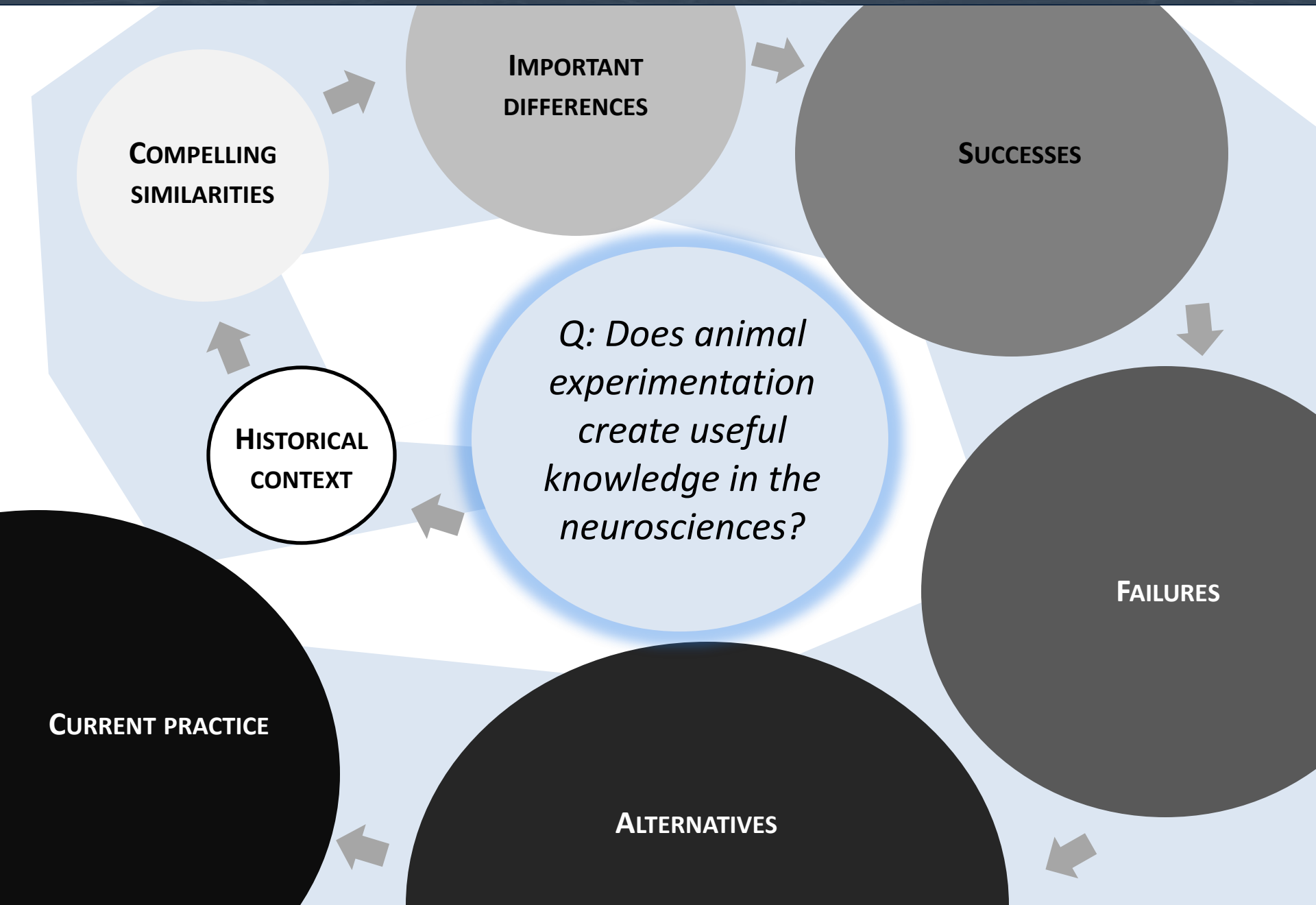
(2009-2010)

M.Sc., 경희대학교
동서의학대학원
(2015)

어학연수

北京语言大学 (2009)
清华大学 (2009-2010)
연세대학교 (2012)

Overview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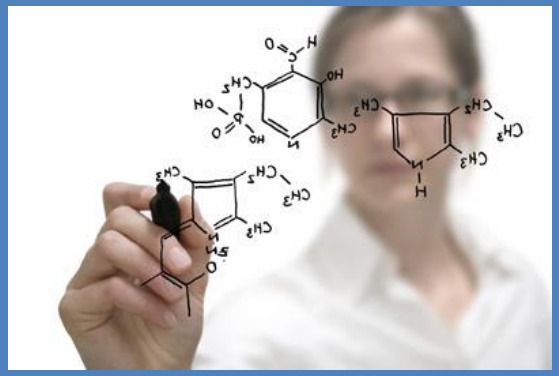
What is useful knowledge?

Science defines "useful knowledge" according to the principles of empiricism and positivism.

Empiricism: All rationally acceptable propositions are knowable only through experience. (Fumerton, 2015)

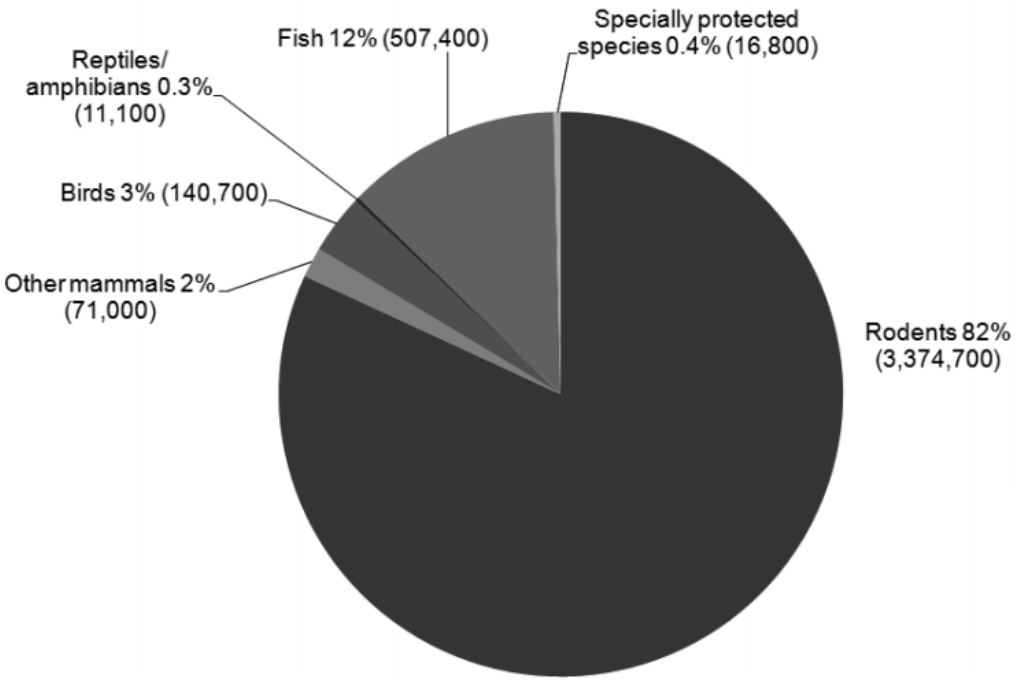
Logical positivism: The only meaningful philosophical problems are those that can be solved by logical analysis, including empirical verification when applicable. (Creath, 2011; Oxford Dictionaries)

Useful scientific knowledge enables accurate predictions and effective technologies.



DOES ANIMAL RESARCH PRODUCE USEFUL KNOWLEDGE?

Figure 3: Procedures by species of animal, 2013



(Home Office Science Group, 2014)

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Essay

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John P. A. Ioannidis

Philosophy, Ethics, and Humanities in Medicine

BioMed Central

Review

Open Access

Are animal models predictive for humans?

Niall Shanks[1], Ray Greek*[2] and Jean Greek[2]

Address: [1]Wichita State University, Department of History, 1845 N Fairmont, Fiske Hall, Wichita KS 67260, USA and [2]Americans For Medical Advancement, 2251 Refugio Rd Goleta, CA 93117, USA

Email: Niall Shanks - niall.shanks@wichita.edu; Ray Greek* - drraygreek@aol.com; Jean Greek - jeangreek@aol.com

* Corresponding author

Toxicologic Pathology, 00: 1-11, 2012

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623312457273

Use of Animal Models of Human Disease for Nonclinical Safety Assessment of Novel Pharmaceuticals

Sherry J. Morgan[1], Chandikumar S. Elangbam[2], Shawn Berens[3], Evan Janovitz[4], Allison Vitsky[5], Tanja Zabka[6], and Laura Conour[7]

IMPROVING THE UTILITY AND TRANSLATION OF ANIMAL MODELS FOR NERVOUS SYSTEM DISORDERS

WORKSHOP SUMMARY

Diana E. Pankevich, Theresa M. Wizemann, and Bruce M. Altevogt, *Rapporteurs*

InsightPharma Reports
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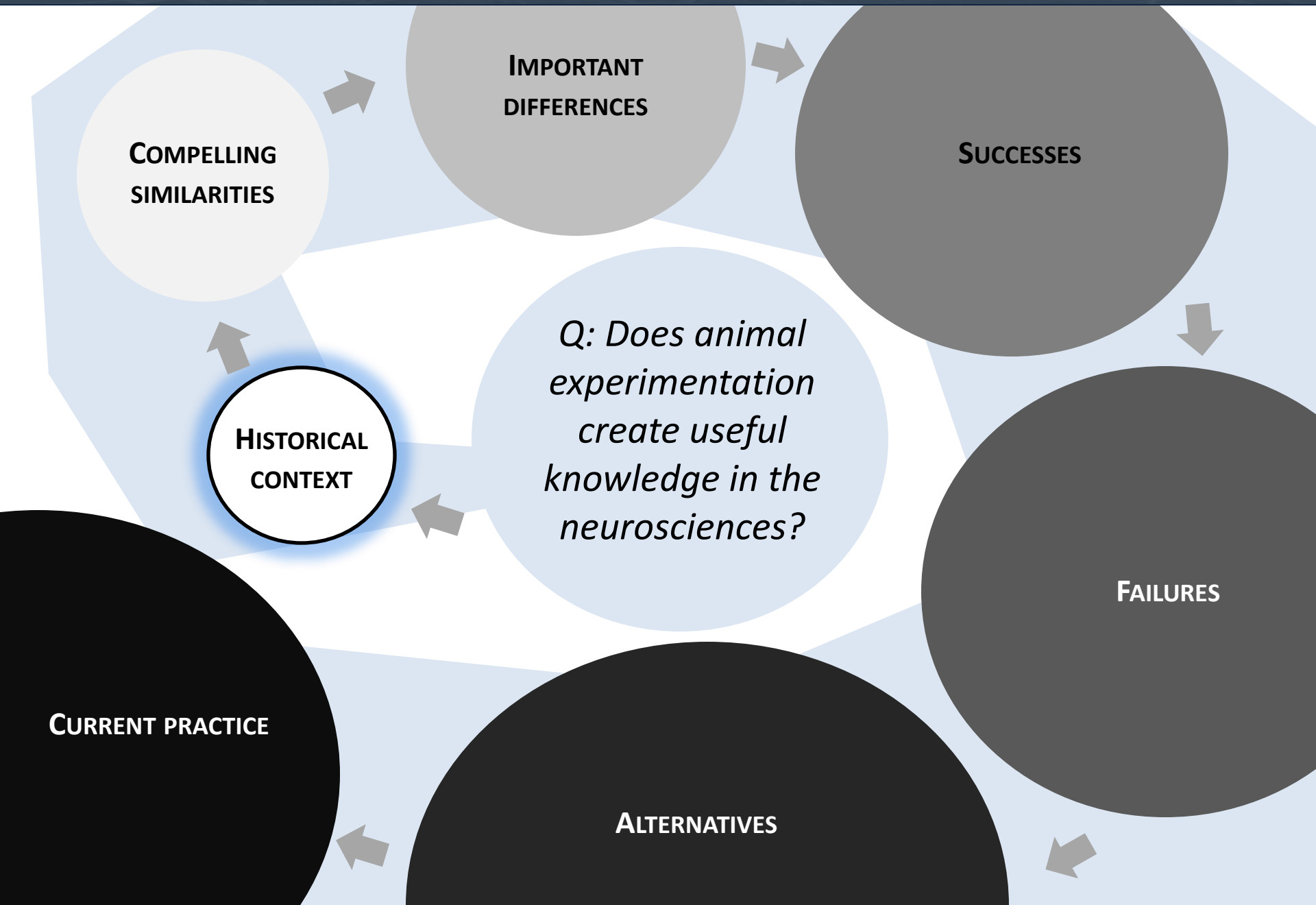
Moving from Animal Models to the Clinic

A Complimentary Market Research Study
as included in the Animal Models for Therapeutic Strategies Report

www.InsightPharmaReports.com

We do a lot of animal research, but the limits and maximization of its ability to produce useful knowledge in neuroscience are still under debate.

Overview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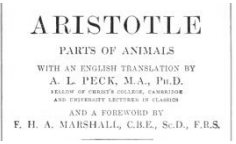
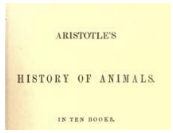
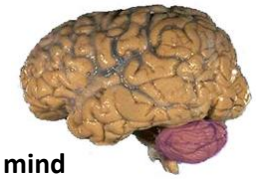
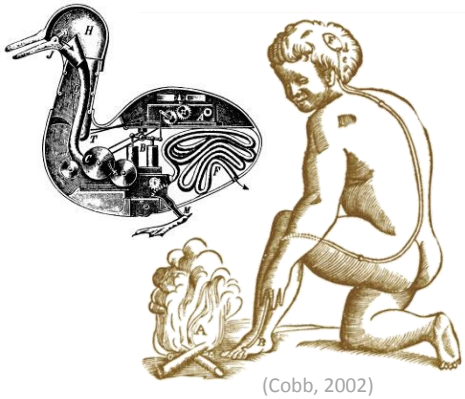
THE LONG HISTORY OF ANIMAL RESEARCH IN NEUROSCIENCE





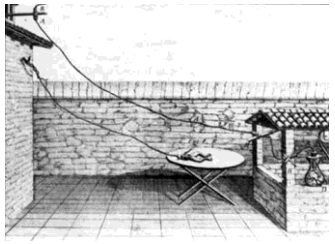


Heart as mind
Aristotle

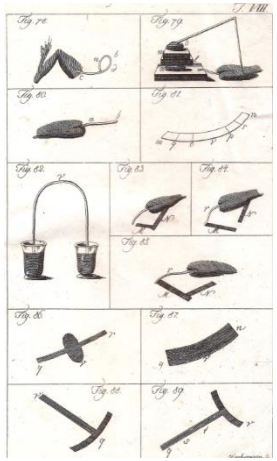


(Cobb, 2002)

Balloonist theory
Descartes



Animal electricity
Von Humboldt
Galvani



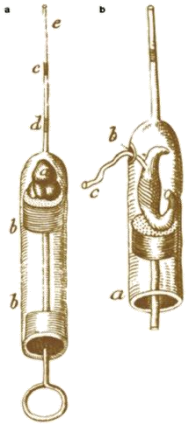
(Finger et al., 2013)

4th c. B.C. | 3rd c. | 16 c. | 18 c.

Mechanism of fluid energies
Galen

(BBAW, 2004)

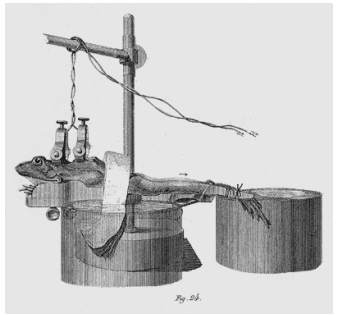
Balloonist theory disproven
Swammerdam



(Cobb, 2002)

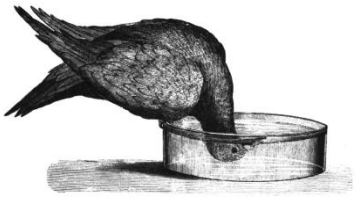
(Mangels)

THE LONG HISTORY OF ANIMAL RESEARCH IN NEUROSCIENCE

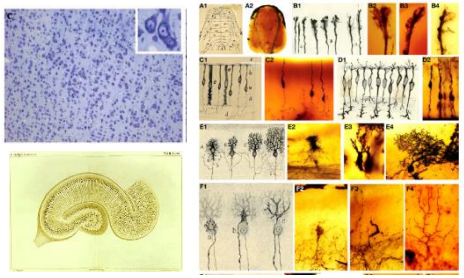


(Dierig, 2002)

Doctrine of specific nerve energies
Mueller



Aggregrate field theory
Flourens

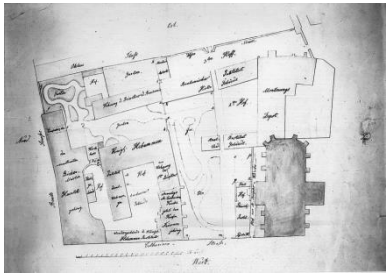


Development of neurohistology
Nissl
Golgi
Cajal

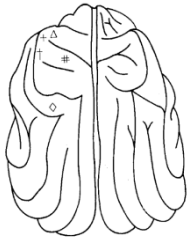
Connectionism

19th c. | 20th c. | 21st c.

