ANBI 139

Evolution of Human Disease

Lecture 16: Mental Disease

Pascal Gagneux

Spring 2019

Edward Munch, The Scream

The Human Brain a galaxy of its own

100 billion stars in the milky way,

more cells in your brain!

86 billion neurons and 85 billion non-neurons

The Human Brain in Numbers: A Linearly Scaled-up Primate Brain
Suzana Herculano-Houze 2009 ***Front Hum Neurosci.*** 3: 31.

100 billion stars in the milky way, more cells in your brain!

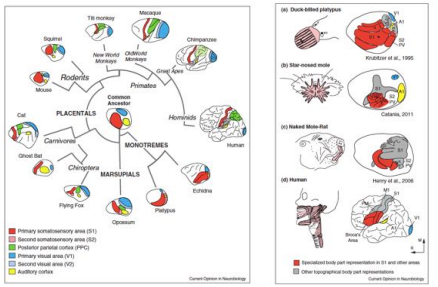
Practice question:

Why is the human brain regularly compared to our galaxy?

similar number of cells as stars in the galaxy.

Cortical area and ecological function

Size of a neural region is related to its functional significance in mammals



Krubitzer & Stolzenberg 2013

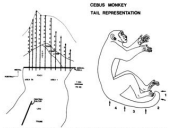
How an animal interacts with its environments (ecology) and what specialized body parts it uses is reflected in the area of the brain cortex devoted to such tasks.

By the Tail!

Muruqui, an atelid monkey of Brazil

Capuchin, a cebid monkey of S. America

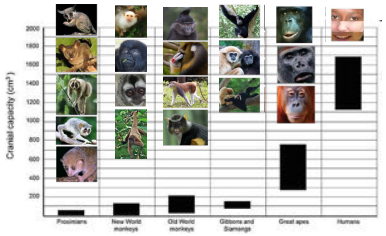
Your brain reflects your body parts and how you us them



Fellemen et al., J Brain Science 1983

Prehensile tails evolved twice, independently into groups of New World Primates. Their brain devote substantial part of their cortical “real estate” to control of the tails and sensory detection via the “fingerprint” like pad on the underside of the tail.

Absolute Brain Size

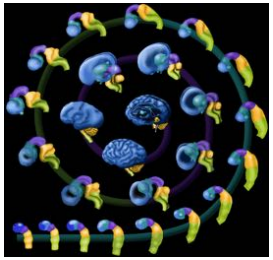


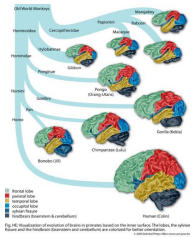
Humans have the largest brain size among primates

D. Falk, 1986

Size is not everything, cellular architecture, speed of development and wiring (connectivity between neurons) have also changed in the lineage leading to humans.

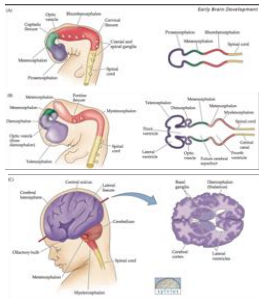
From tube to walnut





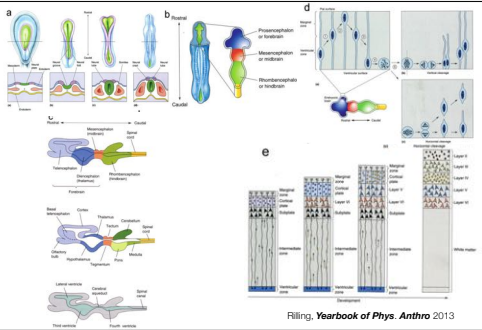
vertebrate neural development

Brain development, more views:



from front-rear alignment, to area specific growth of the cortical layers

Mechanisms of neurodevelopment



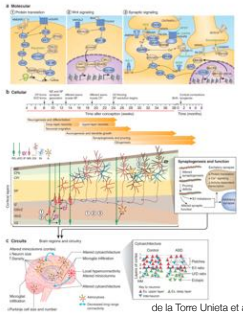
Rilling, ***Yearbook of Phys. Anthro*** 2013

(a) Formation of the neural tube, (b) development of forebrain, midbrain, and hindbrainvesicles, (c) development of major CNS divisions, (d) neurogenesis, (e) neuronal migration. [Reprinted from Bear MF et al. 2001. Neuroscience: Exploring the Brain. Pages 179–711. C 2001 with permission from Lippincott Williams and Wilkins.] Practice question:

Name three levels of organization of the brain:

