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Restful REM sleep, depression, and anxiety

Brain size and problem solving among carnivores

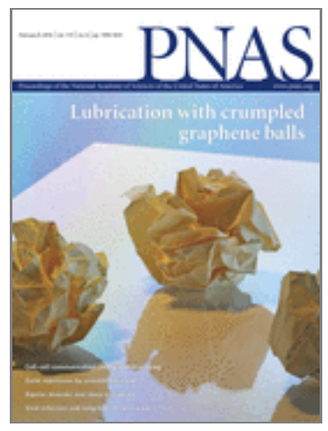
Sustainability Science

Measuring real-world value of natural capital

Anthropology; Psychological and Cognitive Sciences

Human languages may share a common semantic structure

Researchers have attempted to develop methods to determine whether there are universal properties of human cognition that underlie the structure of human languages, or whether language is instead a reflection of culture or environment. Hyejin Youn et al. empirically measured semantics and quantified how meanings compare between languages. The authors used cross-linguistic dictionaries from



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81 diverse human languages and designed a model to analyze semantic similarities across languages. Further, the authors examined words related to material objects (stone, ash, sand), celestial objects (sun, moon, stars), natural settings (night, day), and geographic features (mountain, lake, river) that could be strongly affected by the environment in which a language evolved. By examining the words in each language that have multiple meanings and how those meanings are related to each other and to other words, the authors created semantic network maps. The semantic networks were found to be universal among human languages. For example, “sea/ocean” and “salt” are universally more closely related to each other than either is to “sun,” and this relationship held for languages at the coast and inland. According to the authors, concepts expressed in language may stem from universal properties of human cognition. — B.A.

"On the universal structure of human lexical semantics,” by Hyejin Youn, et al.
[Abstract (/cgi/doi/10.1073/pnas.1520752113)] **OPEN ACCESS ARTICLE**

Applied Biological Sciences

Observing cellular metabolite production in real time

Cells can be engineered to produce useful chemicals, but the potential of such metabolic engineering has been limited by the arduous methods needed to measure the concentration of cellular metabolites. Jameson Rogers and George Church have developed a strategy for fluorescence-based, real-time monitoring of the production of cellular products. The authors used genetically encoded biosensors based on inducible small-molecule systems to link the expression of fluorescent proteins to the intracellular amount of a product. The authors combined these biosensors with cells engineered to produce a particular metabolic product and used fluorescence intensity to track product formation in real time. The authors also used the system to produce various plastic precursors and confirmed that higher fluorescence indicated higher product concentrations. In addition, the authors developed two biosensors for 3-hydroxypropionate (3HP), a renewable plastic precursor, and used real-time observation to improve 3HP production by 23-fold compared with previous reports. Finally, the authors developed a method for in vivo production of acrylate, an important plastic precursor, from glucose, and monitored the production of two other commercially important chemicals, glucarate and muconate, showing that the technique had wide-ranging applications. According to the authors, the technique could be used for high-throughput evaluation of metabolic engineering methods. — S.R.

"Genetically encoded sensors enable real-time observation of metabolite production,”
by Jameson K. Rogers and George M. Church
[Abstract (/cgi/doi/10.1073/pnas.1600375113)] **OPEN ACCESS ARTICLE**

Biophysics and Computational Biology; Engineering

Cockroach-inspired robots navigate crawlspaces

American cockroach traversing a crevice. Image courtesy of the PolyPEDAL Lab (University of California, Berkeley, CA).

Cockroaches can infest virtually any space by exploiting rigid, jointed exoskeletons to slip through seemingly impassable crevices. To quantify the limits of this ability, Kaushik Jayaram and Robert Full constructed an obstacle course for the American cockroach (*Periplaneta americana*). The authors found that *P. americana* can slip through a space smaller than a quarter of its standing body height in less than 1 second by compressing its exoskeleton to around half its original size. Also, these insects continue to move rapidly in confined spaces, at speeds of approximately 20 body lengths per second. Next, the authors altered the friction of the ceiling and ground and determined that cockroaches run in confined spaces using a previously unreported mode of locomotion dubbed body-friction legged crawling. The authors’ material tests show that cockroaches can withstand forces of around 300 times their own body weight when slipping through extremely narrow spaces and can withstand nearly 900 times their own body weight without injury. Inspired by *P. americana*, the authors built a palm-sized, soft-legged robot that can compress itself by more than half to negotiate confined spaces, aided by a low-friction shell. According to the authors, cockroaches represent a suitable model for insect-inspired robots that can navigate challenging spaces, such as rubble piles in disaster zones. — T.J.