Beginnings of neurophysiology
Purkinje

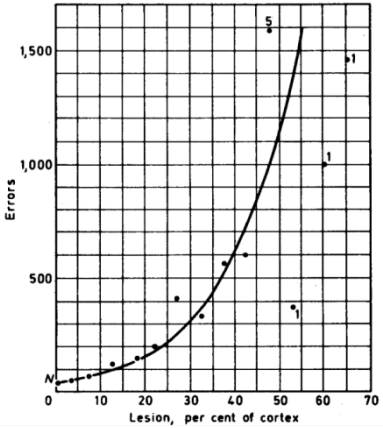


Localization theory
Broca
Wernicke
Fritsch and Hitzig



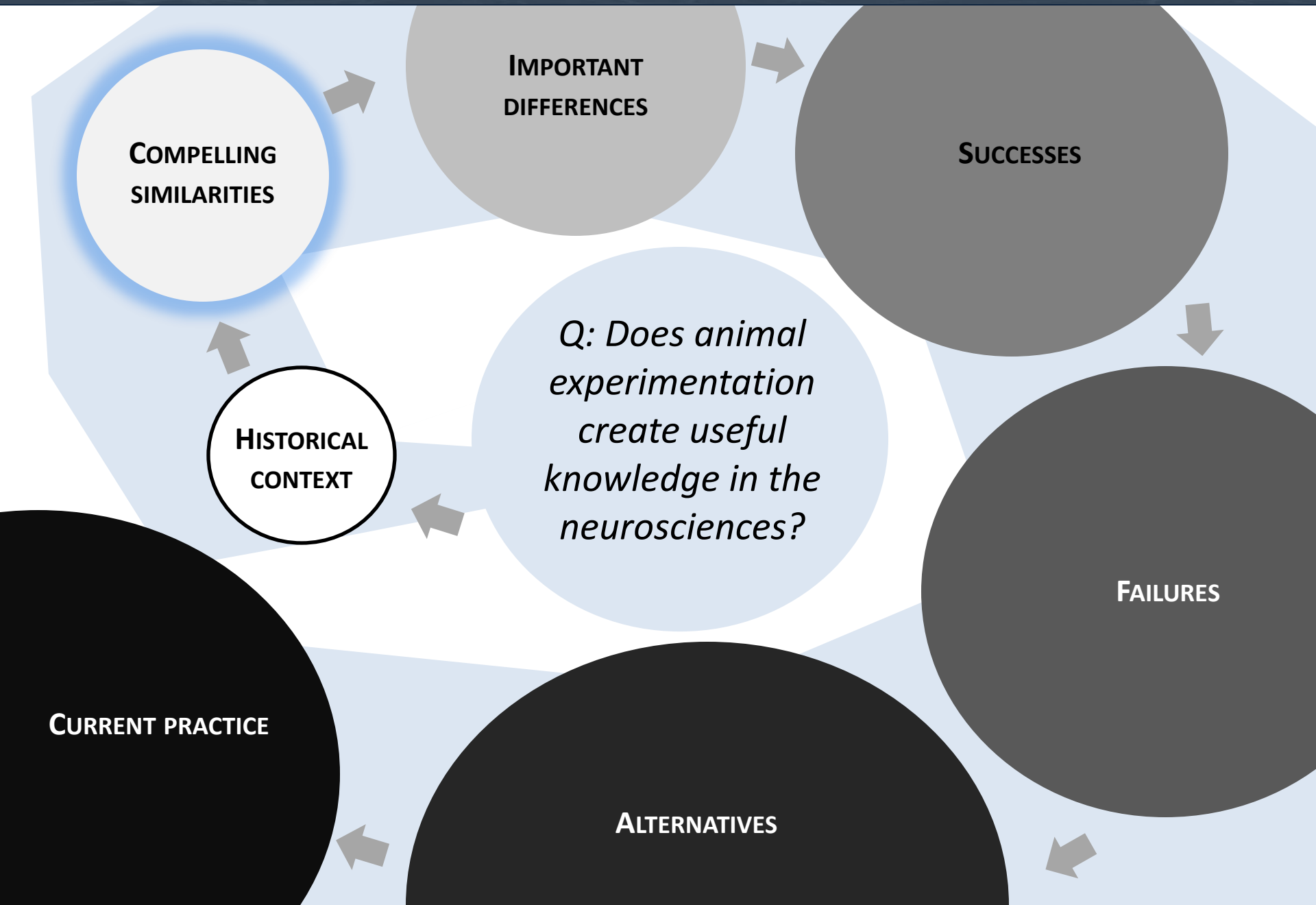
(Gross, 2007)

Localization versus holism
Penfield
Lashley



(Mangels)

Overview


Compelling similarities
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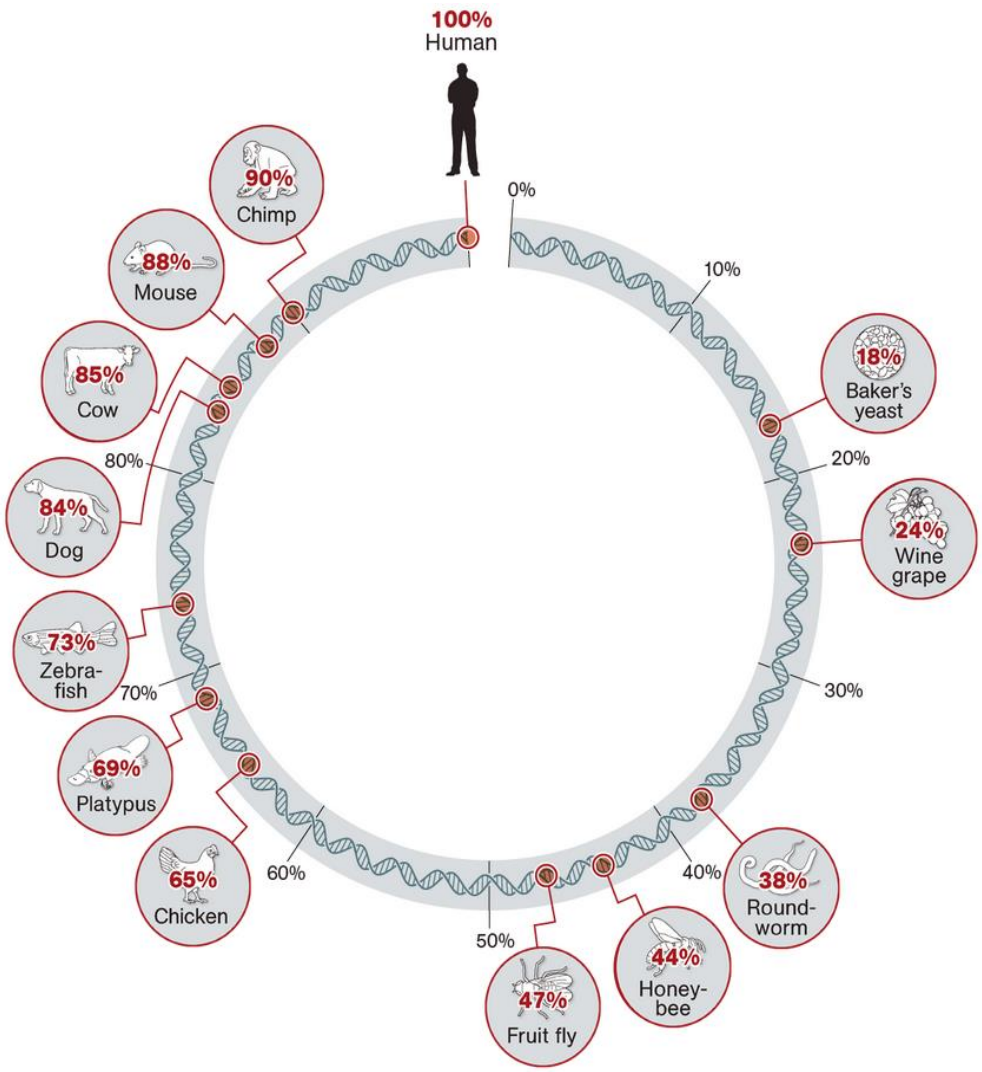
GENETIC SIMILARITY: THE MEANING OF %



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Humans share 50% DNA with bananas: The fascinating facts about the scientific world around us

00:00, 23 October 2013 | By Emma Pietras

Do you know how much the internet weighs? Teachers reveal fascinating facts to get kids interested in science and engineering

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When is it least likely to rain?

Want to know about the first text message ever sent?

These are just some of the fascinating facts chosen by a group of teachers to inspire youngsters to pick a career in science and engineering.

They are launching a "guerilla science" campaign, posting up a range of amazing and amusing facts in parks, chippies and skate parks.

The project has been organised with The Big Bang UK Young Scientists and

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We felt shame and guilt at cancelling an adoption

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http://www.mirror.co.uk/news/weird-news/humans-share-50-dna-bananas-2482139
http://ngm.nationalgeographic.com/2013/07/125-explore/shared-genes

GENETIC SIMILARITY: THE MEANING OF %

69.1%

DNA sequence identity

(MGSC, 2002)

Bonobo autosomes 98.7%
(Prufer et al., 2012)
Chimpanzee 98.77%
(CSAC, 2005)

85%

Protein-coding gene sequence identity

(MGSC, 2002)

But >95% of human DNA does not code for proteins!
(Taft et al., 2007)

80%

% of orthologous protein-coding genes

(MGSC, 2002)

Rat to human 90%
(RGSPC, 2004)
Human to zebrafish 70%
(Howe et al., 2013)
Human to fruit fly 15%
(Shih et al., 2015)

82.3%

% of orthologous protein subset (non-olfactory GPCRs)

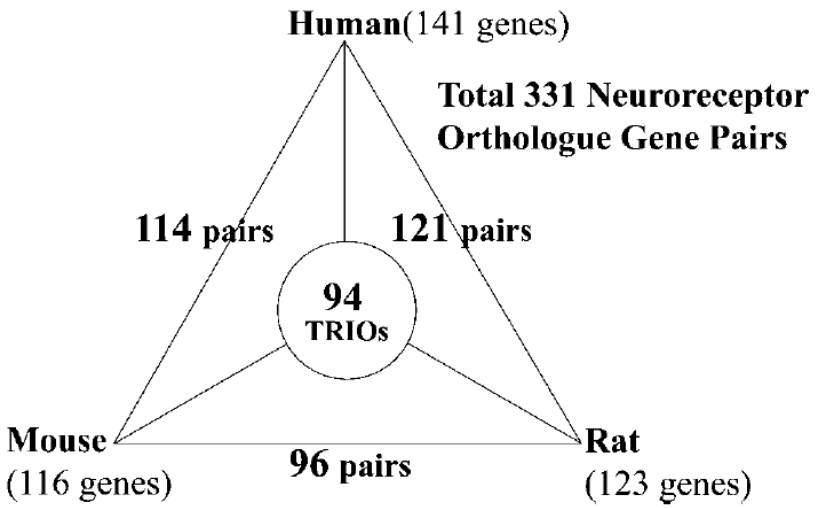
(Bjarnadóttir et al., 2006)

Rat to human 58% (GPCRs)
(Gloriam et al., 2007)

Homo sapiens* versus *Mus musculus

Protein similarity: Orthology and distribution

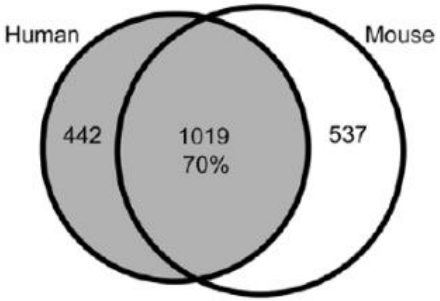
Humans, mice, and rats share orthologues from most major neurotransmitter receptor families.



Adenosine
Adrenergic
Cholinergic (muscarinic, nicotonic)
Dopamine
GABA (A, B)
Glutamate (metabotropic, ionotropic)
Glycine
Histamine
Opioid
Purinergic
5HT (metabotropic, ionotropic)
Peptides (bombesin, galanin, somatostatin, cholecystekinin, neuropeptide Y, VIP, neurotensin, TRH, GRH, gastrin releasing peptide, GHRH, CRH, angiotensin, calcitonin, bradykinin, secretin, tachykinin, neuromedin U, glucagon)

(Iwama and Gojobori, 2002)

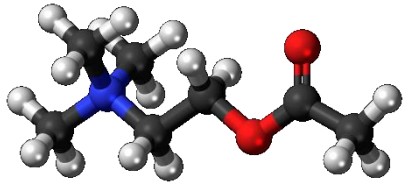
Similar protein types have been found in mouse and human postynaptic densities.



(Bayes et al., 2012)

Even single-celled animals can exhibit similar neurotransmitter receptors to humans.

http://101science.com/paramecium.htm



acetylcholine

(Roschina, 2010)

Neurotransmitter similarity

E. coli

(http://www.cdc.gov/ecoli/)

Genus *Musa*

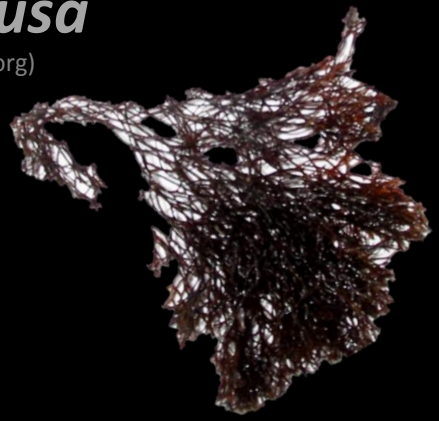
(www.evermotion.org)

Candida guillermondi

(http://atlas.microumftgm.ro/)

Solanum tuberosum

(www..greeneryco.uk)



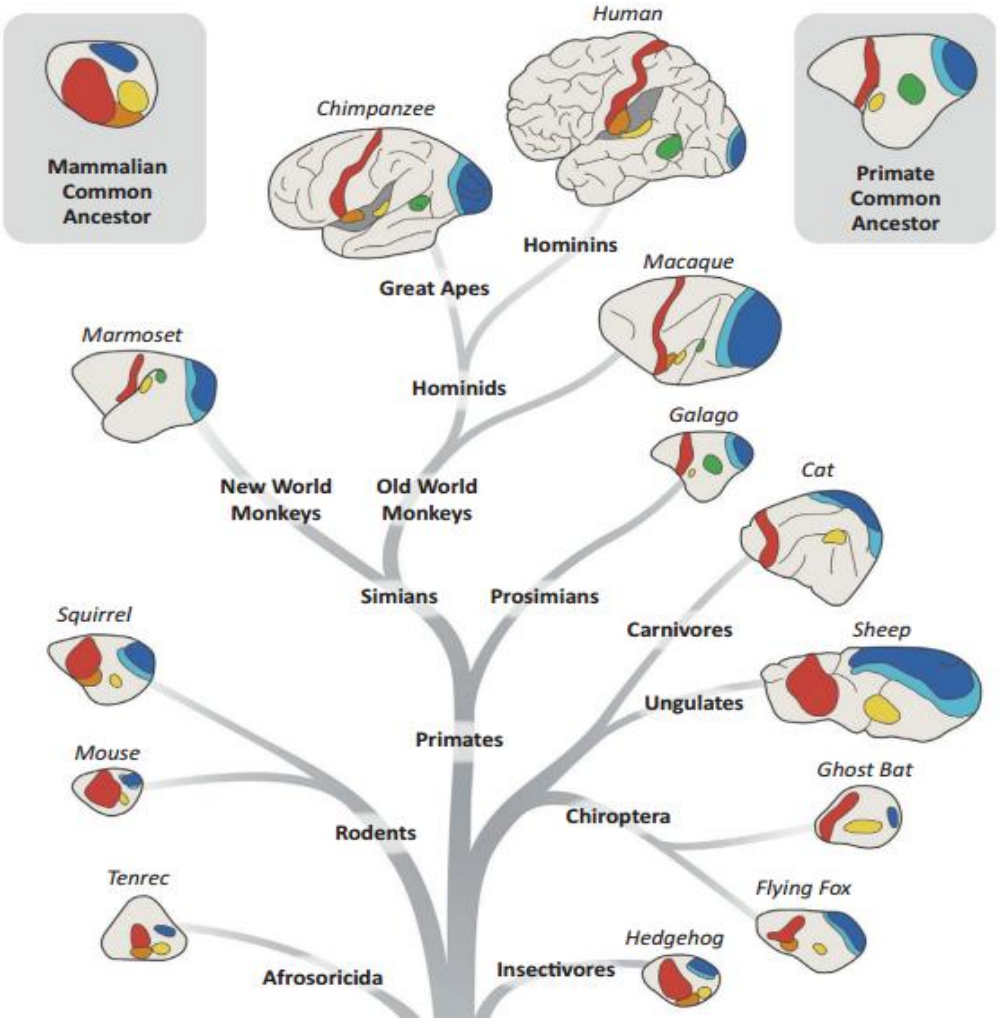
Furcellaria lumbricalis

(http://www.cybercolloids.net/)

Acetylcholine, dopamine, norepinephrine, serotonin, histamine, and other neurotransmitters have been found in a wide variety of microorganisms, plants, fungi, and non-human animals.