molecular, cellular and cricuits

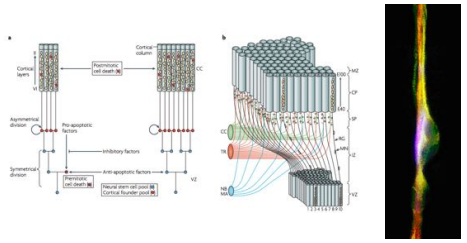
Molecular, cellular and network



de la Torre Unieta et al., ***Nature Med*** 2016

Convergent neurobiological mechanisms in ASD. Normal brain development requires the generation and positioning of the correct number and type of cells, the growth and targeting of neuronal processes, and the formation of the precise number and type of synapses. (a) These events are regulated by molecular pathways in development. Genes within these pathways for which there is genetic evidence for a link to ASD18 (Fig. 1), including from our meta-analysis of SNVs and CNVs, are colored in gold. Chemical compounds that reverse behavioral or cellular ASD phenotypes in modelsystems are indicated in green font near their predicted site of action. (b) The cellular events leading to changes in the higher-order organization of the brain, including disruption of fetal cortical development and synaptic function. The cortical laminae are depicted from early fetal to neonatal stages (not to scale). The numbers indicate the molecular pathways important at each stage of development. (c) The widespread pathology10 and functional phenotypes observed in ASD, including altered brain growth trajectories, altered cortical cytoarchitecture (red triangles indicate excitatory upper layer neurons; green triangles are excitatory deep-layer neurons; blue triangles are interneurons; numbers indicate cortical layers; WM, white matter) and connectivity, may arise from combined deficits in neurogenesis, cell fate, neuronal migration and morphogenesis during fetal development and dysregulated synaptic function, possibly in combination with reactive microglia infiltration and astrocytosis. RG, radial glia; oRG, outer radial glia; IP, intermediate progenitor; MN, de la Torre-Ubieta et al. migrating neuron; EN, excitatory neuron; IN, interneuron; A, astrocyte; E/I, excitatory orinhibitory neuron; U/D, upper-layer or deep-layer neuron. MPEP, 2-methyl-6-(phenylethynyl)-pyridine; CDPPB, 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide; DCS, D-cycloserine; IGF1, insulin-like growth factor 1. VZ, ventricular zone; ISVZ, inner subventricular zone; OSVZ, outer subventricular zone; IZ, intermediate zone; SP, subplate; CPi, inner cortical plate; CPo, outer cortical plate; MZ, marginal zone

Building a Cortex



Rakic, P 2009 ***Nature Rev Neurosciences***

radial unit lineage model of cortical neurogenesis. a | Based on the radial unit hypothesis. the model illustrates how changes in the mode and the rates of cell proliferation and/or programmed cell death within the neural stem cell pool (blue circles) in the ventricular zone (VZ) that divide symmetrically at early embryonic stages causes an exponential increase in the number of radial columns, which, in turn, results in surface expansion of the cerebral cortex without changes in its thickness. By contrast, similar changes in proliferation kinetics occurring in the founder cells (red circles), which divide asymmetrically, cause a linear increase in the number of neurons within radial columns without a change in the cortical surface area. b | The model of radial neuronal migration that underlies columnar organization based on. The cohorts of neurons generated in the VZ traverse the intermediate zone (IZ) and subplate zone (SP) containing 'waiting' afferents from several sources (cortico-cortical connections (CC), thalamic radiation (TR), nucleus basalis (NB), monoamine subcortical centers (MA)) and finally pass through the earlier generated deep layers before settling in at the interface between the cortical plate (CP) and marginal zone (MZ). The timing of neurogenesis (E40–E100) refers to the embryonic age in the macaque monkey. The positional information of the neurons in the VZ and corresponding protomap within the SP and CP is preserved during cortical expansion by transient radial glial scaffolding. Further details can be viewed in the Rakic laboratory animated video of radial migration. RG, radial glia cell; MN, migrating neuron.

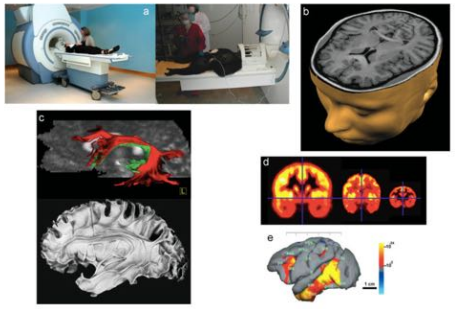
Imaging techniques

TABLE 1. Summary of neuroimaging methods

Technique	Example	Purpose	Advantages	Disadvantages
MRI		Anatomical image of gray matter, white matter, and CSF	Can be conducted on anesthetized subjects	Microscopic (cellular) features not visible
DTI		Reconstruction of white matter fiber tracts – imaging anatomical connectivity	Can be conducted on anesthetized subjects	Cannot track individual axons because of limited spatial resolution, cannot discriminate origin from termination of pathways
PET		Imaging brain function (glucose metabolism or blood flow) and receptor density and distribution	^{18}F-FDG PET enables functional imaging without restraint, outside the scanner	Limited temporal resolution (on the order of minutes), involves the administration of radioactive tracers, ^{15}O water PET requires immobilization of awake animals, dependent on access to cyclotron
fMRI		Imaging brain function (blood flow)	Good temporal resolution (seconds), tracer administration not required	Loud, confining environment, requires immobilization of awake animals

Rilling, ***Yearbook of Phys. Anthro*** 2013

Imaging of brain activity allows to correlate certain areas of neuronal activity with cognitive tasks during (fMRI) or briefly after (PET) and activity. There are still many issues with temporal and spatial resolution….the signals still reflect the activity of millions of cells, rather than that of particular circuits.



Rilling, Yearbook of Phys. Intro 2013

Structural neuroimaging.

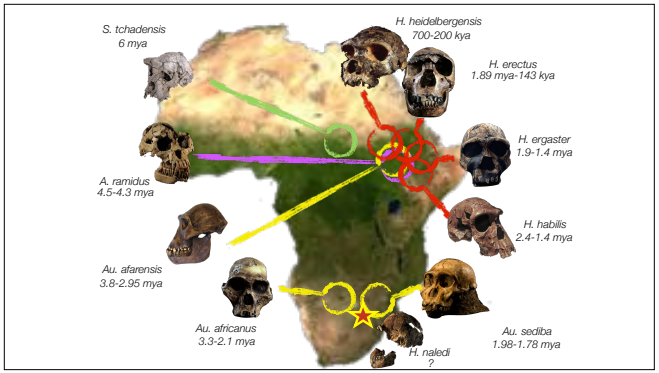
(a) MRI scanner with human (left) and chimpanzee (right) subject,

(b) (b) axial section through human T1-weighted MRI scan,

(c) DTI-based reconstruction of the human arcuate fasciculus pathway (top) and postmortem equivalent (bottom),

(d) 18F-FDG PET images from human (left), chimpanzee (middle), and rhesus macaque (right), brighter colors (yellow to white) indicate higher levels of radioactivity and glucose metabolism.

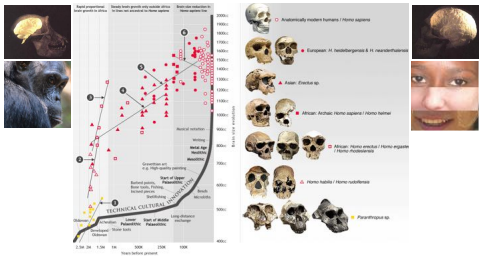
(e) fMRI activations related to object processing in awake rhesus macaque. Colored areas are more active when processing intact compared with scrambled objects. Activation is particularly strong in the ventral temporal cortex, the presumed location of the macaque object recognition or "what" pathway. [(a) Left, from:
http://www.epilepsynse.org.uk/media/pics/piclibrary/3T2_high.jpg; right, personal photograph. (e) Reprinted from Tsao DY, et al. 2003. Faces and objects in macaque cerebral cortex. Nature Neuroscience 6:989–95. C 2003



Hominid fossil skulls dating 6 million years back from chimpanzee size brains in genus *Australopithecus* to triple that in the genus *Homo*.

Brain expansion over time

Driven by culture and/or driving culture?



Bradshaw Foundation adapted from Steven Oppenheimer, 2012 Out of Eden

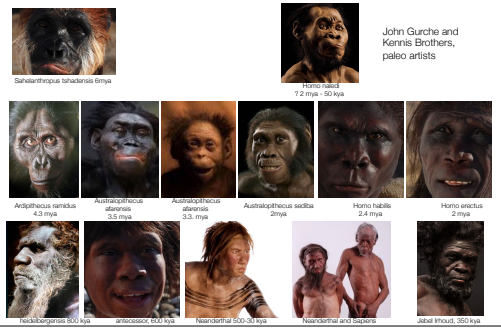
How we went from an ancestor with a chimp sized 400 cc brain to a modern 1500cc brain and the technology accompanying, driving?

Practice question:

Did bipedalism cause brain enlargement in our ancestors?

Not directly, our lineage became bipedal 4 million years prior to massive brain enlargement.

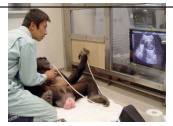
Meet the ancestors and extinct relatives



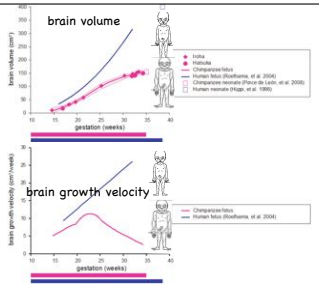
We have no way of knowing how prevalent mental disease was among our distant ancestors.

The Jebel Irhoud male at bottom right is from the site with a 300 ky and is considered by some to represent a modern human

How to grow a big brain



Satoshi Hirata



Sakai et al. **Current Biology**, 2012

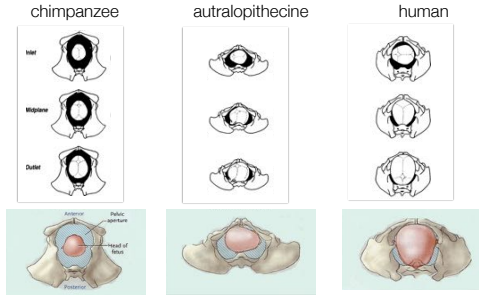
Gestational age-related changes in brain volume in chimpanzee (Hatsuka and Iroha) and human fetuses.Gestational age-related changes in the growth velocity of brain volume in chimpanzee and human fetuses

Practice question:

How do humans manage to grow a brain thee times larger than that of a chimpanzee?

Steady growth rate throughout pregnancy and continued fetal rate of growth form first year after birth.

Obstetrics: birthing a big-brained baby



The obstetric dilemma: adaptation of the human pelvis of bipedality clash with the need for birthing a large brained baby. Prolonged problems with delivery when the baby has to switch from umbilical chord oxygen delivery to lung air breathing can curtail the oxygen supply to the brain and cause cerebral palsy.

Practice question:

What is cephalon-pelvic disproportion?

The mismatch between a baby's head and the pelvic outlet of the mother.

Growth schedule

- Delayed maturation allows increased transmission of behavior and concepts.
- Human minds are effective copying devices and idea generators.
- Language is one of the major target of imitation and idea transmission.
- Increased chances of maintaining key innovations.
- Delayed development: biological assimilation of culture?

minds as copying machines and idea generators

Practice question:

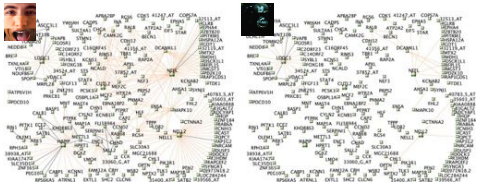
What is one of the worst things that can happen to the brain of a developing child?

Poverty, malnutrition (usually follows from poverty), abuse (very often coincides with poverty)

trauma..