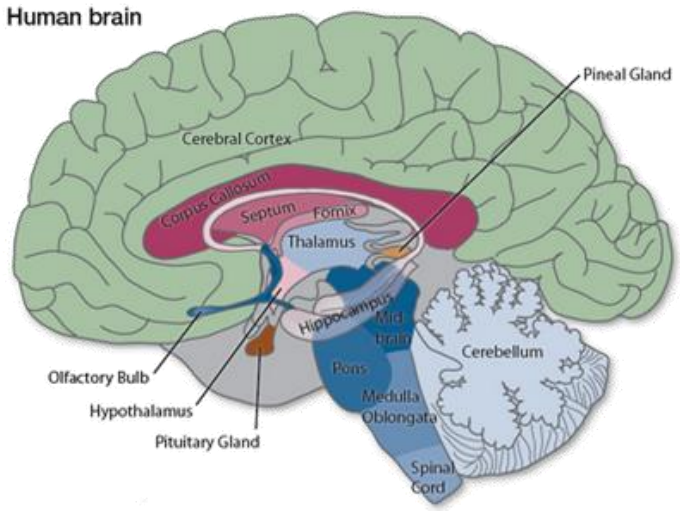
(Roschina, 2010)

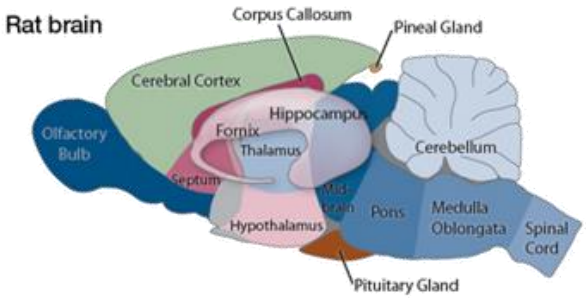
STRUCTURAL SIMILARITY



primary visual area (V1) • secondary visual area (V2) • middle temporal (MT) visual area • primary auditory area (A1) • primary somatosensory area (S1) • secondary somatosensory area (S2)

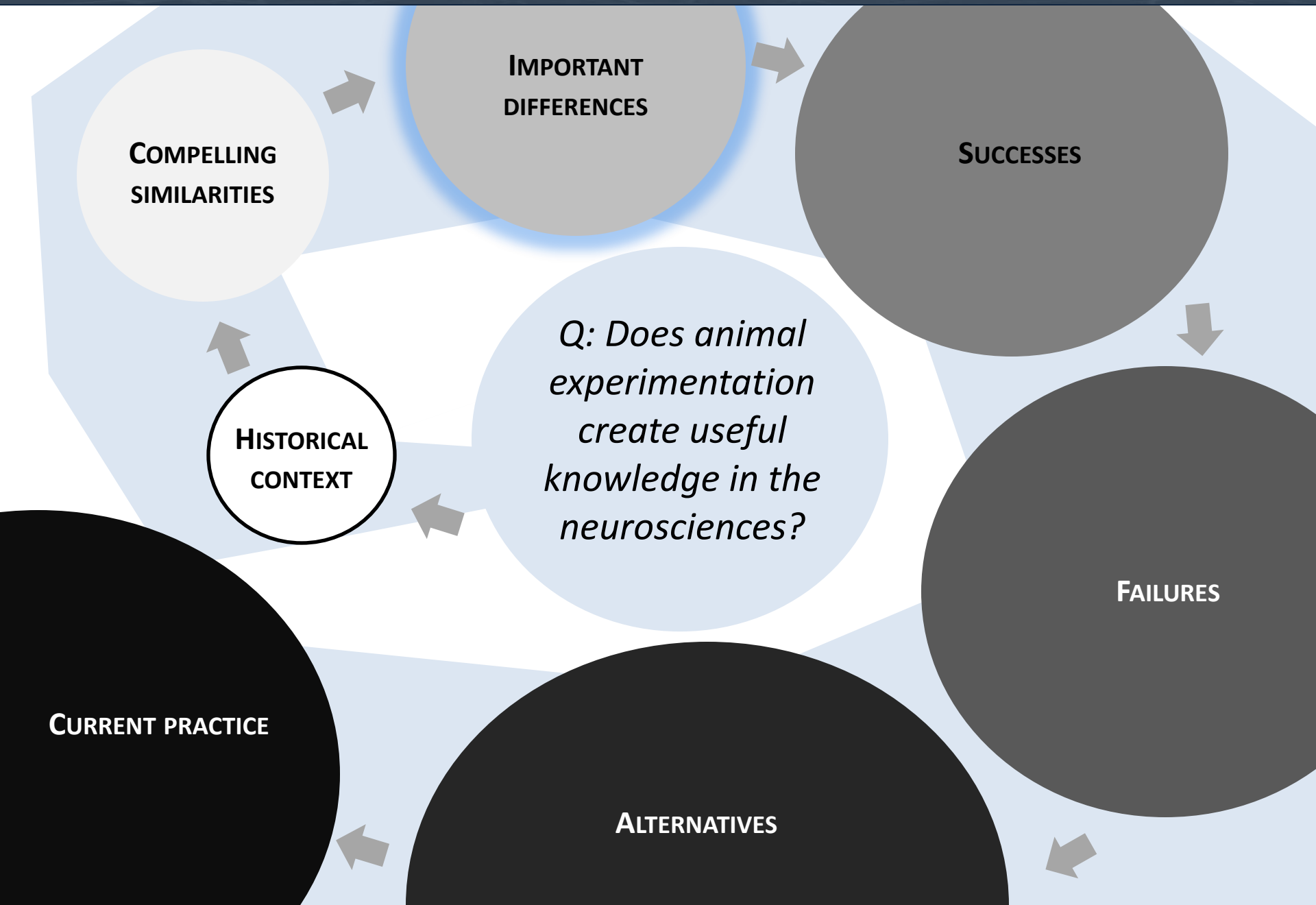
(Buckner and Krienan, 2013)





(University of Utah, 2014)

Overview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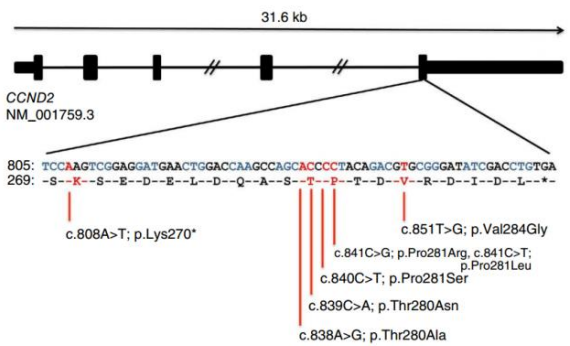
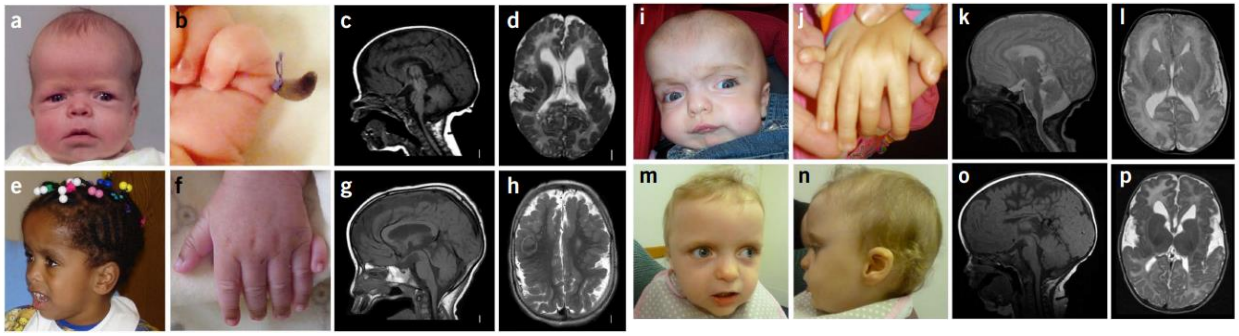
DNA: SMALL DIFFERENCES, BIG EFFECTS

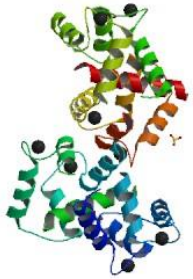
Single nucleotide polymorphisms in the gene for cyclin D2 are associated with a syndrome of diverse symptoms.



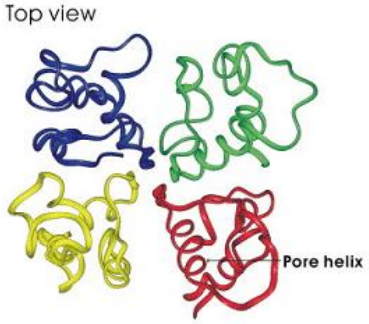


(Mirzaa et al., 2014)

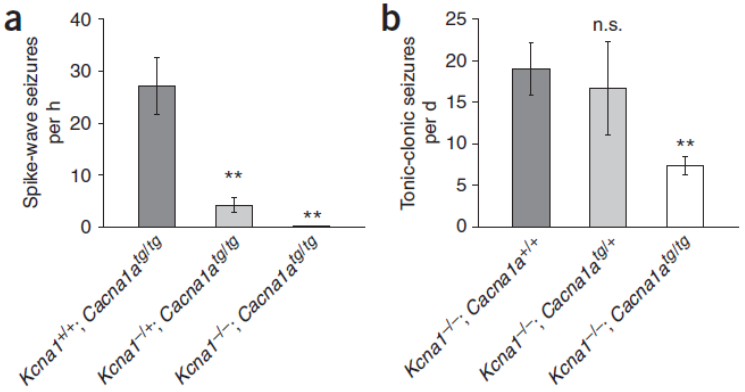
Whether a Ca^{2+} channel gene mutation causes seizures depends on the presence of a separate K^+ channel gene.



P/Q type Ca^{2+} channel, 1a subunit (*Cacna1a*)
(canSAR)



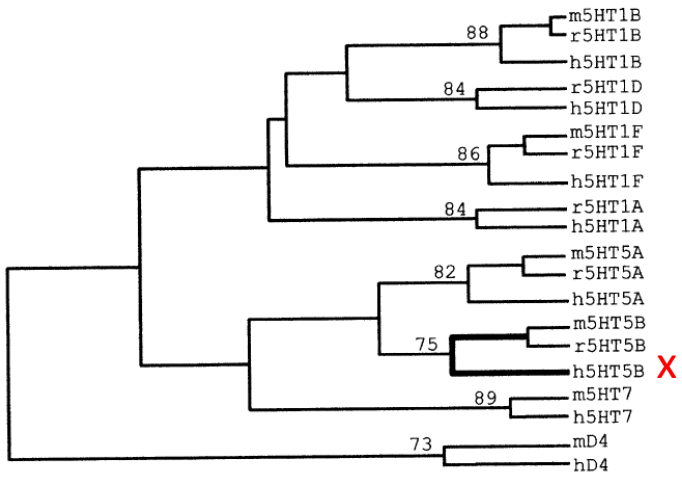
K_v1.1 (*Kcna1*)
(Channelpedia)



(Glasscock et al., 2007)

Proteins and neurotransmitters: Many ways to be different

Different protein subclasses



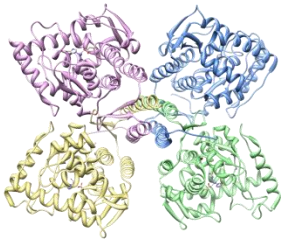
Humans lack a functional 5HT-5B receptor retained in rodents.

(Grailhe et al., 2001)

Differential protein and neurotransmitter distribution

Receptor subtype	Primate/human distribution	Rodent distribution
$mGlu_{1a}$	In cortex, both pyramidal and interneurons	Exclusively on interneurons in cortex
$mGlu_5$	In cortex, both pyramidal and interneurons	Exclusively on interneurons in cortex
NK_3	Cortical >> striatal expression	Striatal >> cortical expression
$5\text{-}HT_3$	Striatal >> cortical expression	Cortical >> striatal expression
$5\text{-}HT_6$	High density in ventral dorsal striatum	High striatal density in rats, but not in mice

(Geerts, 2009)



tyrosine hydroxylase (TH)

TH interneurons

Humans: Layers V, VI

Great apes: X

Rodents: Layers II, III

(DeFelipe, 2011)

Differential ligand binding

D1

D4

5HT-2A

5-HT7

M4

Exhibit up to >50x different binding affinities for several drugs in rats and humans

(Geerts, 2009)

Different proteins!

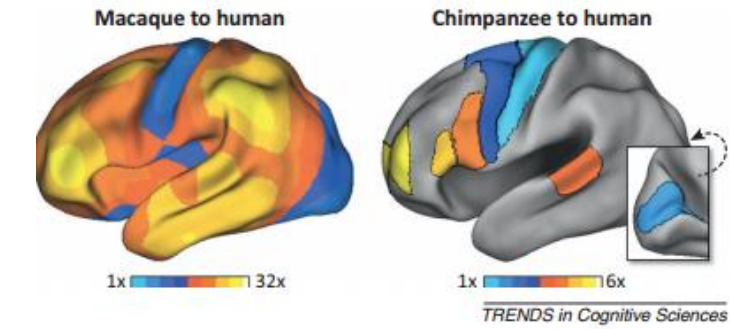
42%

Percent of rat G-protein-coupled receptor proteins found to have no orthologue in humans.

(Gloriam et al., 2007)

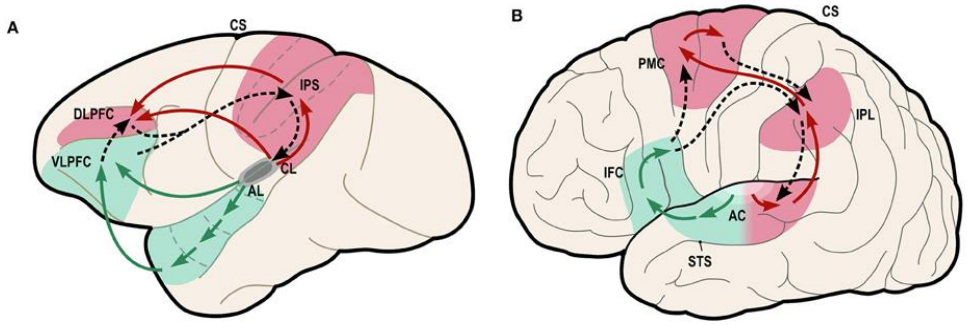
STRUCTURAL DIFFERENCES

Regional size differences



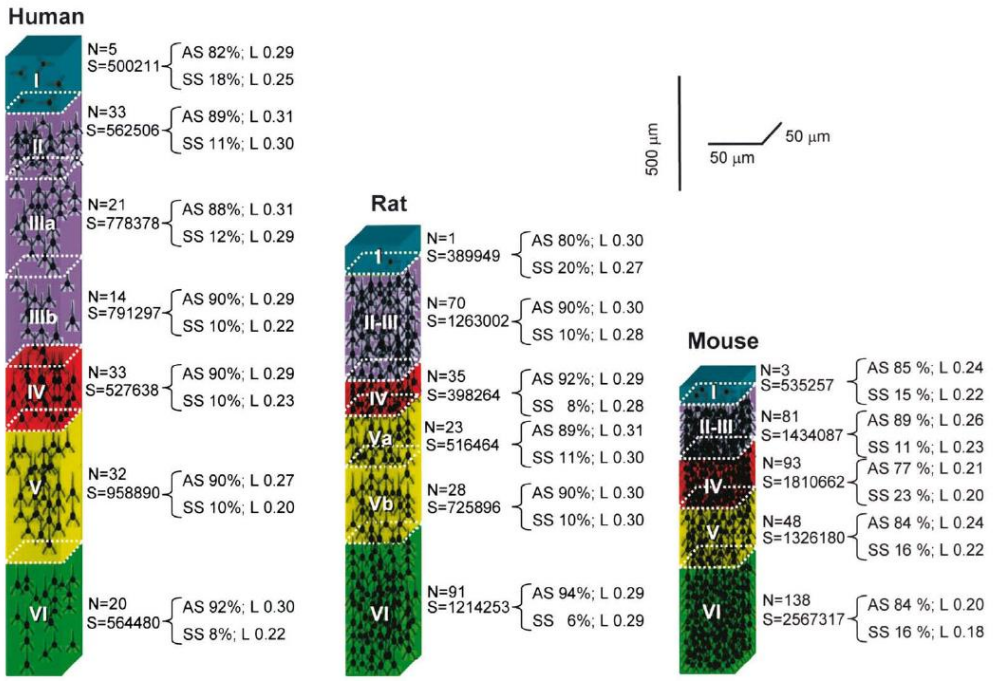
(Buckner and Krienan, 2013)

Wiring differences



(Patel and Iversen, 2014)

Differences in cellular organization and properties



(DeFelipe, 2011)

Homo sapiens

Cortical thickness= 2622 µm
Neurons (N)= 158
Synapses (S) =4683400
AS synapses= 89%; L 0.30 µm
SS synapses= 11%; L 0.25 µm
Nº synapses/neuron (S/N)= 29642

Rattus norvegicus

Cortical thickness= 1827 µm
Neurons (N)= 249
Synapses (S) =4507828
AS synapses= 89%; L 0.30 µm
SS synapses= 11%; L 0.28 µm
Nº synapses/neuron (S/N)= 18104

Mus musculus

Cortical thickness= 1210 µm
Neurons (N)= 364
Synapses (S) = 7673503
AS synapses= 84%; L 0.23 µm
SS synapses= 16%; L 0.21 µm
Nº synapses/neuron (S/N)= 2108

STRUCTURAL DIFFERENCES

Brain (1980), 103, 221–244

THE BASIC UNIFORMITY IN STRUCTURE OF THE NEOCORTEX

by A. J. ROCKEL, R. W. HIORNS *and* T. P. S. POWELL

(*From the Departments of Human Anatomy and Biomathematics, University of Oxford*)

INTRODUCTION

SEVERAL quantitative studies have shown that the cell density may vary in different laminæ and in different areas of the neocortex in the same brain and between different species (*see* Tower, 1954; Brody, 1955; Cragg, 1967). The cells are usually most closely packed in layer IV, the density is high in the visual cortex and low in the motor and in general the neurons are more widely separated in larger brains. In an electron microscopic study of the motor cortex of area 4 and of area 3b of the somatic sensory area of the monkey (Sloper, 1973; Sloper, Hiorns and Powell, 1979) the number of neuronal cell bodies was counted in a narrow width through the full depth of the cortex from the pia to the white matter. Surprisingly it was found that despite the marked difference in the thickness of the cortex of these two areas, and their different cytoarchitecture and function, the absolute number of neurons through the cortex was the same and the proportions of the two main cell types, the pyramidal and stellate, were similar. A comparison has now been made of the number of cells through the entire thickness of the cortex in most of the major structural and functional areas in the monkey and in several other species, ranging from mouse to man. With the exception of area 17 of the visual cortex of primates the figures are similar for the different areas, and despite the marked differences in the size of the brains the absolute number of cells through the thickness of the cortex has been found to be constant in the brains of different animals. The results may be of relevance to our understanding of the evolution of this part of the brain, and perhaps to the question of the anatomical basis of the functional columnar organization which is a feature of many areas of the cortex (Mountcastle, 1957, 1978; Hubel and Wiesel, 1962, 1977). A preliminary communication of the results has already appeared (Rockel, Hiorns and Powell, 1974).

MATERIAL AND METHODS

All of the animals (Table 1) were normal adults and the brains were fixed by perfusion through the heart with 0.9 per cent saline followed by 10 per cent formalin. The two human brains were from 26-year-old males who had been killed suddenly in accidents not involving the brain; these were fixed

Structural uniformity of neocortex, revisited

C. Nikoosh Carlo[1] and Charles F. Stevens[1]

The Salk Institute for Biological Studies, La Jolla, CA 92037

Contributed by Charles F. Stevens, December 12, 2012 (sent for review June 16, 2012)

The number of neurons under a square millimeter of cortical surface has been reported to be the same across five cortical areas and five species [Rockel et al. (1980) *Brain* 103(2):221–244] despite differences in cortical thickness between the areas. Although the accuracy of this result has been the subject of sharp debate since its publication approximately 30 y ago, the experiments of Rockel et al. have never been directly replicated with modern stereological methods. We have replicated these experiments and confirm the accuracy of the original report. In addition, we have observed that the number of

methods, and with care to minimize systematic errors: we used only material prepared by our laboratory to minimize variability caused by histological processing procedures, we used counting columns that are oriented perpendicular to the surface of the cortex and within distinct cortical regions, and we studied the species and cortical regions that match the ones Rockel et al. used. The work of Rockel et al. was carried out before stereological procedures were in common use, and complete details about their counting procedures are not presented in the published work. From information given, however, each of two independent observers counted ~750 neurons for each cortical region, a sample that could have been sufficient to provide a good estimate of the number of neurons present under a square millimeter of cortical surface.