Brain Expression Networks in Humans and Chimpanzees
6 regions in 3 humans and 3 chimps
4000 genes each
Gene networks between 300 pairs of genes
Some unique pairwise expression patterns in humans

Fig. 3. Module visualization identifies hub genes and human-specific connections



Oldham, Michael C. et al. (2006) ***Proc. Natl. Acad. Sci. USA*** , Geschwind Group, UCLA

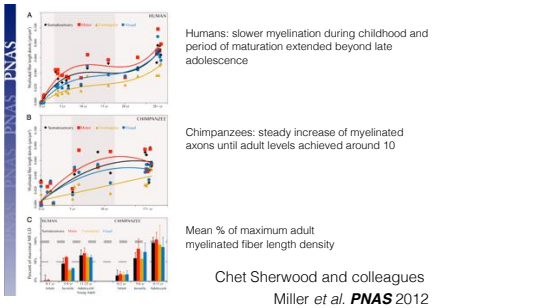
Changes in entire gene networks are more pronounced than massive changes in just one or few genes. Humans have altered their primate brain with the help of some key mutations, but probably more so with re-orchestrating the "choreography" of which sets of genes changed their expression patterns to from novel co-expressed gene networks.

Practice question:

How can human brains be so different from chimpanzee brain s when both express very similar genes?

Humans and chimpanzees express entire networks of genes in different combinations.

Prolonged myelination in human neocortical evolution



Humans: slower myelination during childhood and period of maturation extended beyond late adolescence

Chimpanzees: steady increase of myelinated axons until adult levels achieved around 10

Mean % of maximum adult myelinated fiber length density

Chet Sherwood and colleagues

Miller *et al.* ***PNAS*** 2012

Developmental trajectory of myelinated fiber length density (MFLD). Graphs show best-fit curves for MFLD data in humans (A;n=24) and chimpanzees (B;n=20) arranged by age in years. The shaded vertical area represents time between weaning and full sexual maturation. Diamonds represent somatosensory area (area 3b), squares represent motor area (area 4), triangles represent frontopolar area (area 10), and circles represent visual area (area 18). (C) Bar graph depicts mean percent of maximum mature adult MFLD across development in humans (Left) and chimpanzees (Right). Error bars represent SEM. The thin and thick horizontal dashed lines represent 50% and 100%, respectively, of maximum MFLD. Black represents somatosensory area (area 3b), red represents motor area (area 4), gold represents frontopolar area (area 10), and blue represents visual area (area 18).

Practice question:

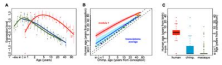
What is the major difference in myelination of human and chimpanzee neurons?

Timing: human brains become fully myelinated in the third decade, chimpanzees at age ten.

Extension of cortical synaptic development

gene expression in two cortical areas of chimps, humans and monkeys

Time shift in expression of "module 1" genes



Synaptic density changes.

5 major human specific gene expression modules found in PFC.

Key player: Transcrition Factor MEF2A

Positively selected since divergence from Neanderthal

Liu *et al* 2012 ***Genome Research***

Phillip Khaitovich

Figure 1. Age-related gene expression change in the PFC and CBC. (A) Age distribution of samples used in this study. Each point represents an individual, with technical replicates shown as a second point below the
first. Only one of the two replicates was used in the main analysis. The colors indicate brain regions (red, PFC; gray, CBC). The x-axis represents individual age in fourth root (age1/4) scale. Numbers of age-related genes (B) and genes with species-specific expression profiles (C) identified in the PFC (red) or CBC (gray). The red arrows highlight excess human-specific
expression changes in the PFC. Figure 7. Synaptic density changes during human, chimpanzee, and macaque PFC development. (A) Example of synapses viewed by electron microscopy (red arrows), in the PFC of a 32-d-old chimpanzee.
(B)Mean synaptic density per 100 mm2 measured in the PFC of humans (red), chimpanzees (blue), and rhesus macaques (green) at different ages. (Error bars) 95% confidence intervals obtained by bootstrapping synaptic density values within samples 1000 times. Independent assessment of synaptic density by another investigator is plotted on Supplemental Figure S11. (C) Mean synaptic density in macaque per 100 mm2 and in human per 100 mm3 measured in previous studies (Rakic et al. 1986; Huttenlocher and Dabholkar 1997). (D) Statistical analysis of synaptic density in three age groups. The distribution ofmean synaptic density from samples within each age group is shown in a boxplot.Within the age range of 0–2 mo, PFC synaptic density in humans is significantly lower than in both chimpanzees and macaques (one-sided Wilcoxon test, P = 0.016 in human–chimpanzee comparison and P = 0.018 in human–macaque comparison), while there was no significant synaptic density difference between chimpanzees and macaques (P > 0.1). Sample numbers were not sufficient to estimate statistical significance in the other two age intervals.
Figure 8. Signature of recent positive selection upstream of the MEF2A gene. (A) The phylogenetic relationship of human, Neanderthal, chimpanzee, and rhesusmacaque species. (Red arrow) Human lineage. The numbers show approximate divergence time inmillions of years (Kumar and Hedges 1998; Païa'bo 1999; Chen and Li 2001). (B) Proportion of human-derived SNPs measured using a 50-kb slidingwindow in the MEF2A gene region (red). SNPs were classified as derived according to the method described by Green et al. (2010). (Gray dashed line) Genome average. (Red arrow) Location, upstream of MEF2A, with significant excess of human-derived SNPs (one-sided Fisher's exact test, P = 0.00006). (C) Distribution of the proportion of human-derived SNPs for all windows across the human genome. (Red arrow) Probability of finding the observed proportion of human-derived SNPs in the location 50–100 kb upstream of MEF2A, estimated from the genome distribution.

Insults to brain development:

Causes of mental disease often combine genetic and environmental factors, both during development and adult life.

Practice question:

Apart from genetic accidents, malnutrition, social insults and infection, what other factor can dramatically derail normal brain development?

Toxins such as lead paint or mercury poisoning, or alcohol poisoning via a drinking mother.