Our goal is to evaluate the conclusion of Rockel et al. that the number of neurons underneath a square millimeter of neocortical surface (an idea termed here numerical uniformity) is approximately constant in four cortical areas and in four species Rockel et al. studied: mouse, rat, cat, and monkey. We wished simply to discover if their reported observations are repeatable with modern methods, and do not engage the larger questions relating to structural uniformity across areas and species.

Our data agree with the observations of Rockel et al.: across neocortical regions (excluding primate V1) and across species, we find statistically the same number of neurons underneath a square millimeter of neocortical surface as Rockel et al. reported. We also have extended their initial observations by discovering that the number of glial cells changes systematically with the thickness of the cortex but in a way that is independent of species and cortical area, and we interpret the observation in the context of a theory assuming that astrocytic territories occupy a constant volume of neuropil. In the *Discussion*, we review the literature relevant to the findings of Rockel et al. and attempt to account for the divergences in findings among the various studies.

Results

As noted, our goal in the present work is to reevaluate the conclusions drawn by Rockel et al. by repeating, with more modern methods, their original experiments (1) as closely as possible. The material we have studied differs in three ways from that of Rockel et al. First, because human brains are not available to us, that species has been excluded from the replication. Second, we have excluded primary visual cortex in this report because of fundamental differences between primates and the other species studied; although we have replicated Rockel et al.'s observations on area 17, those observations and extensions of them to other visual areas and primate species will be reported separately. Finally, we have also excluded prefrontal cortex because its small radius of curvature in rodents made it impossible for us to carry out counts perpendicular to the cortical surface

Author contributions: C.N.C. and C.F.S. designed research; C.N.C. performed research; C.F.S. contributed new reagents/analytic tools; C.N.C. analyzed data; and C.N.C. and C.F.S. wrote the paper.

The authors declare no conflict of interest.

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The basic nonuniformity of the cerebral cortex

Suzana Herculano-Houzel*[1], Christine E. Collins[a], Peiyan Wong[a], Jon H. Kaas[1b], and Roberto Lent*

*Instituto de Ciências Biomédicas, Universidade Federal Rio de Janeiro, Brazil; and [b]Department of Psychology, Vanderbilt University, Nashville, TN 37203

Contributed by Jon H. Kaas, June 3, 2008 (sent for review December 19, 2007)

Evolutionary changes in the size of the cerebral cortex, a columnar structure, often occur through the addition or subtraction of columnar modules with the same number of neurons underneath a unit area of cortical surface. This view is based on the work of Rockel *et al.* [Rockel AJ, Hiorns RW, Powell TP (1980) The basic uniformity in structure of the neocortex. *Brain* 103:221–244], who found a steady number of approximately 110 neurons underneath a surface area of 750 μm² (147,000 underneath 1 mm²) of the cerebral cortex of five species from different mammalian orders. These results have since been either corroborated or disputed by different groups. Here, we show that the number of neurons underneath 1 mm² of the cerebral cortical surface of nine primate species and the closely related *Tupaia* sp. is not constant and varies by three times across species. We found that cortical thickness is not inversely proportional to neuronal density across species and that total cortical surface area increases more slowly than, rather than linearly with, the number of neurons underneath it. The number of neurons beneath a unit area of cortical surface varies linearly with neuronal density, a parameter that is neither related to cortical size nor total number of neurons. Our finding of a variable number of neurons underneath a unit area of the cerebral cortex across primate species indicates that models of cortical organization cannot assume that cortical columns in different primates consist of invariant numbers of neurons.

allometry | brain size | primates | number of neurons | cortical surface

The expansion of a cerebral cortex that varies in surface area by more than five orders of magnitude across mammals (1) is considered a key event in mammalian brain evolution (2, 3), even though evolution is not always associated with increased brain or cortical size (4). Given that the cerebral cortex is a columnar structure (2, 5, 6), the most accepted view of cortical expansion proposes that this is achieved through the addition of columnar modules (7, 8). This view is so pervasive that the cortical surface area, rather than cortical volume, has often been used as a measure of the information processing capacity of the brain (3, 9).

Moreover, the columnar modules that build the cerebral cortex have been assumed to be composed of a constant number of neurons underneath a unit area of cortical surface, since Rockel *et al.* reported that there is a constant number of ≈147 thousand neurons beneath 1 mm² of cortical surface of various mammalian species (10). In that study, the authors used two-dimensional counts of neurons in sections of the cerebral cortex from mouse, rat, cat, macaque, and man, and concluded that a uniform number of neurons beneath 1 mm² is present across species. The notion of numerical uniformity, although supported by data obtained through light microscopy analysis in the mouse (11), has since been disputed by separate research studies within (12, 13) and across mammalian orders (14). Despite the evidence to the contrary, most models of cortical evolution and connectivity still assume that cortical columns hold a constant number of neurons across species (7, 8, 15, 16).

To test whether the number of neurons underneath a given unit of cerebral cortex is invariant across primate species, we used the Isotropic Fractionator (17) to determine the total number of neurons in one hemisphere of the cerebral cortex of nine primate species, ranging 18× in cortical gray matter mass from *Callithrix* to *Papio*, and in the closely related *Tupaia* spp. (18). Next we examined whether this number varied with total cortical surface area, gray matter thickness, gray matter mass, and neuronal density. We also examined predictions of the models of cortical expansion based on the addition of columns of constant numbers of neurons, such as the expected inverse proportionality between cortical thickness and neuronal density (10). Our results agree with stereological data from other mammalian orders that indicate the number of neurons beneath a surface unit of cerebral cortex is not constant but rather covaries with neuronal density (12–14).

Results

Across the nine primate species examined and in the closely related *Tupaia* sp., we found that the average number of neurons beneath one square millimeter of cerebral cortex (N/A; calculated as the ratio between the total number of neurons in the cerebral cortex, N, and the total cortical surface area, A) varied threefold from 42,710/mm² in *Macaca fascicularis* to 129,670/mm² in *Saimiri* sp. (Table 1), with an average of 83,945 neurons/mm² across species. Despite this variation, these values as a whole were not significantly different from the N/A of 97,351/mm² that was predicted by Rockel *et al.* (10) from which a nominal value of 147,000/mm² was corrected for 18% shrinkage in each of two dimensions ($P = 0.1903$, one sample t test). Because exclusion of *Tupaia* sp. from the analyses did not modify the results (data not shown), all comparisons henceforth include all 10 species studied.

One prediction of models of cortical expansion based on the addition of uniform columns of cerebral cortex is that total surface area (A) should increase linearly with the number of cortical neurons (N) across species. In contrast, we found that A increased as a power function of N with an exponent of 0.805 ($P < 0.0001$; Fig. 1a), which is significantly smaller than 1.0 (95% confidence interval, 0.614–0.996). Across species, a larger cortical mass (M) correlated with a larger cortical surface by a power function of A with an exponent of 1.123 ($P < 0.0001$; Fig. 1b), and with a larger number of neurons by a power function of N with an exponent of 0.934 ($P < 0.0001$, Fig. 1c). Similar relationships are obtained if cortical volume (V) is used instead of M (data not shown). These exponents indicate that cortical surface (A) increases slightly slower than cortical mass (M), and, thus, also more slowly than the number of neurons in the cortex (N).

N/A = D × T: Predictions Are Not Supported by Evidence. The number of neurons (N) in the cerebral cortex can be expressed as the product of surface area (A), cortical thickness (T), and cortical neuronal density (D), such that $N = A \times T \times D$. Given this mathematical relationship, for the ratio N/A to remain constant across species, it is necessary that D and T be inversely corre-

Author contributions: S.H.-H., and R.L. designed research; S.H.-H., C.E.C., P.W., J.H.K., and R.L. performed research; S.H.-H. analyzed data; and S.H.-H. wrote the paper.

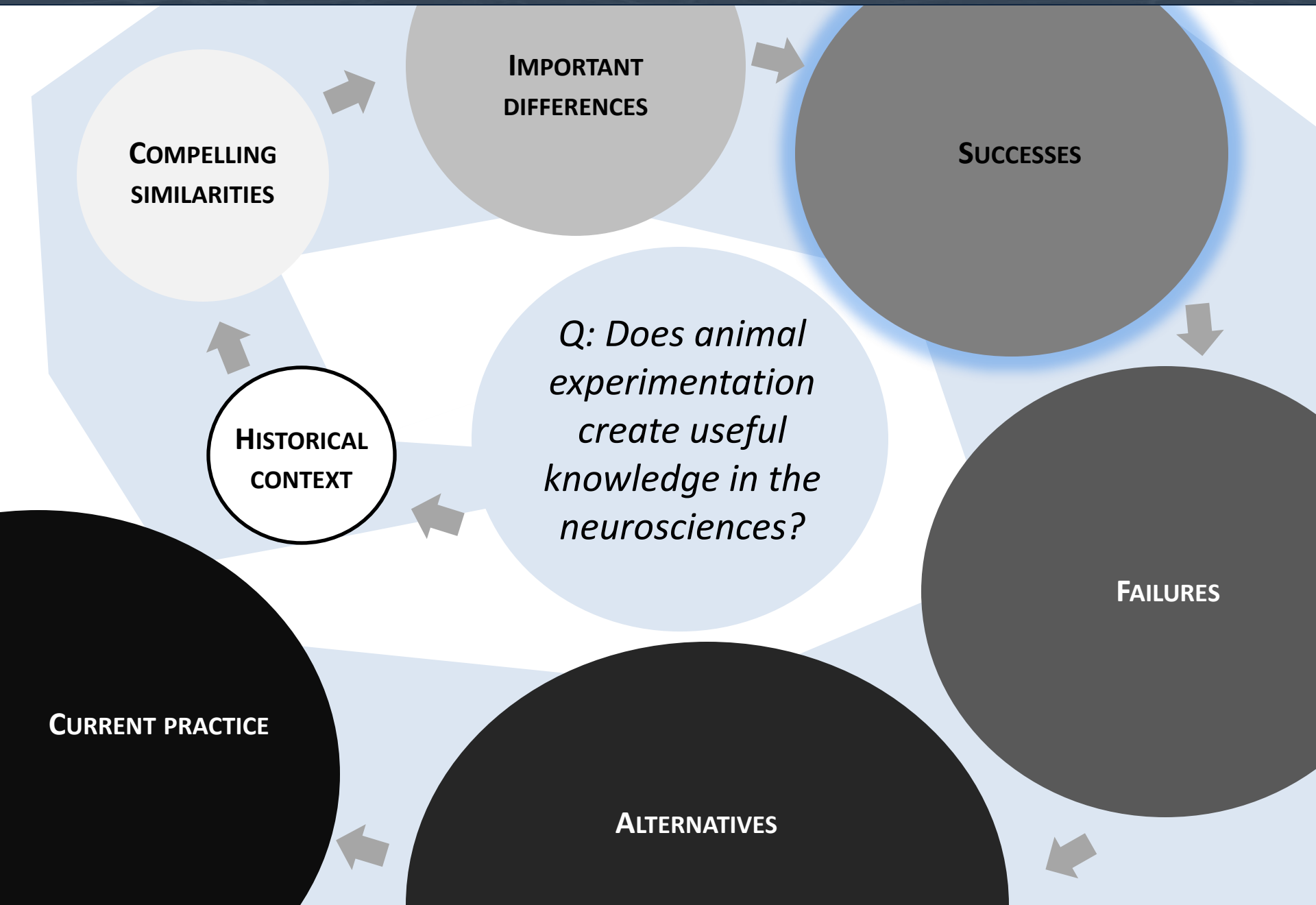
The authors declare no conflict of interest.

See Commentary on page 12099.

*To whom correspondence may be addressed. E-mail: suzanahh@ism.com.br or jon.h.kaas@vanderbilt.edu.

Since the publication of a difficult-to-replicate analysis in 1980, the extent to which neocortical organization is conserved across mammalian species has been a matter of intense debate.

Overview


Compelling similarities
Important differences
Successes
Historical context
Q: Does animal experimentation create useful knowledge in the neurosciences?
Failures
Current practice
Alternatives

ALL BUT ONE NOBEL PRIZE FOR RESEARCH IN NEUROSCIENCE USED ANIMALS

Year	Awardees	Discovery	Species
2014	O'Keefe, Moser, Moser	place/grid cells	rat
2013	Rothman, Schekman, Sudhof	molecular mechanisms of vesicle trafficking	hamster, mouse, rat, [yeast]
2004	Axel, Buck	olfactory receptor organization	*Drosophila*, mouse, rat
2003	Mansfield, Lauterbur	MRI	[human finger], rat
2000	Kandel, Greengard, Carlsson	dopamine signaling in motor and memory function	guinea pig, mouse, rat, reptiles, *Aplysia*
1997	Prusiner	prions	hamster
1991	Nehar, Sakmann	patch-clamp technique and ion channel dynamics	frog, rat
1981	Sperry, Hubel, Wiesel	hemispheric division in cerebral function; visual processing	monkey, human patient, cat
1977	Guillemin, Yalow, von Schally	peptide hormone visualization and signaling	human patient, sheep, pig
1973	Lorenz, Tinbergen, von Frisc	organization of social behavior	bee, stickleback, goose
1967	Hartline, Wald, Granit	light transduction and visual processing in eye	cat, crustaceans, frog, guinea pig, rat, reptiles
1963	Eccles, Hodgkin, Huxley	ionic mechanisms of action potential generation and propagation	squid
1950	Kendall, Reichstein, Hench	structure and effects of adrenal hormones	rat
1949	Hess, Moniz	vegetative nervous function; development of lobotomy	human patient, cat
1944	Erlanger, Gasser	discovery and classffication of variant nerve fiber types	cat, frog
1932	Sherrington, Adrian	reflex pathways; constant size in nerve impulse	cat, dog, frog
1911	Gullstrand	image formation in eye	[theory]
1906	Golgi, Ramon y Cajal	visualization and characterization of nervous tissue	many different species

(AnimalResearch.info; NobelPrize.org)

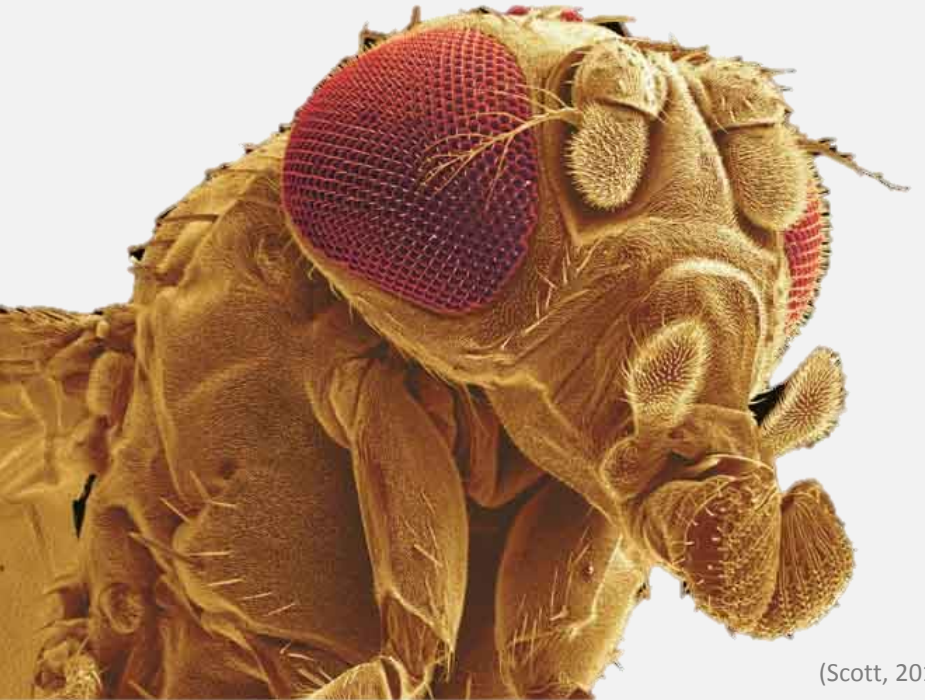
SUCCESS 1: MUTATION SCREENING IN *DROSOPHILA MELANOGASTER*

Notch (1915), achaete (1918), Hedgehog, Wingless, Dpp/TGF-beta (1984) (Bellen et al., 2010)

Table1 | **The roles of Hedgehog, Wingless, Dpp/TFGβ and Notch signalling in the nervous system**

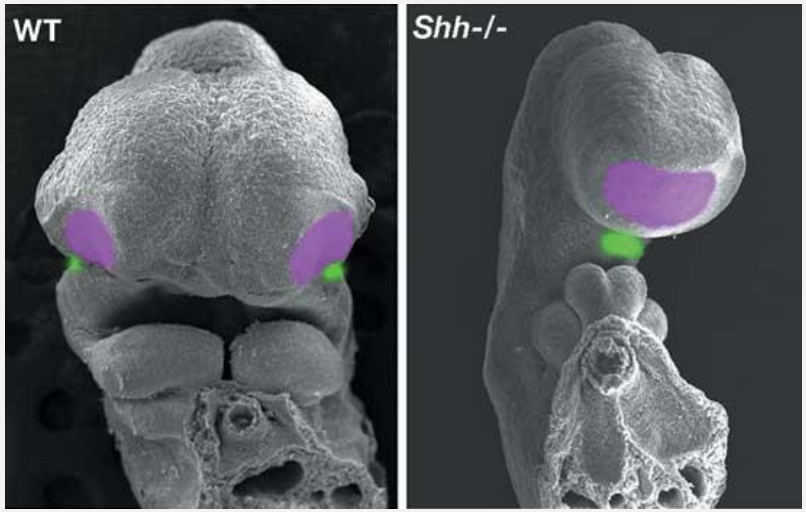
Pathway	Neuronal specification	Neuronal migration	Growth cone guidance	Synapse formation	Neuronal stem cell maintenance
Hedgehog	Mammals[182] and flies[183]	ND	Mammals[182]	Flies[183]	Mammals[182] and flies[184]
Wingless	Mammals[185] and flies[186]	Mammals[185]	Mammals[185]	Mammals[185,187] and flies[188]	Mammals[185]
Dpp/TGFβ	Mammals[189] and flies[190,191]	Mammals[189]	Mammals[189] and flies[192,193]	Mammals[189] and flies[194]	Mammals[195,196] and flies[184]
Notch	Mammals[197] and flies[37,198,199]	Mammals[197]	Flies[200]	Flies[201]	Mammals[184] and flies[184]

Dpp, Decapentaplegic; ND, not determined; TGFβ, Tumour growth factor-β



(Scott, 2013)

Sonic hedgehog knockout: Developmental consequences

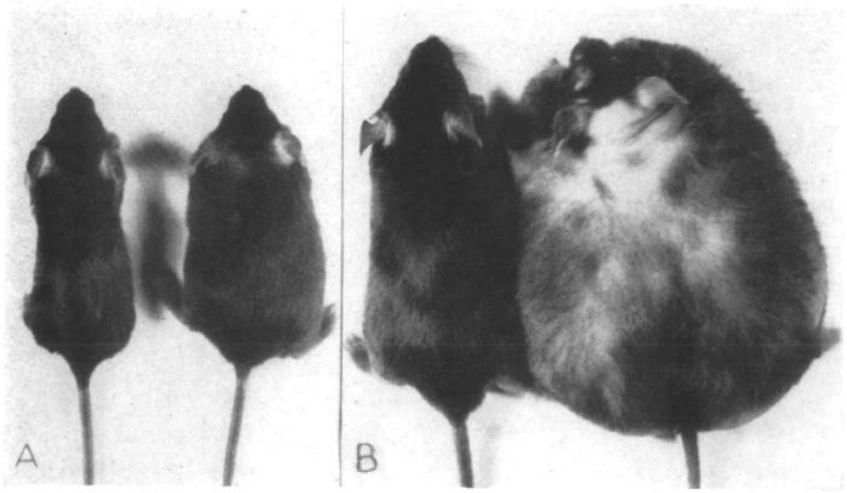


(Motoyama, 2006)

SUCCESS 2: DISCOVERY OF LEPTIN IN THE MOUSE

OBESE, A NEW MUTATION IN THE HOUSE MOUSE*

ANN M. INGALLS, MARGARET M. DICKIE AND G. D. SNELL
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine



THE FAT MOUSE GROWS UP

Figure 4

A—shows normal control and an obese mouse at 21 days of age. The former weighed 12 grams; the latter 16. *B* shows a normal and obese mouse at ten months of age, when the obese mouse weighed 90 grams and the normal mouse 29 grams.

OBESITY, other than that occurring in yellow mice, is relatively rare in mice. The obese yellow animals attain weights up to 75 or 80 grams but the average weight is around 60 grams and then there is a decrease in weight as age increases.† In the summer of 1949 some very plump young mice were found in the V stock.‡ Others occurred shortly after

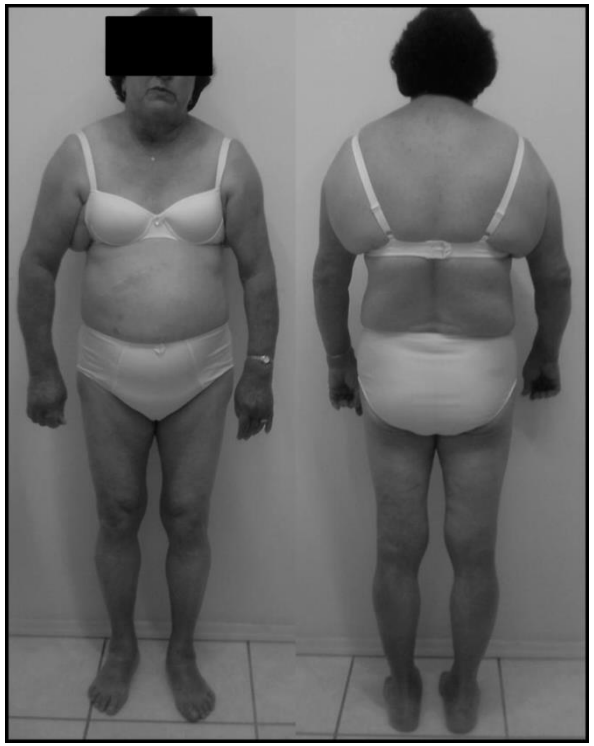
*This work has been aided by grants to the Roscoe B. Jackson Memorial Laboratory from the Commonwealth Fund, Anna Fuller Fund, Jane Coffin Childs Memorial Fund for Medical Research and the National Advisory Cancer Council.

†DICKIE, M. M., and G. W. WOOLLEY. *Jour. Hered.* 37:365-368. 1946.

‡V stock of Jackson Laboratory mice (*Mus musculus*) carries genes *aa lnln ss wa-1wa-1 vv*.

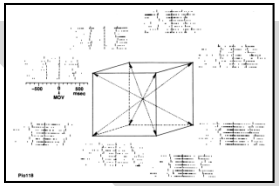
myalept®
(metreleptin) for injection 11.3mg per vial

lipodystrophy

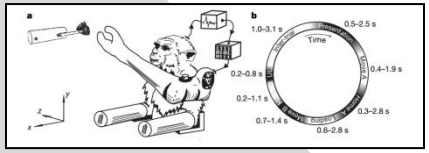


Patricia B Mory et al. *Eur J Endocrinol* 2012;167:423-431

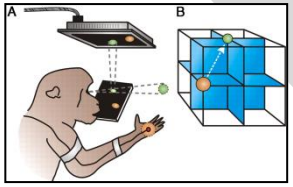
Success 3: Neural prosthesis development in non-human primates



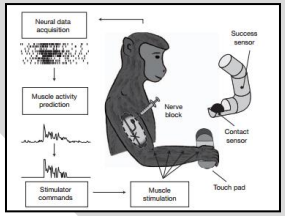
(Georgopolous et al., 1986)



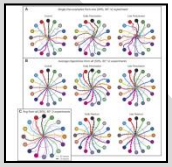
(Velliste et al., 2008)



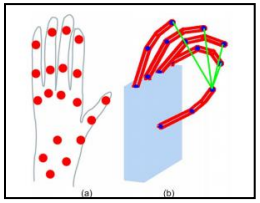
(Wang et al., 2007)



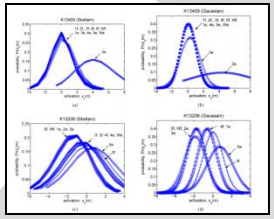
(Ethier et al., 2012)



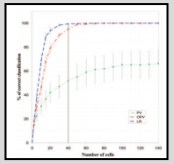
(Chase et al., 2012)



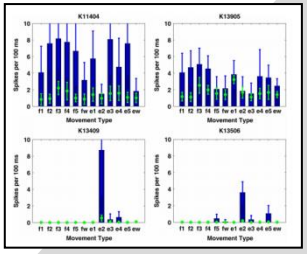
(Artemiadis et al., 2007)



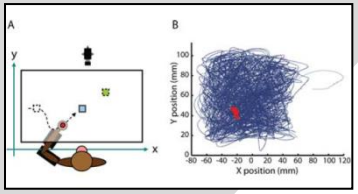
(Shin et al., 2010)



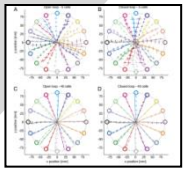
(Hamed et al., 2015)



(Aggarwal et al., 2008)

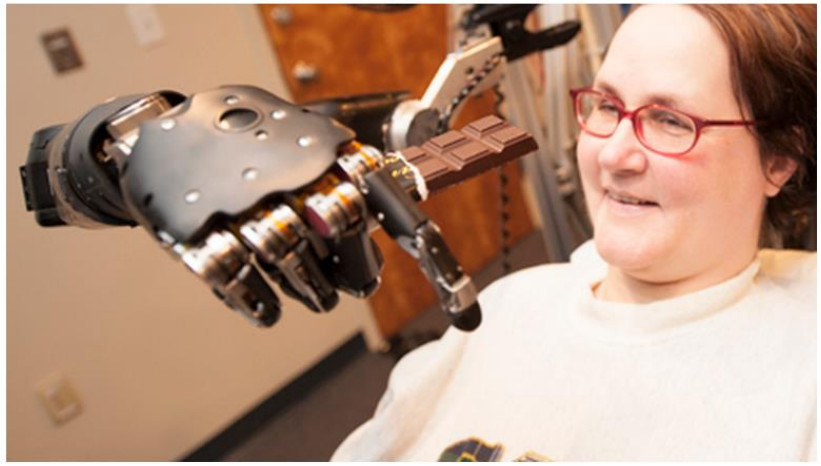


(Tkach et al., 2007)



(Chase et al., 2009)

UPMC LIFE CHANGING MEDICINE University of Pittsburgh

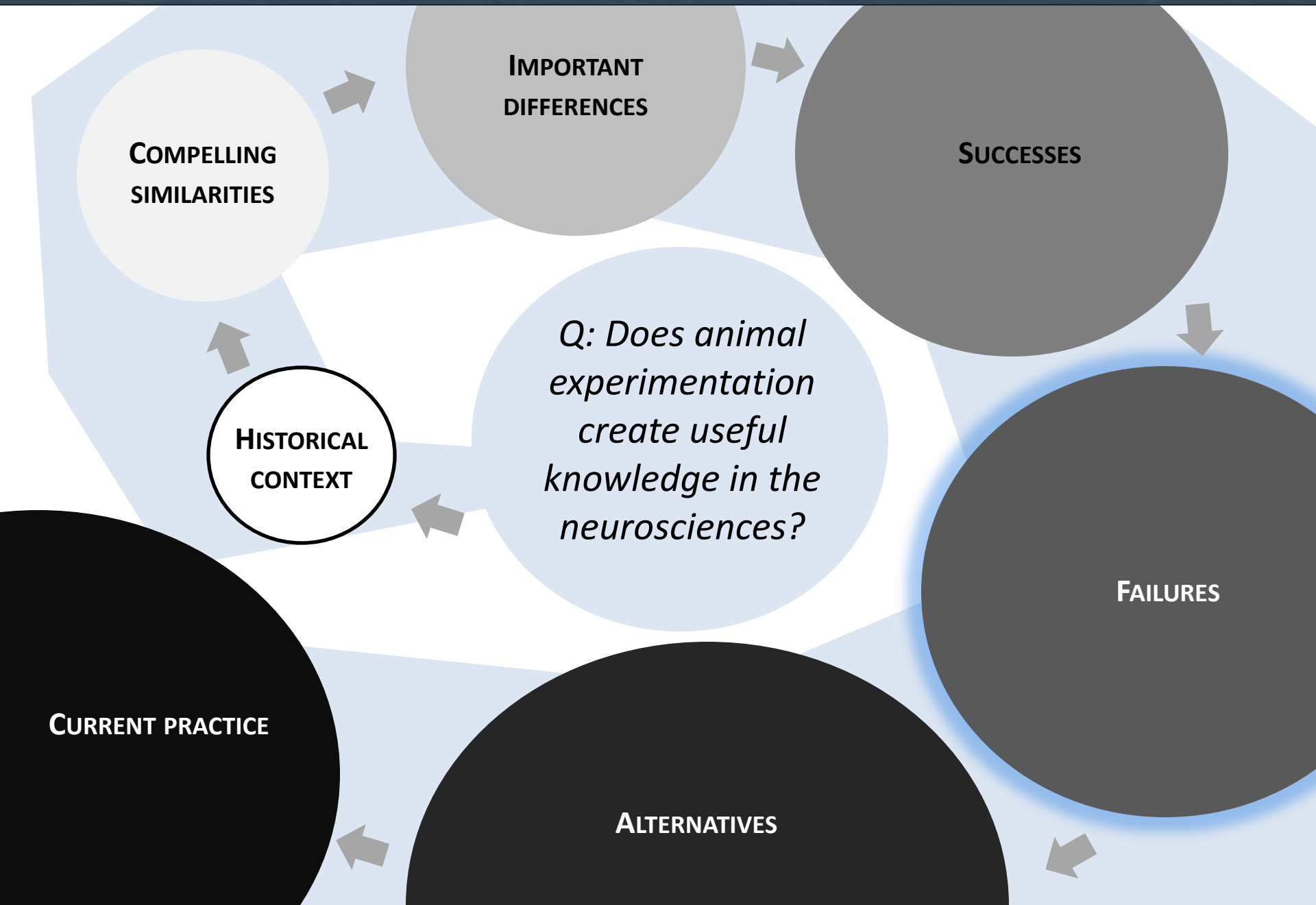


Jan Scheuermann, who has quadriplegia, brings a chocolate bar to her mouth using a robot arm she is guiding with her thoughts. Researcher Elke Brown, M.D., watches in the background. Click the photo to download it in high resolution. Photo credit: "UPMC"

More than 1/3 of the experiments cited by the publication introducing the first use of **motorized neural upper-limb prosthesis** by a quadriplegic human used **non-human primates.**

(Wodlinger et al., 2015)

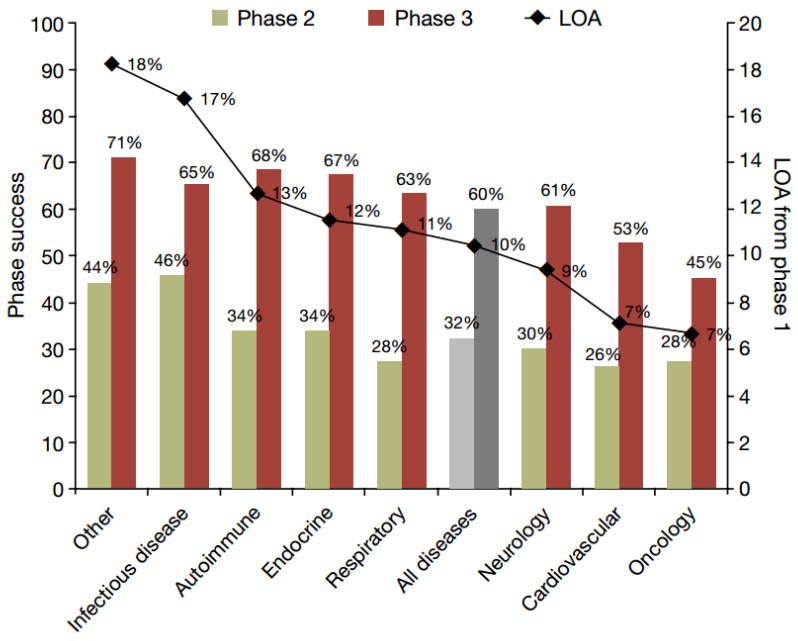
Overview


Compelling similarities
Important differences
Successes
Historical context
Q: Does animal experimentation create useful knowledge in the neurosciences?
Failures
Current practice
Alternatives

FAILURE OF PRECLINICAL ANIMAL SCREENING IN DRUG DEVELOPMENT

"Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies."

Mike Leavitt, U.S. Secretary of Health and Human Services, 2007



(Hay et al., 2014)

Neuroprotection in stroke:

500 preclinical successes = **2 new therapies**

(van der Worp et al., 2010)

Alzheimer's:

200 preclinical successes = **no new therapies**

(Zahs and Ashe, 2010)

Traumatic brain injury:

Thirty years of preclinical success = **no new drugs**

(Xiong et al., 2013)

Problems inherent in animal models: The case of Alzheimer's

(-)-Epigallocatechin-3-gallate (EGCG), the main polyphenolic constituent of green tea
(Active) intranasal immunization with dendrimeric Aβ1-15
(Aged) garlic extract
(S)-N -(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol
1-(3',4'-Dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid (CHF5074)
17β-estradiol (ovotoxicant-treated Tg2576)
17β-estradiol (ov-x 3XTg-AD)
17β-estradiol (ov-x APP/PS1)
17β-estradiol (ov-x Tg2576)
17β-estradiol (ov-x Tg2576, APP/PS1)
17β-estradiol + progesterone (ov-x 3XTg-AD)
17β-estradiol or 17α-estradiol (ov-x APPswe)
2-3-chlorophenylaminophenylacetate (anti-glycation properties)
8-hydroxy quinoline analog PBT2 (Cu/Zn ionophore)
AAV-CB (B sub-unit of cholera toxin)-Aβ42 vaccine
Acetyl-L-carnitine
Active immunization with Aβ
Active immunization with Aβ (nasal boosting protocol)
Acyl-coenzyme A: cholesterol acyltransferase (ACAT)
Adeno-associated viral mediated gene delivery of endothelin-converting enzyme
Adeno-associated virus delivery of anti-APPsw short-hairpin RNA
Adeno-associated virus delivery of dominant-negative CCL2 mutant
Adeno-associated virus gene therapy with cholesterol 24-hydroxylase
AF267B
All-trans retinoic acid (Vit A metabolite)
Alpha-phenyl-N-tert-butyl nitrone (PBN) (anti-oxidant)
Amino-caprolactam sulfonamides
Anti-Aβ42 immunization
Anti-CD40
Anti-GM-CSF
Anti-hypertensive drugs
Anti-TNFα
Apo A-I mimetic peptide D-4F w/pravastatin
Arundic acid (decreases astro S100B)
Aβ immunization
Aβ immunotherapy
Aβ vaccination
Aβ vaccination (APP/NOS2-null)
Aβ-specific Th2 cell infusion
BACE inhib [OM00-3]DR9
BACE-1 inhibitor
BDA-410 (specific calpain inhbib), E64
BDNF (lentiviral delivery)
BDNF-expressing neural stem cells (3xTg-AD)
Begasestat
Benzolactam, PKC activator
Beta secretase inhibition
Beta-secretase immunization
Blueberry
BMS-289948 and BMS-299897
BMS-299897
BMS-561392 (inhibitor of TNFα converting enzyme)
Bryostatin, PKC activator
Butyl-cholinesterase inhibitor (-)-N 1-phenethylnorcymserine (PEC)
CA074Me, E64d
Cabernet sauvignon
Caffeine
Caffeine (equiv 5 cups/day)
Calcineurin inhibitor FK506
Caloric restriction
Caloric restriction (3xTg-AD)
Captopril
Celastrol (NFκB inhibitor)
celecoxib
Cerebrolysin
CHF5074
Cholinesterase inhibitors
Citrus flavonoid (luteolin)
Citrus flavonoid (nobiletin)
Clioquinol
Clioquinol
CNI-1493, a tetravalent guanylhydrazone with antiinflammatory properties
Copper-bis(thiosemicarbazonoto) complexes
Coxibs
Cryptotanshinone, an active component of the medicinal herb Salvia miltiorrhiza
Cu(II)(gtsm)
Curcumin
Curcumin (3xTg-AD on high-fat diet)
Cyclohexyl sulfone-based gamma-secretase inhibitor
Cysteine protease inhibitors
DAPT
Di-allyl-disulfide, major lipid-soluble component of aged garlic extract
Diarylpropionitrile (selective estrogen [β] receptor modulator) (ov-x 3XTg-AD)
Diclofenac
Dietary copper
Dietary zinc
Diflunisal
Dihydrotestosterone (gonad-X 3XTg-AD)
Docosahexaenoic acid (DHA)
Donepezil
Dual BACE-AChE inhibitor
ECGC + fish oil
EFRH-phage immunization
EGCG
EGCG
Electromagnetic field treatment
Environmental enrichment
Epi-inositol
Erythromycin
Estradiol (ov-x 3XTg-AD)