Mental Illness

http://www.psychiatrictimes.com/cultural-psychiatry/improving-mental-health-care-america-opportunity-comprehensive-reform

The cost and human tragedy of untreated mental illness

Crazy?

mwendawazimu
τρελός
気違い
fou
狂风
pazzo
nut
Schpinner
loco
verrückt

mwendawazium: the one who follows delusions (Swahili)
fou:(French, from Latin for fickle, wind)
nut: crazy (English)
loco: crazy (Spanish, from Andalusian Arabic)
狂风: kuang feng: crazy “feng= wind” (Chinese)

気違い: kichigai “different Ki” (Japanese)

Schpinner: “the one who spins fabric at a loom (Swiss German)
verrückt: “removed, yanked away” (German)
pazzo: crazy (Italian)
τρελός: trelos, crazy (Greek)

Mad Genius?

Aristotle once said, “no great mind has ever existed without a touch of madness,”

Individual with more creativity are at higher risk for schizophrenia

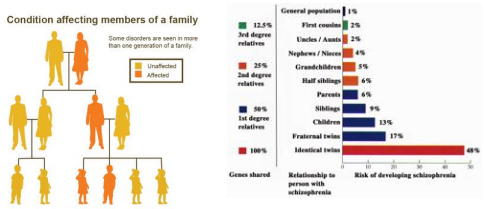
Power et al. Kari Stefanson.Polygenic risk scores for schizophrenia and bipolar disorder predict creativity, ***Nature Neuroscience*** 2015

Kyaga et al.Mental illness, suicide and creativity: 40-year prospective total population study. 2013. ***J. Psychiatry. res.***

Kyaga S et al. (2011): Creativity and mental disorder: family study of 300,000 people with severe mental disorder. ***British Journal of Psychiatry*** 199:373-379.

A large number of studies have documented the link between creativity and risk for mental disorder

Inheritance of psychiatric conditions



Gottesman 1991

Mental disorder runs in families, but how strong is the influence of your heritage? Even identical twins only have a 50% chance of sharing a diagnosis of schizophrenia.

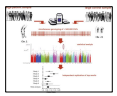
Practice question:

What is the chance of identical twins both suffering fro schizophrenia?

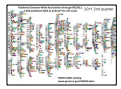
50%!

Genomics Studies of Mental Disorders

Genome-Wide Association Studies (GWAS) test each common variant in the genome for a statistical relationship with a trait of interest.



They have been performed for 100’s of traits and revealed 1000’s of associations [including many brain and cognitive traits].



The associations explain only a small proportion of the disorders studied.

Genome wide association studies: Now routinely carried out on thousands of genomes. Fail to find small number of genes with large effects, BUT highlight hundreds of genetic variants with small effects. This is referred to as missing heritability.

Practice question:

What does the acronym GWAS in genetics stand for?

genome wide association study.

Summary of genetic analyses performed on 13 psychiatric disorders

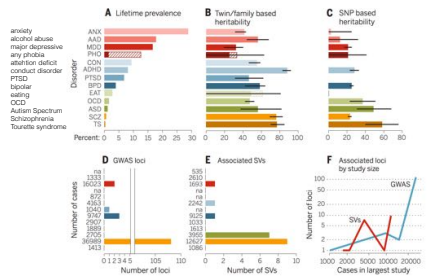


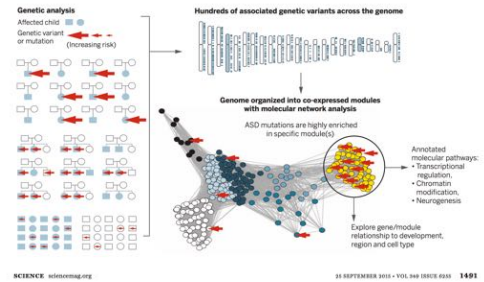
Fig. 1. Summary of genetic analyses performed on 13 psychiatric disorders. (A) Highest lifetime (point for ASD) prevalence in percentages. The discontinuous bar in phobias represents the range in different forms. (B) Heritability estimates; bars, standard error (SE). (C) SNP-based heritability estimates; bars, SE. (D) Number of genome-wide significant loci.The x axis is discontinuous because of the large difference of associated loci between disorders. (E) The number of associated structural variants (SVs include copy number variation and chromosomal changes) that either reach genome-wide significance or have been replicated with $P \leq 0.01$ in another study. (F) The y axis shows associated GWAS loci (blue) and SVs (green) by the number of cases (x axis) in the largest study for that disorder. The number of cases in the largest study for GWAS (D) and SV studies (E) is reported next to each disorder..The order of disorders and their color coding are maintained throughout the bar plots. SNPs are single nucleotide polymorphisms.

Practice question:

What is the most common psychiatric disorder in the USA?

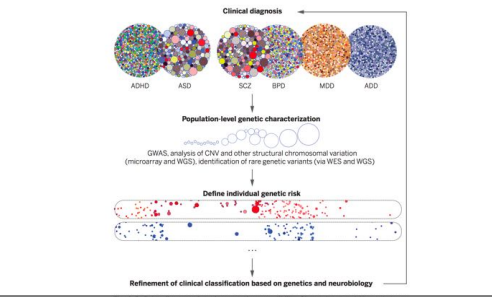
Anxiety disorder.

Heterogeneous genetic risk factors converge in biological networks



Heterogeneous genetic risk factors converge in biological networks. Different study designs, such as trios, multiplex affected families, or case-control (shown at far left) identify different forms of genetic risk in cases(the arrow size indicates the relative effect size). By integrating these data with biological network data, one can assess in a genome-wide manner whether disease-associated risk variants are enriched in specific biological networks. Here, for illustration, we depict rare de novo variants associated with ASD, enriched in the yellow module.The function of this module of co-regulated genes can be further annotated using gene ontology, which implicates these large effect ASD-associated variants in chromatin remodeling, transcriptional regulation, and neurogenesis. Networks can be subsequently mapped onto developmental time points, brain regions, circuits, or cells.