Problems inherent in animal models: The case of Alzheimer's

Estradiol (ov-x PDAPP)
Exercise
Exercise + alpha-lipoic acid
Exercise training (treadmill)
Ferulic acid
Fish oil (3xTg-AD on high-fat diet)
Flurbiprofen
FLZ, a synthetic cyclic analogue of natural squamosamide
Furosemide
Galantamine
GEPT, a combination of herbal extracts
Ginkgo biloba extract
Ginkgo biloba extract (EGb 761)
Ginkgo biloba extract (flavonols)
Glucagon-like peptide analog Val(8)GLP-1
Glucagon-like peptide-1(7-36)-amide (GLP-1)
Gonadal steroids
Granulocyte colony-stimulating factor
Granulocyte colony-stimulating factor
Grape-seed extract
Growth factors
GSI-953 (begacestat)
GSK188909
GSK-3 inhibitors
Histone deacetylase inhibitors
HSV amplicon-mediated Aβ vaccination
HU210 (synthetic cannabinoid)
Hyperforin (St. John's wort) derivative (IDN5706)
Hyperforin (St. John's wort) derivative (IDN5706)
Ibuprofen
Ibuprofen (3xTg-AD)
IGF-I
immune cells from Aβ-vaccinated littermates
Immunization with a soluble nonamyloidogenic,
Immunization with an altered myelin-derived peptide
Immunization with anti- Aβ (2H6) or deglycosylated anti- Aβ (de-2H6)
Immunization with anti-APP beta-site antibodies
Indirubin-3'-monoxime
Indomethacin
inhibitor, CP-113,818
Inhibitors of APP synthesis
Inositol stereoisomers
Intracerebral injection of neprilysin-transfected fibroblasts
Intranasal Aβ vaccination
Ketogenic diet
KMI-429, a transition-state mimic
Lentiviral delivery of siRNAs targeting BACE1
Leptin
Leuprolide acetate (gonadotropin-releasing hormone analogue)
Lithium
Lithium (3xTg-AD)
Liver X Receptor agonists
Losartan (intranasal)
Lovastatin
LY-2434074
LY-411,575
Macrophage colony-stimulating factor
Meclofenamic acid
Melatonin
Memantine
Memantine + folic acid
Metal chelators
Metrifonate
MF-tricyclic
Minocycline
Monoaminergic drugs
MRK-560
Muscadine
Myricetin
N-[N-(3,5-difluorophenacetyl-L-alanyl)]-S-phenylglycine t-butyl ester (DAPT)
N-acetyl cysteine (antioxidant)
Naproxen
Nasal proteosome-based adjuvant (Protollin)
NCX-2216 (nitric oxide-releasing derivative derivative of flurbiprofen)
Nicotine
Nimesulide
nontoxic Aβ homologous peptide
Nordihydroguaiaretic acid
NP12 (APPswe, mtau)
NSAIDs
N-trifluoroethyl-substituted cyclic sulfamide
Olmesartan
Omega-3 fatty acids
Oral vaccination with a viral vector containing Aβ cDNA
Other anti-inflammatory drugs
Palmitylated-Aβ1-15 liposomal vaccine
Paroxetine (SSRI)
Passive Aβ immunotherapy
Passive immunization (human Aβ42)
Passive immunization with anti-Aβ
Passive immunization with deglycosylated antibody (D-2H6)
Passive immunization with DNA peptide vaccine
Passive immunization with monoclonal anti-Aβ
Passive immunization with NAB61
Passive immunotherapy with intracerebral monoclonal antibodies
Passive immunotherapy with monoclonal anti-Aβ3-6
PAZ-417 (inhibitor of plasminogen activator inhibitor 1)
Phenserine-related analog
Physostigmine
Picrotoxin (non-epileptic dose)

Problems inherent in animal models: The case of Alzheimer's

PKA inhibitor H89 (intracerebral)
Pomegranate juice
Posiphen, (+)-[phenserine]
Pravastatin
Progesterone (ov-x 3XTg-AD), cyclic tx
Progesterone (ov-x APP/PS1)
Propentofylline
Propylpyrazole triol (selective estrogen [α] receptor modulator) (ov-x 3XTg-AD)
Pyrrolidine
Pyrrolidine dithiocarbamate
Quetiapine, atypical antipsychotic drug
Resveratrol
R-flurbiprofen (tarenflurbil) (not a cyclooxygenase inhibitor)
Rivastigmine
Rosiglitazone (peroxisome proliferator activated receptor-gamma agonist)
Rosmarinic acid
S18886, thromboxane receptor antagonist
S-allyl-cysteine, major water-soluble component of aged garlic extract
Scyllo-inositol
Selective M1 muscarinic agonist
Selenium-enriched diet
Semi-naturalistic environment
Simvastatin
Single infusion of Aβ-specific
SK-PC-B70M (extract Pulsatilla koreana root)
Small-molecule Aβ-binding agents
Sodium butyrate
Soluble Nogo receptor fragment
Sorafenib (cRaf-1 inhibitor)
Statins
Stem cells (bone-marrow derived, intracerebral injection)
Subcutaneous Nogo receptor
Sulindac
T cell-based vaccination with glatiramer acetate
T0901317
Tacrine-melatonin hybrid
Tamibarotene (synthetic retinoid)
TO901317
Tricyclic pyrone (CP2) (5xTg-AD)
Trolox (anti-oxidant)
TSG, main component of Polygonum multiflorum
Ubiquitin C-terminal hydrolase L1 (Uch-L1) injected ip (acute)
Umbilical cord blood cells
Vaccination with adenovirus vector carrying tandem repeats of Aβ1-6
Vaccination with adenovirus vector containing Aβ
Vaccination with adenovirus vector containing Aβ42 intrabodies
Vaccination with adenovirus vector containing Aβs (3XTg-AD)
Vaccination with Aβ
Vaccination with Aβ1-15
Vaccination with Aβ-displaying virus-like particles
Vaccination with HSV amplicon containing Aβ42 and IL-4
Valproate (also inhibits GSK-3)
Valproate (also inhibits histone deacetylases)
Valsartan
Viral-directed overexpression of gelsolin in brain
Viral-vector-mediated gene transfer of neprilysin
Virus-like peptide vaccines
Vitamin C (acute)
Vitamin C + Vitamin E
Vitamin E
Voluntary exercise
Vorinostat
XH-1, lipophilic molecule has both amyloid-binding and metal-chelating moieties
Y-27632 (selective inhibitor of rho-associated kinase)
Yokukansan, a traditional Japanese medicine
α-lipoic acid
γ-Secretase Inhibitors/modulators

These are all the interventions shown to have some beneficial effect on the cognitive deficits of trangsenic mouse models of Alzheimer's from 1995 to 2010.

(Zahs and Ashe, 2010)

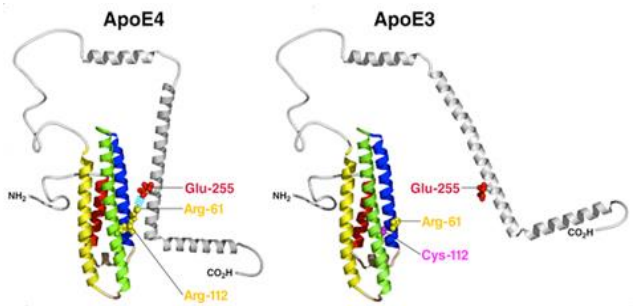
None of these has yielded any novel therapies for humans.

(Zahs and Ashe, 2010)

Problems inherent in animal models: The case of Alzheimer's

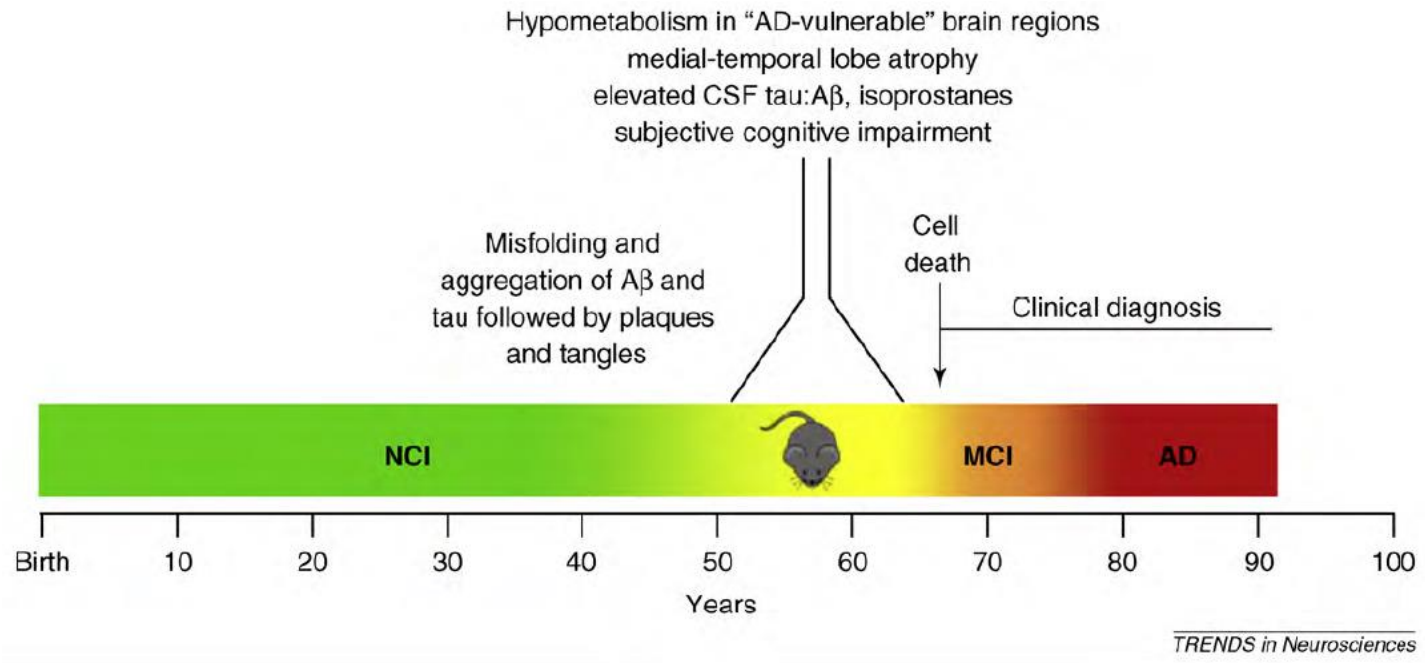
APP/presenilin mutations

Humans	Mice	
✓	✓	***Memory loss***
✓	✓	***Plaques***
✓	x	***Neurofibrillary tauopathy***
✓	x	***Neuronal death***



http://labs.gladstone.ucsf.edu/huang/pages/apoe-research

Mice naturally lack the APOE4 isoform associated with increased AD risk in humans.



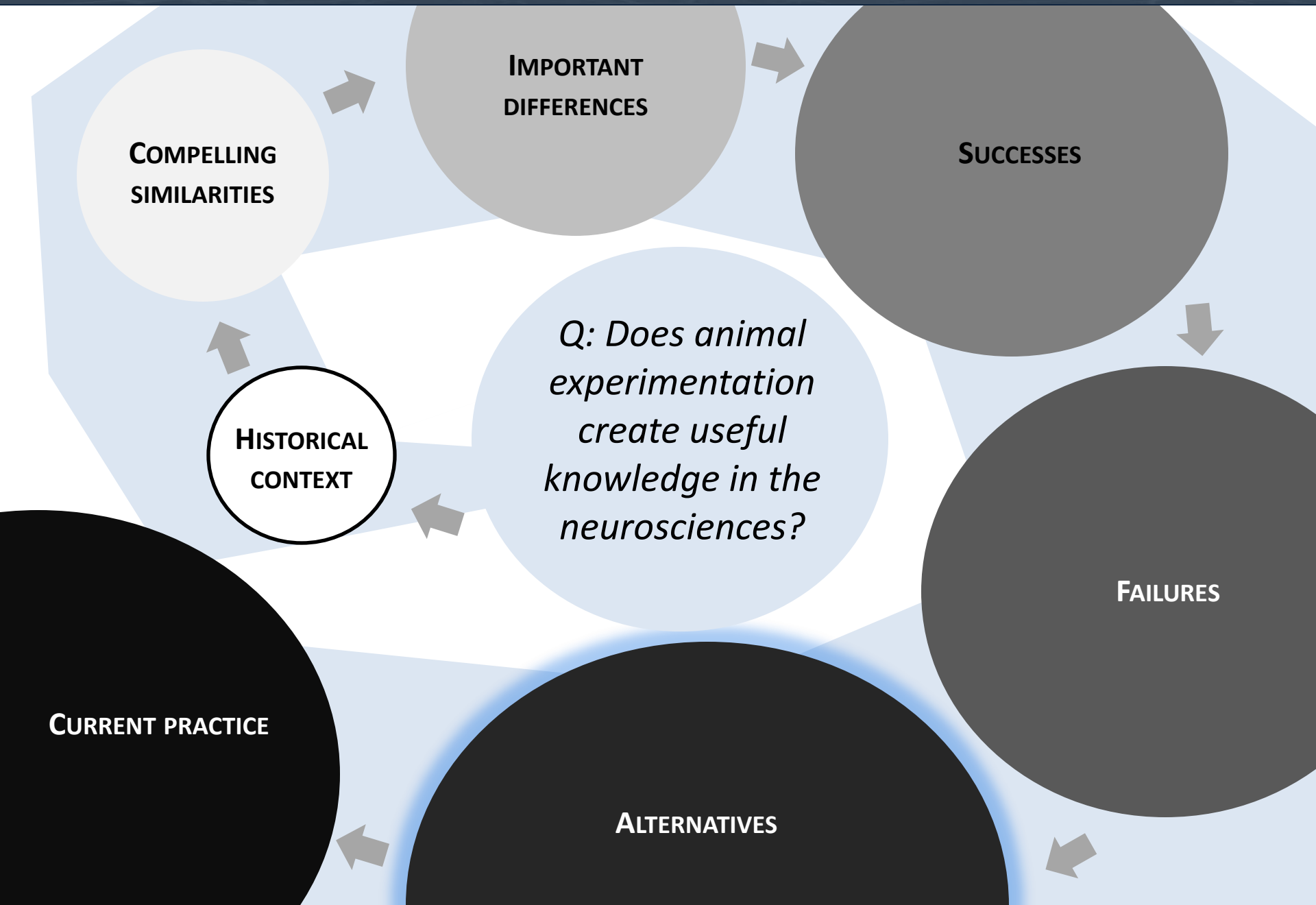
(Zahs and Ashe, 2010)

The use of animal models: Basic versus applied research?

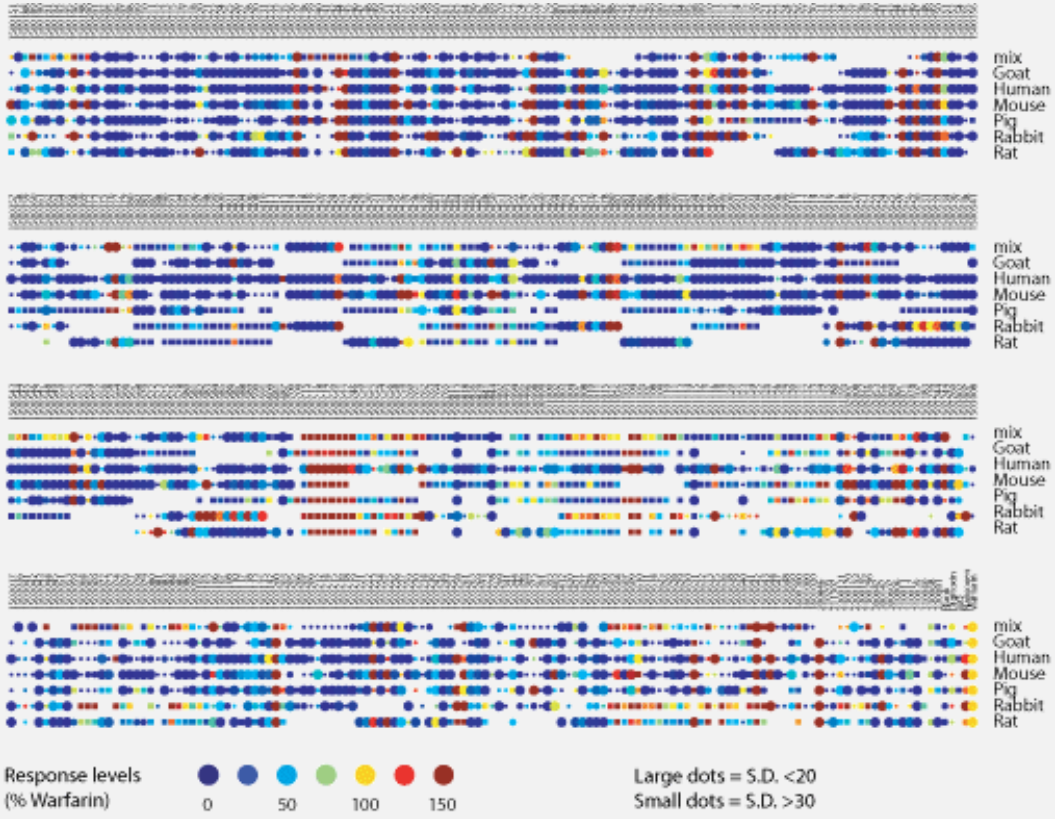
"Animal models are sometimes able to identify possible and innovative mechanisms, such as metabotropic glutamate receptor 2 agonism as a possible treatment for schizophrenia; however, they are less useful for the actual drug discovery process."