Refining diagnoses based on genetic susceptibility



Refining diagnoses based on genetic susceptibility. Clinical disorders (abbreviations are as in Fig. 1) and their overlap, represented by the big circles.The smaller dots within each circle represent contributing genetic or environmental risk factors. Once genetic risk is defined in population studies, it can be used to define factors underlying disease risk in individuals, identifying distinct (or overlapping) entities, two of which are represented by the elongated ovals at the bottom, grounded in causal mechanistic understanding. These subtypes should more clearly inform prognosis and treatment than do current categorical disease entities. The sizes of the dots within the circles represent the relative effect sizes of variants

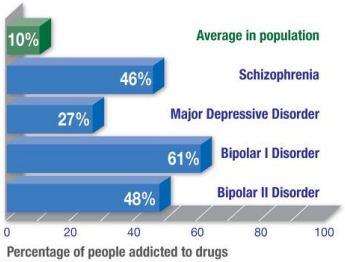
Drugging the Mind

1 in six US citizens take psychiatric drugs.
85% of them take them long-term. Market is worth over 70 billion $.

The most commonly used type of drug was an antidepressant like Zoloft and Celexa, followed by an anti-anxiety or sleeping pill like Xanax and Ambien. All of these drugs can have withdrawal effects, including panic attacks and sleep problems, for many people on them long term.

NYT

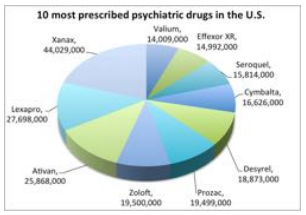
Dual Diagnosis

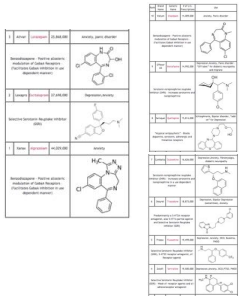


http://learn.genetics.utah.edu/content/addiction/mentalillness/

Mental illness and drug addiction often occur together. This condition of dual diagnosis presents a challenge to physicians. The patient has two brain diseases that influence one another, and which both need treatment.

Top ten psychiatric drugs





IMS Institute for Healthcare Informatics in 2009

Mostly used to treat anxiety and depression

Over drugging the Mind?

In 2006, the US, with 6% of the world's population, bought about 2/3 of the world's psychiatric drugs.

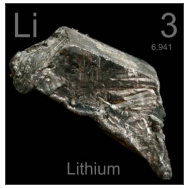
Practice question:

What fraction of the world's psychiatric drugs are consumed by the US (6% of global population)?

2/3!

Serendipity in discovery of drugs

Lithium to treat Mania/depression



Cade J.FJ, 1949 Lithium salts in the treatment of excitement. ***Medical Journal of Australia***

Many block buster psychiatric drugs were discover by sheer accident.

Their precise mechanisms of action are still poorly understood.

Cannabinoid Receptors

Mammals have an endocannabinoid system:
Your body produces two different endocannabinoids (anandamide and 2-arachidonylglycerol) that activate two different cannabinoid receptors:
CNR_1 expressed mainly in neurons in the brain and
CNR_2 expressed on the immune system including microglia cells in the brain.

Both receptors are stimulated by the main compound THC in the plant *Cannabis sativa* also known as pot.

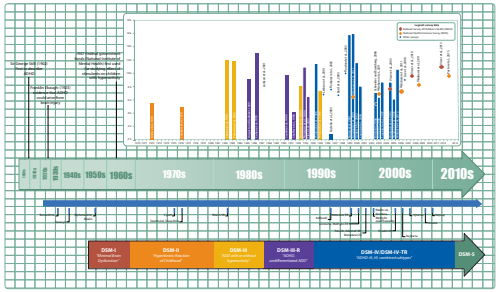
The endocannabinoid system is involved in memory and mood and appears to be one of the bridges between the brain and the immune system, providing a mechanisms by which mood can influence your immune status and vice versa.

Practice question:

What are endocannabinoids?

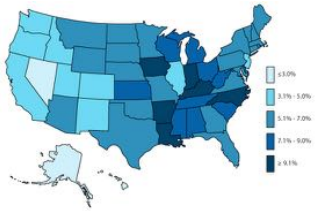
Molecules made by the human body that signal through cannabinoid receptors and affect immune and brain functions.

ADHD Timeline



Change in the diagnosis of attention deficit hyperactivity disorder. Old diseases disappear, new ones are defined…..

Medication of ADHD



Percent of Youth Aged 4-17 Years Currently Taking Medication for ADHD by State: National Survey of Children's Health

Almost 10% of kids drugged!

What Psychoanalysis?

International Psychoanalytic Congress. Photograph, 1911. Freud and Jung in the center

Sigmund Freud, Carl Jung, Jacques Lacan etc….

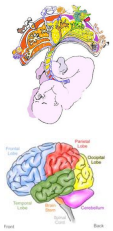
The influence of psychoanalysis lingers in the social sciences, but is remarkably absent in neuroscience.

Cognitive Behavioral Therapy

Talk and cognitive behavioral therapy remain important ways of managing mental disorders.

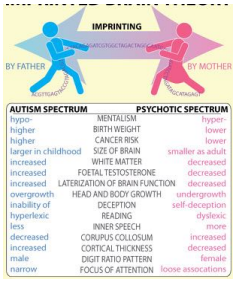
IMPRINTED GENE EXPRESSION IN DIFFERENT TISSUES

- About 100 imprinted genes are known (possibly many more)
- Primary site of imprinted-gene expression is the (social) placenta, which mediates the transfer of resources between mother and child.
- Small deviations in placental function can benefit the child, or the mother.
- Large deviations are costly to both.
- The second-most important site of imprinted gene expression is the (social) brain.



Imbalances of sex-specific genetic imprinting in the brain may underlie many mental conditions.

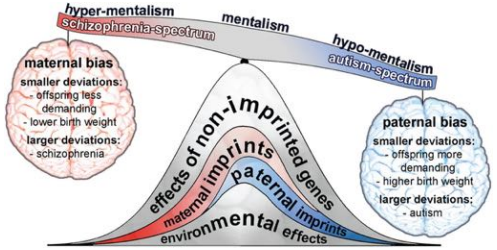
Sexually imprinted brain theory



Simon Baron Cohen, Bernard Crespi and colleagues

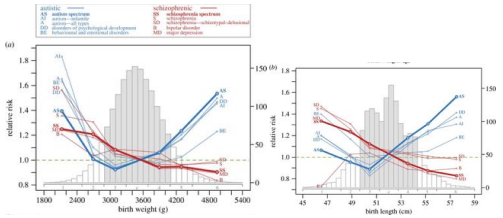
The extreme male or female brain hypothesis for mental diseases

Extreme female or male brain?



Opposite risk patterns for autism and schizophrenia are associated with normal variation in birth size: phenotypic support for hypothesized diametric gene-dosage effects
Sean G. Byars, Stephen C. Stearns, Jacobus J. Boomsma 2014 ***Proc R Soc B***

Risk of AS and SS disorders by birth weight and birth length



Opposite risk patterns for autism and schizophrenia are associated with normal variation in birth size: phenotypic support for hypothesized diametric gene-dosage effects
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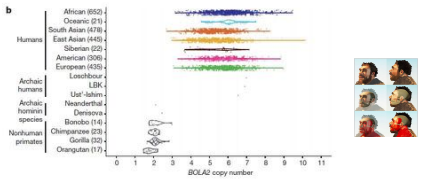
Risk of AS and SS disorders by birth weight (a) and birth length (b). Points show relative risks (RRs) obtained from Cox regression for each disorder (see the electronic supplementary material, table S4, for corresponding risk ratios, confidence intervals and p-values). Risk for other disorders related to AS and SS are also shown. Grey histogram bars represent the majority of birth data within approximately ±1 s.d. of the mean, including groups 3 (2891–3290 g or 49.7–51.2 cm), central (3291–3690 g or 51.3–52.7 cm) and 4 (3691–4090 g or 52.8–54.3 cm). Smaller babies beyond ±1 s.d. included groups 1 (1850–2490 g or 45–48.0 cm) and 2 (2491–2890 g or 48.1–49.6 cm). Larger babies included groups 5 (4091–4490 g or 54.4–55.9 cm) and 6 (4491–5400 g or 56.0–59 cm). Histograms represent birth weight and length distributions by frequency (×1000) on the right y-axis.

Recent genomic features of humans as risk factors?

Complex set of segmental Duplications on Chromosome 16

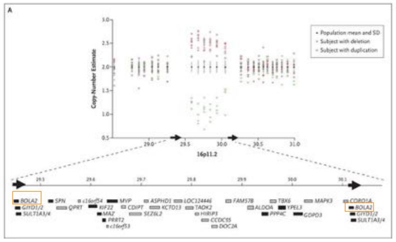
281 kya this event simultaneously increased copy number of gene associated with iron homeostasis and predisposed our species to recurrent rearrangement associated with disease.



Nuttle *et al.* ***Nature*** 2016

All healthy modern humans studied have 6 copies of this recently duplicated segment on chromosome 16.

Association between Microdeletion and Microduplication at 16p11.2 and Autism

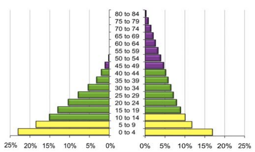


Weiss LA *et al.* ***N Engl J Med*** 2008;358:667-675.

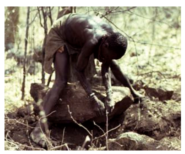
Having less (or more) than 6 copies is associated with autism spectrum disorders!

Aging and survival

Age distribution in chimpanzees and humans



Hadza grandmother at work



(Hawkes et al. 1997 Current Anthropology)

(Hawkes 2010, PNAS)

Many more old individuals in our species than in any “great ape”

New genes for old minds

CD33 (Siglec 3) and other genetic variants for cognitive maintenance selected late in life.

- Contributions of older adults via cultural transmission to younger kin in group or wider social network (tribe) result in selection after reproductive period.

Gene	Associated disease	SNP	Derived allele	Frequency of derived allele* ALL	AFR	AMR	ASN	EUR	SAS	Reference
CD33	LOAD	rs3865444	A	0.21	0.05	0.48	0.19	0.31	0.16	12
		rs12459419	T	0.21	0.05	0.48	0.19	0.31	0.16	25, 26
APOE	LOAD, cardiovascular disease	rs7412	T	0.08	0.10	0.05	0.10	0.06	0.04	31
		rs429358	T	0.85	0.73	0.90	0.91	0.84	0.91	
AGT	Sodium retention, sodium-sensitive hypertension	rs699	A	0.29	0.10	0.36	0.15	0.59	0.36	44, 45
SCG2	Hypertension	rs1017448	G	0.88	0.63	0.95	0.96	0.98	0.97	46
CAPN10	Type II diabetes	rs2975760	T	0.88	0.97	0.87	0.91	0.84	0.79	41, 76
TCF7L2	Type II diabetes	rs7903146	C	0.77	0.74	0.77	0.98	0.68	0.70	47, 77
EBF1[†]	Cardiovascular disease	rs2149954	C	0.66	0.61	0.73	0.77	0.65	0.59	78
COX-2	Myocardial infarction and ischemic stroke	rs20417	C	0.80	0.65	0.79	0.96	0.85	0.81	79
CYP3A5	Salt retention and hypertension	rs776746[‡]	C	0.62	0.18	0.80	0.71	0.94	0.67	80
PPARG	Type II diabetes	rs1801282	G	0.07	0.01	0.12	0.03	0.12	0.12	39
PON1	Dementia	rs2618516	T	0.34	0.26	0.24	0.30	0.38	0.52	81