(Geerts, 2009)

Overview


Important differences
Successes
Compelling similarities
Historical context
Q: Does animal experimentation create useful knowledge in the neurosciences?
Failures
Current practice
Alternatives

In vitro models



Ligand-binding protein screening libraries

(www.biacore.com)

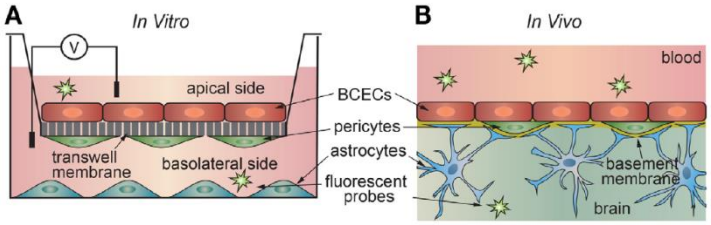
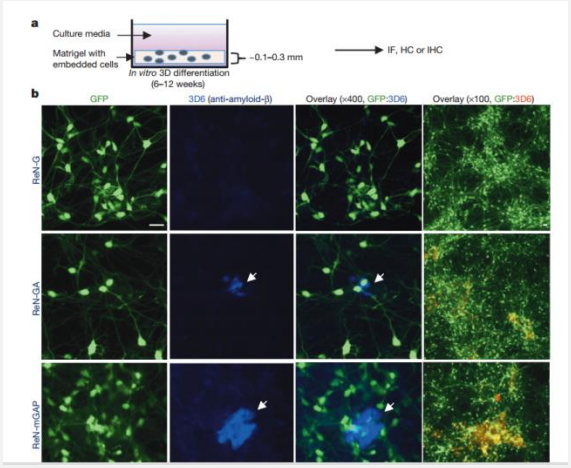


FIGURE 4 | Schematic illustration of (a) *in vitro* and (b) *in vivo* transport measurements. (A) In the 2D transwell assay, a monolayer of cells is formed on a porous membrane separating two compartments. Astrocytes and/or pericytes may be seed on the opposite side of the membrane or in the output chamber. **(B)** *In vivo* studies, a solute is injected into the blood of an animal model, and the penetration into the brain measured using a suitable chemical detection assay or imaging technique.

Blood-brain barrier (BBB) in a dish

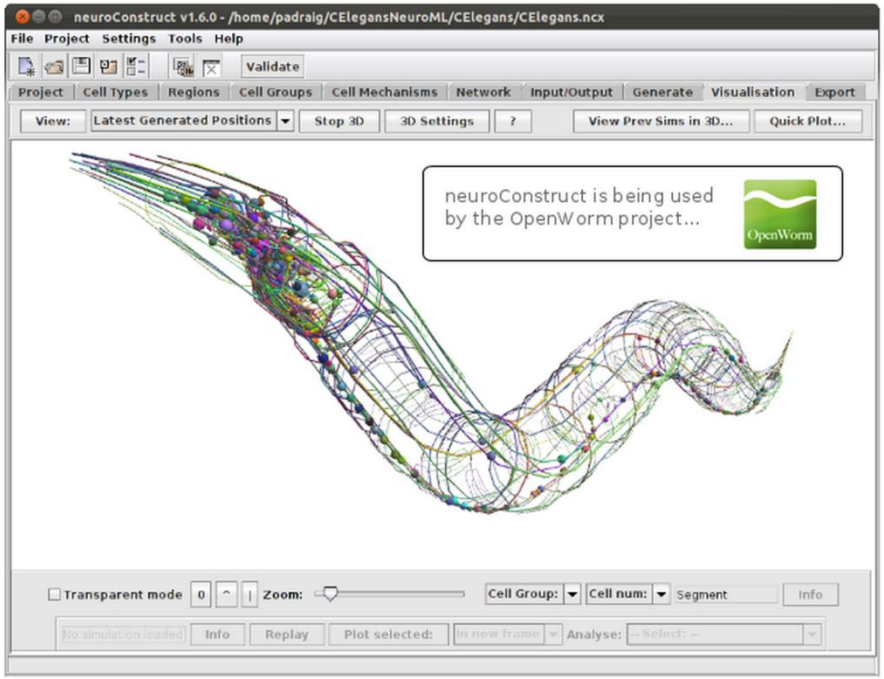
(Wong et al., 2013)



3-dimensional neuronal cultures

(Choi et al., 2014)

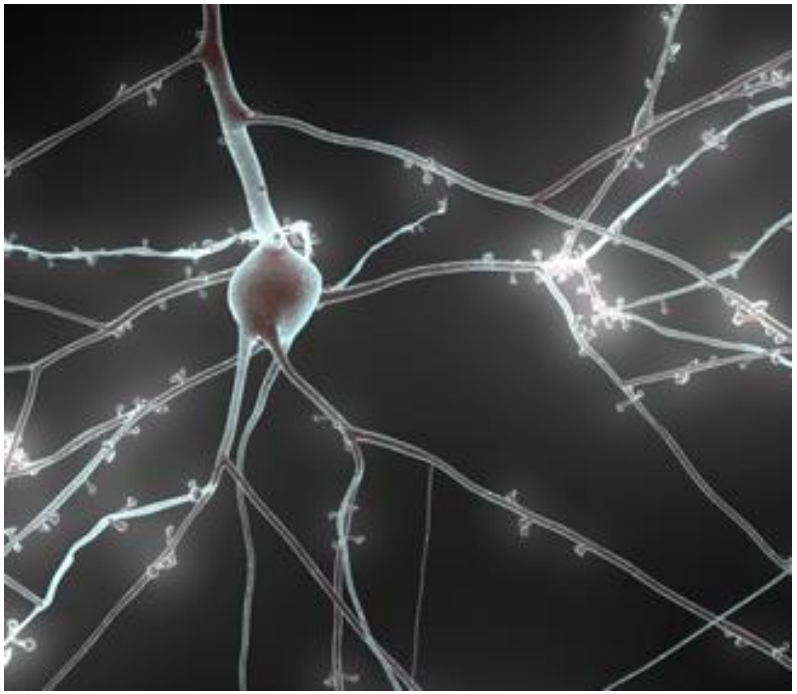
In silico models



OpenWorm project: Building a virtual worm

Already achieved complete connectome of all 302 neurons in C. elegans

(http://www.neuroconstruct.org/)



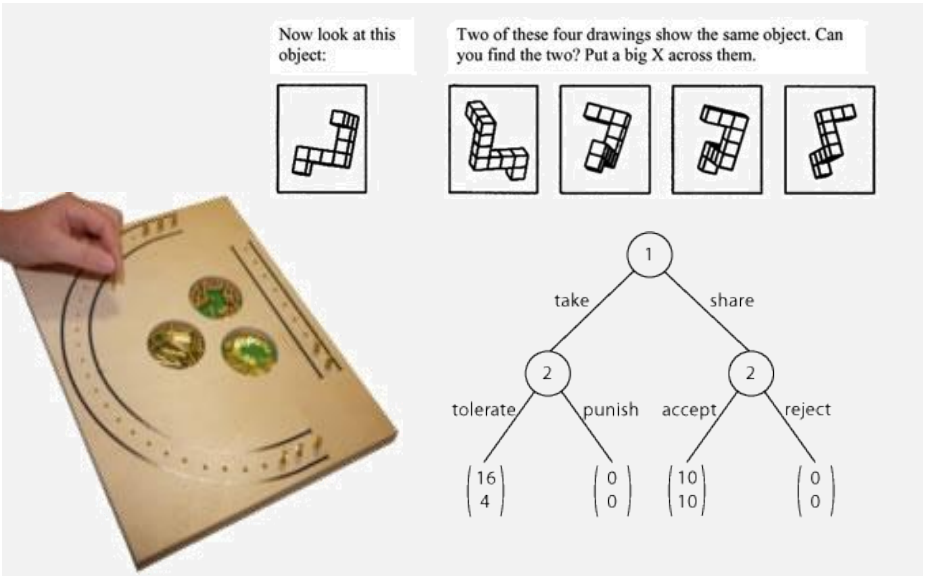
Visualization of a neuron in RTNeuron, a program created for the BBP

Blue Brain project: Modeling rat and human cortical columns

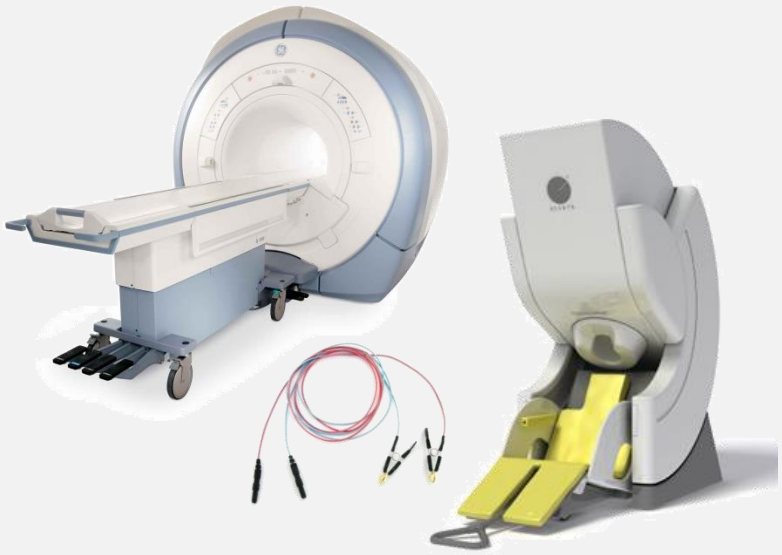
Produced 65 publications in electrical signal processing, cortical organization, neural communication, and processing efficiency maximization

(http://www.artificialbrains.com/blue-brain-project)

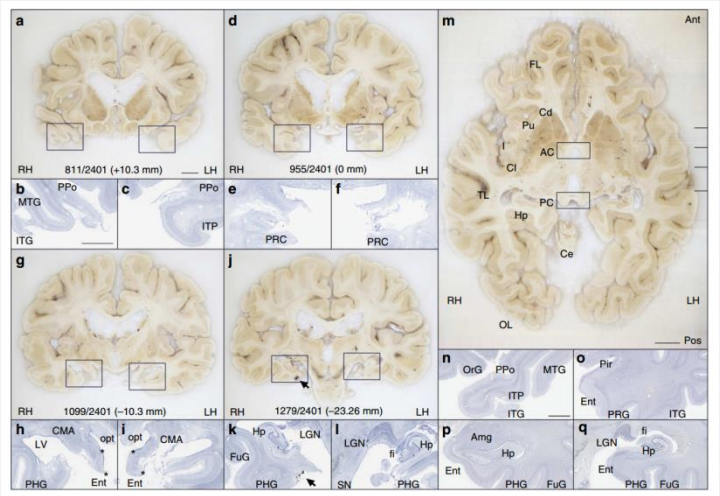
HUMAN STUDIES: BEHAVIOR, IMAGING, POST-MORTEM ANALYSIS, DRUG TRIALS



Behavioral tasks

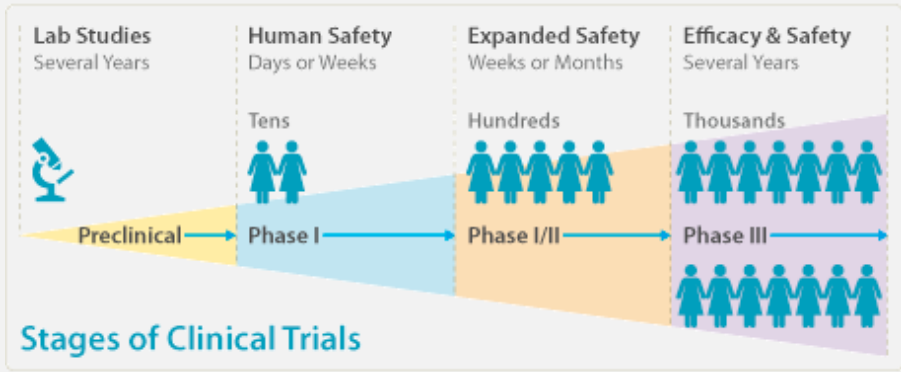


Noninvasive imaging



(Annese et al., 2014)

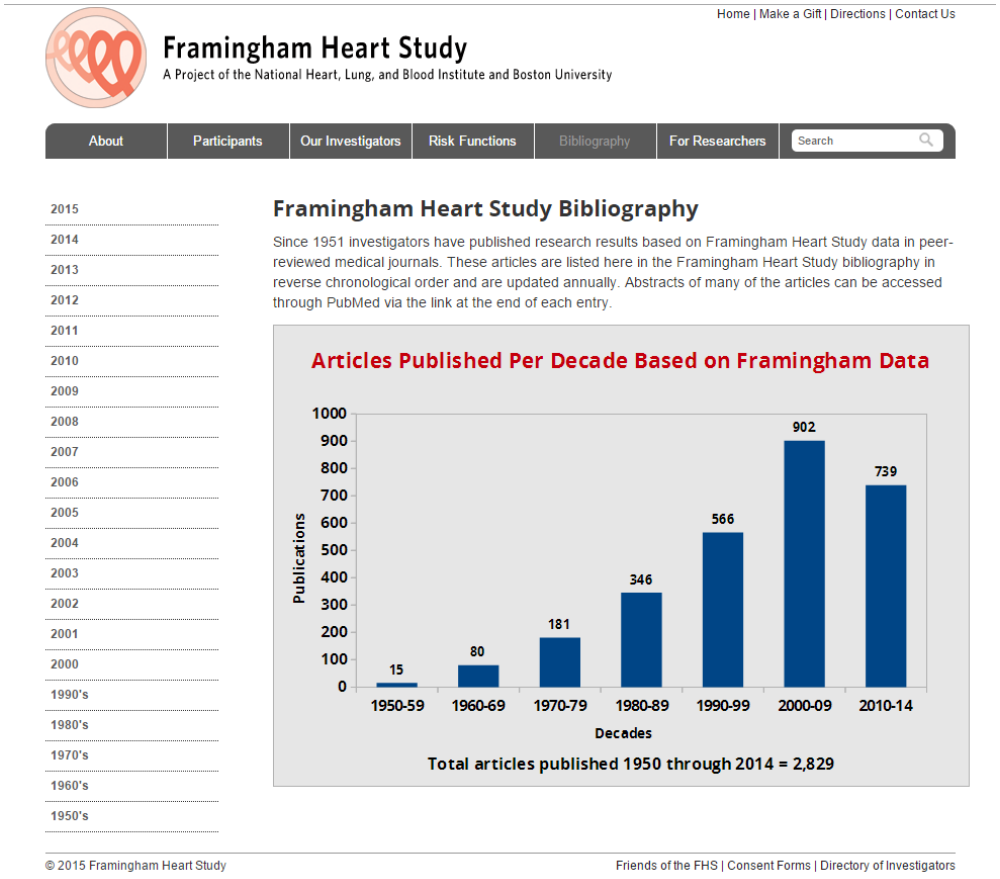
Post-mortem analysis



(http://www.ipmglobal.org/)

Drug trials

HUMAN RESEARCH: EPIDEMIOLOGICAL STUDIES

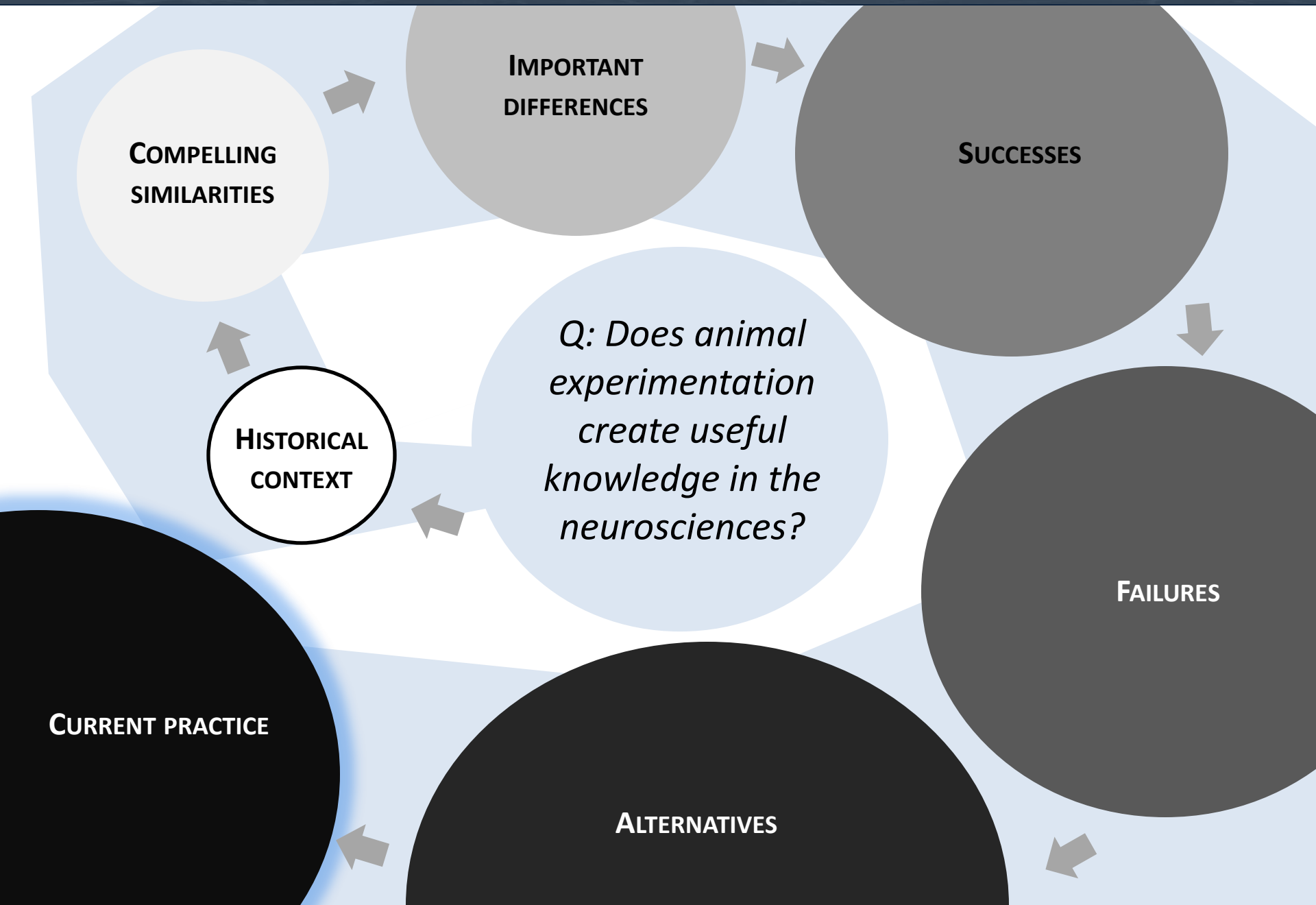


Epidemiological study begun in 1948 that has studied three generations of thousands of residents of Framingham, Massachussetts that has yielded over 1000 publications and a number of insights, including:

sleep apnea increases stroke risk • increased serum cholesterol, hypertension, and ECG abnormalities increase stroke risk • genetic risk of Alzheimer's associated with reduced hippocampal volume • common genetic variants associated with differences in subcortical brain structure • reduced risk of cardiovascular disease and mortality associated with higher circulating BDNF • neurohistological and vascular pathology associated with reduced brain regional volumes • parental longevity associated with slower declines in attention and markers of brain tissue health • higher serum BDNF may protect against dementia • And more!

https://www.framinghamheartstudy.org/fhs-bibliography/fhs-2015-bibliography.php

Overview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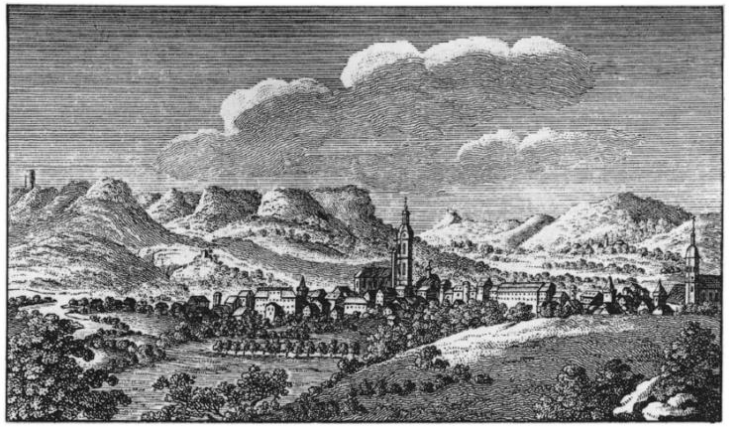
Regulation of animal experimentation: Then and now



(Finger et al., 2013)

In the 1790's Von Humboldt experimented on animals he caught in the wild.