AFR, African; AMR, American; ASN, East Asian; EUR, European; SAS, South Asian.
*Allele frequencies are from the 1000 Genomes database.
†302 kb downstream.
‡Most common nonfunctional.

Schwarz et al. **PNAS** 2015

Making oneself useful while old? The benefit of older wise minds to younger members of the tribe.

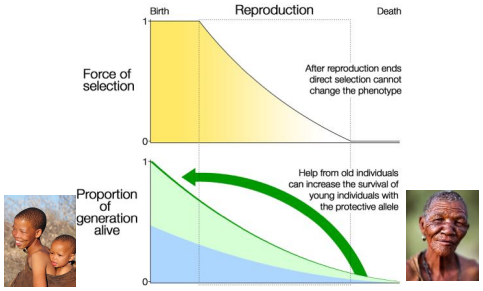
Cognitive maintenance

Different blend of splice variants leads to increased microglia activity, resulting in better amyloid beta clearance —> less plaque accumulation.

Schwarz et al. **PNAS** 2015
Springer and Gagneux *in press*, **Médecine & Sciences**

Two point mutations in DNA are associated with different mix of proteins, resulting in protection from Late onset Alzheimer Disease

Culture can change the selective landscape



Springer and Gagneux 2016, **Médecine & Sciences**

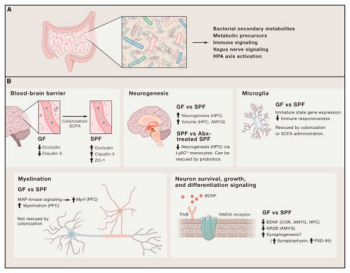
The altered human age pyramid allows for unexpected selection late in life, mediated by help provided by elders to younger group members.

Practice question:

Classical evolutionary theory predicts that natural selection cannot operate strongly in old age. How could selection operate on protective variants for cognitive function?

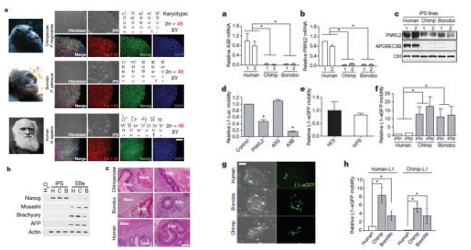
increased survival in younger relatives of the elderly who can still pass on cultural knowledge, could result in selection later in life.

Gut Brain Axis



Intersections of Gut Microorganisms and Basic Developmental Processes
Basic developmental processes driven directly or indirectly by gut microbes and their products.
(A) Gut microorganisms relay messages to the brain via various direct and indirect mechanisms.
(B) Basic neurodevelopmental processes are modulated as a result of colonization of GF animals or depletion of gut bacteria by antibiotics. Specifically, the following processes are modulates: blood-brain barrier (BBB) formation and integrity (Braniste et al., 2014), neurogenesis (Mo¨ hle et al., 2016; Ogbonnaya et al.,2015), microglia maturation and ramification (Erny et al., 2015; Matcovitch-Natan et al., 2016), myelination (Gacias et al., 2016; Hoban et al., 2016) and expressionof neurotrophins (Bercik et al., 2011a, 2011b; Desbonnet et al., 2015), neurotransmitters (Bercik et al., 2011a; O'Mahony et al., 2015), and their respective receptors.

iPS Ape and human neurons ApobecB3 and L1 activity

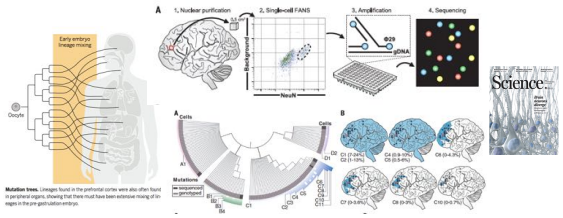


Marchetto et al. 2013 Nature

Human neurons control retrotransposons more stringently than ape neurons (in a dish).

Some human mental conditions e.g. Rett's syndrome, a severe from of autism in girls is associated with increased retrotransposon activity in neurons.

Mutations in individual Neurons: Polyclonal Architecture!!



Lodato et al., SCIENCE 2015

COVER Illustration of projection neurons from the human cerebral cortex, with nuclei colored to reflect distinct sets of somatic DNA mutations. When a mutation occurs in a dividing cell, it marks all of the cell's descendants. Identification of clones marked by mutation enables reconstruction of human brain development. Because developmental defects lie at the heart of many neurological diseases, understanding development is a primary goal of neuroscience.

Summary

The human brain is its own galaxy…

Large, costly, slow to develop and prone to trouble.

Humans around the world carry substantial burdens of mental illness.

Genetic factors influencing mental disease are very complicated and often also underlie creativity and genius.

Different cultures approach mental illness very differently, diagnoses change over time.

Western biomedicine has produced extremely potent neuropharmacological drugs.

The USA consumes 2/3 or these.

Given that substance abuse is often co-occurring with mental disease, drugs are also problematic.

Cognitive behavioral therapy has largely replaced "psychoanalysis".