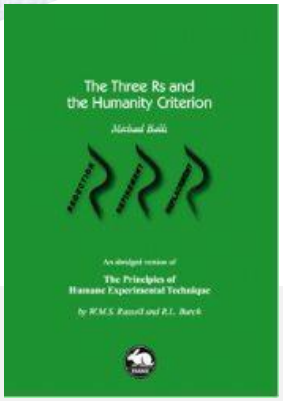
(Finger et al., 2013)

(Not Fritsch or Hitzig)

In the 1870's Fritsch and Hitzig reportedly performed brain surgery without anesthesia on their own pets.

(Gross, 2007)

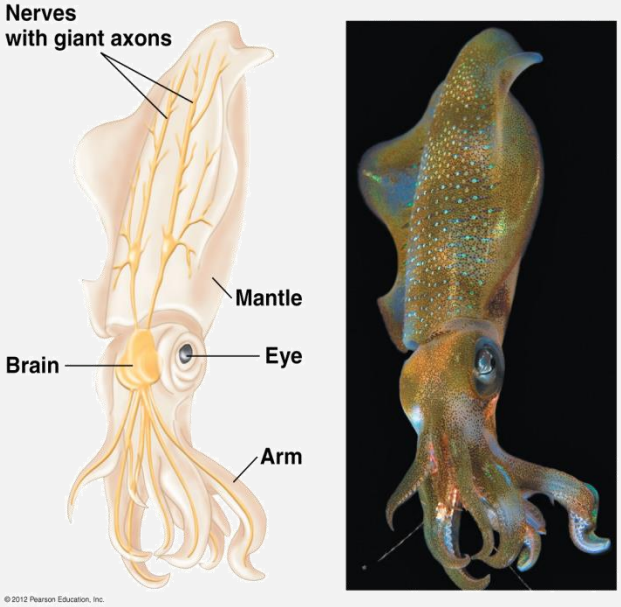
U.K. Cruelty to Animals Act (1876)
U.S. Animal Welfare Act (1966)



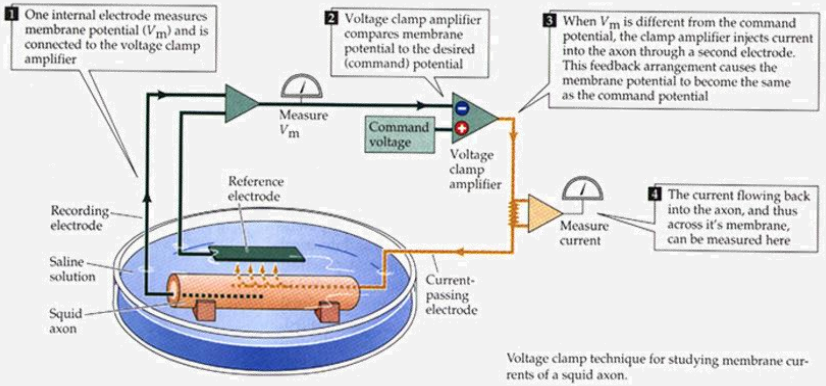
Three R's (1959)

MAXIMIZING POTENTIAL: CHOOSING THE RIGHT TOOL

Squid giant axon for nerve conduction



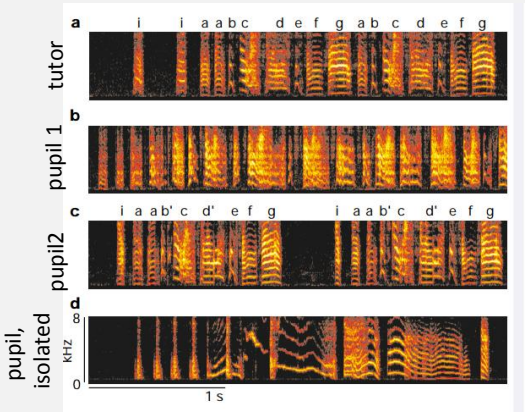
(http://www.mun.ca/biology/desmid/brian/BIOL2060/BIOL2060-13/13_02.jpg)



(http://life.nthu.edu.tw/~g864264/Neuroscience/min/Voltage.html)

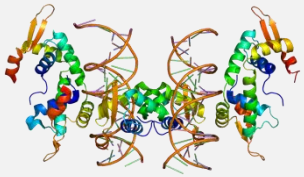
Zebra finch for genetic basis of vocal learning

(http://ofer.hunter.cuny.edu/)



(Brainard and Doupe, 2002)

Evidence of song learning

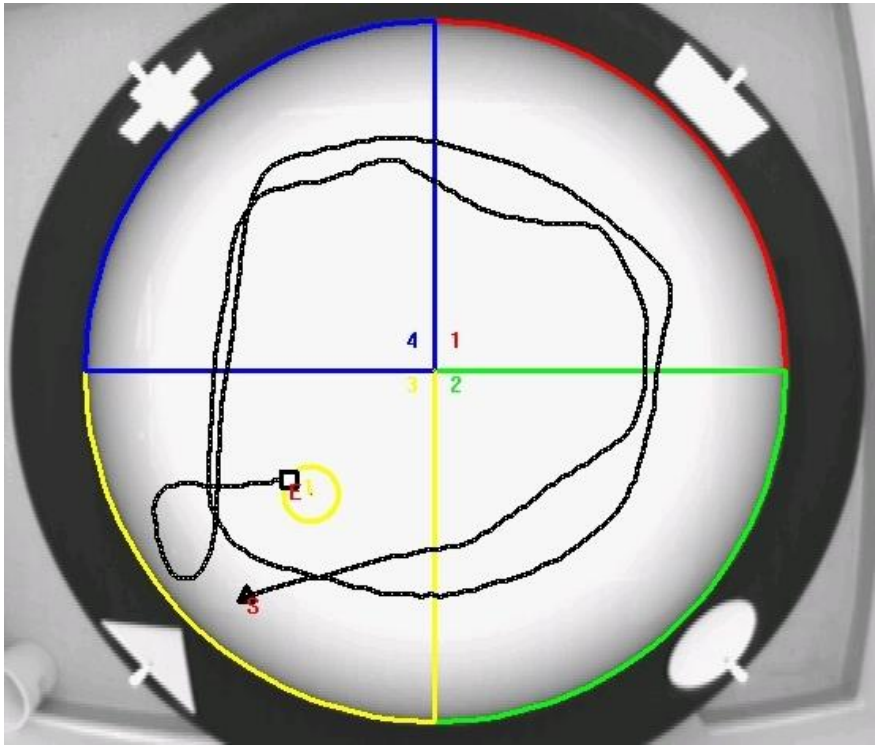


FoxP2

FoxP2 sequence identity

Maximizing potential: Designing valid tests

Case 1: Morris Water Maze as Spatial Memory?



(http://berlinmouseclinic.org/)

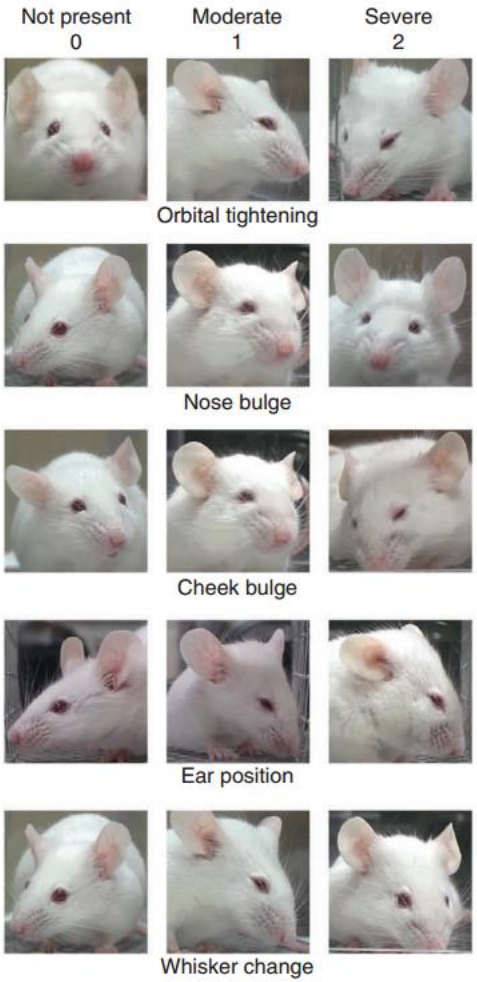
Case 2: Barbering as OCD?

(http://web.stanford.edu/~jeromeg/cgi-bin/Barbering.php)

(Garner, 2014)

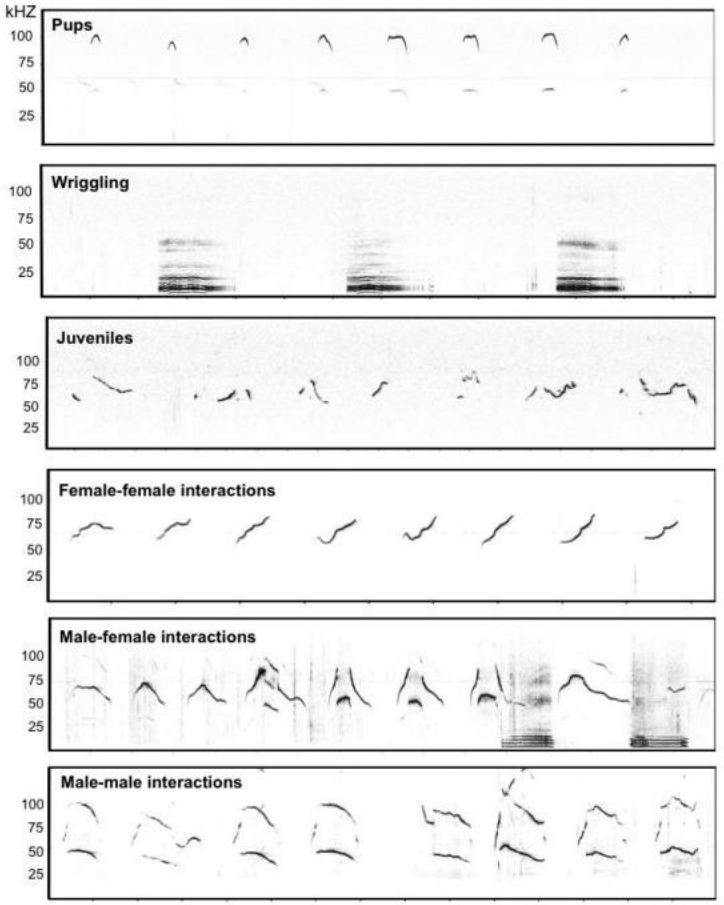
Maximizing potential: Knowing your model

Facial expressions of pain



(Langford et al., 2010)

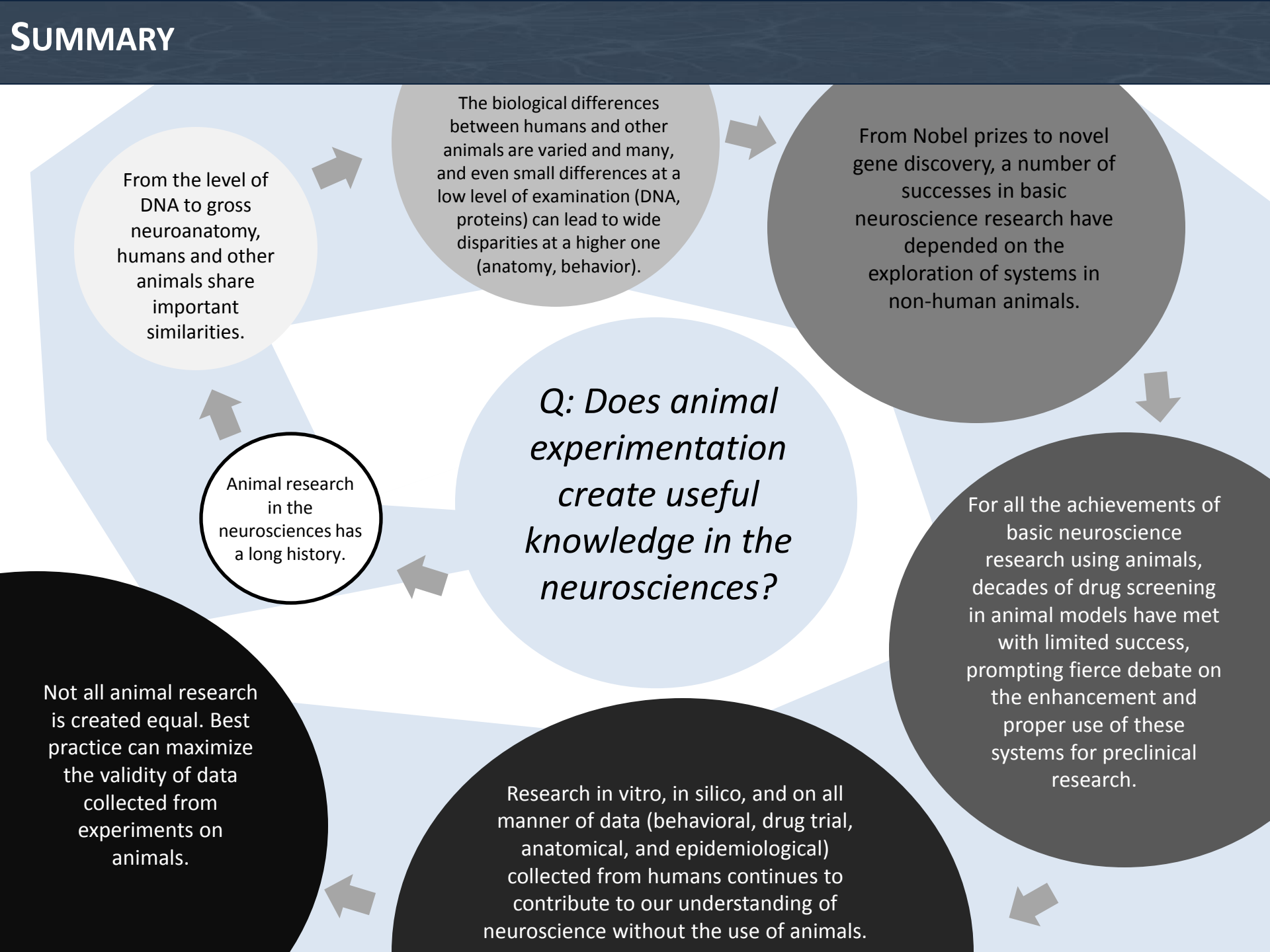
Context-specific ultrasonic vocalizations (USV)



(Lahvis et al. 2011)

As we learn more about the house mouse, we find an increasing number of means by which we might discern their emotional states.

Summary


Animal research in the neurosciences has a long history.
From the level of DNA to gross neuroanatomy, humans and other animals share important similarities.
The biological differences between humans and other animals are varied and many, and even small differences at a low level of examination (DNA, proteins) can lead to wide disparities at a higher one (anatomy, behavior).
From Nobel prizes to novel gene discovery, a number of successes in basic neuroscience research have depended on the exploration of systems in non-human animals.
Q: Does animal experimentation create useful knowledge in the neurosciences?
For all the achievements of basic neuroscience research using animals, decades of drug screening in animal models have met with limited success, prompting fierce debate on the enhancement and proper use of these systems for preclinical research.
Research in vitro, in silico, and on all manner of data (behavioral, drug trial, anatomical, and epidemiological) collected from humans continues to contribute to our understanding of neuroscience without the use of animals.
Not all animal research is created equal. Best practice can maximize the validity of data collected from experiments on animals.

SUMMARY

A: Whether research using an animal model produces useful knowledge depends on a thorough understanding of the system, its applicability, and its limitations.

Animal research in the neurosciences has a long history.

From the level of DNA to gross neuroanatomy, humans and other animals share important similarities.

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Not all animal research is created equal. Best practice can maximize the validity of data collected from experiments on animals.

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