"Cockroaches traverse crevices, crawl rapidly in confined spaces, and inspire a soft, legged robot," by Kaushik Jayaram and Robert J. Full
[Abstract (/cgi/doi/10.1073/pnas.1514591113)] **OPEN ACCESS ARTICLE**

Earth, Atmospheric, and Planetary Sciences

Oxygen levels in the prehistoric atmosphere

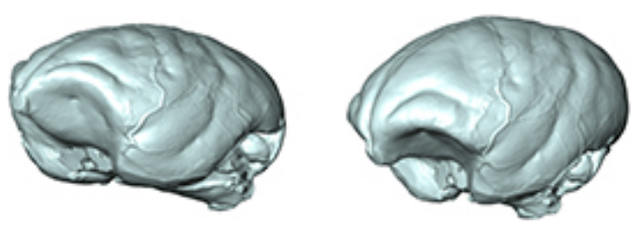
Atmospheric oxygen levels may have been sufficient for sponge respiration hundreds of millions of years before sponges evolved. Image courtesy of the Twilight Zone Expedition Team 2007, NOAA-OE.

Researchers have long argued that oxygen levels on Earth first increased to sufficient levels for animal respiration during the Neoproterozoic Eon, 1,000–542 million years ago, thus explaining why animals first evolved during this period. Shuichang Zhang et al. searched for geochemical evidence of oxygenation in 1,400 million-year-old sediments of the Xiamaling Formation in northern China. Shales with high total organic carbon were enriched in the redox-sensitive trace metals molybdenum and uranium, but not in vanadium. This pattern suggests bottom-water oxygenation during deposition of the sediment layers. The abundance of 2,3,6-trimethyl aryl isoprenoids indicates the presence of anaerobic green sulfur bacteria, suggesting that deposition occurred in an oxygen minimum zone. The authors used the observed geochemical data to constrain ancient oxygen cycling, from which they estimated atmospheric oxygen to be at least 3.8% of present-day levels. This is sufficient oxygen for respiration of sponges and certain small motile animals. The results suggest that oxygen levels sufficient for animal respiration existed on Earth approximately 1,400 million years ago, hundreds of millions of years before the first animals evolved. According to the authors, oxygen levels may not have restricted the emergence of animal life on Earth. — B.D.

"Sufficient oxygen for animal respiration 1,400 million years ago," by Shuichang Zhang, et al.
[Abstract (/cgi/doi/10.1073/pnas.1523449113)] **OPEN ACCESS ARTICLE**

Evolution

Brain shape evolution in New World monkeys



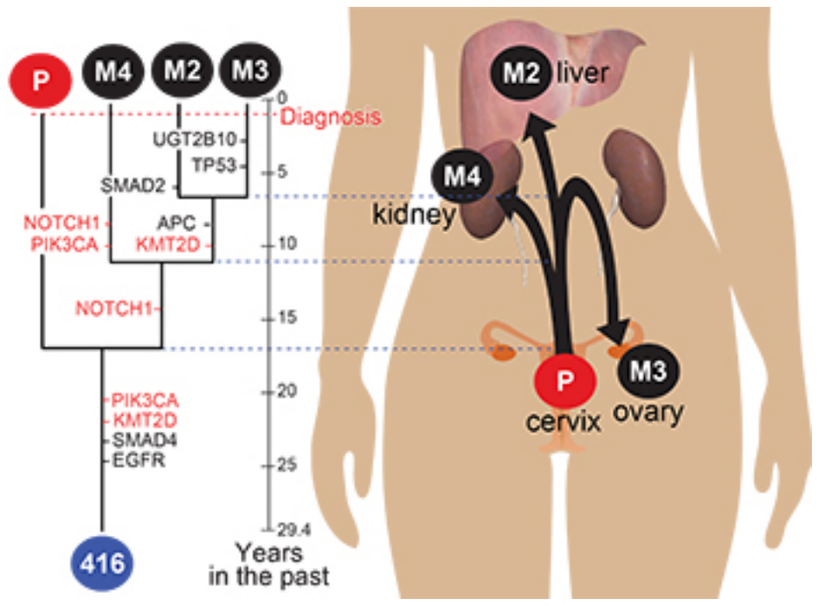
Brain shape variation in New World monkey species.

Brain shape diversification over the course of evolution is an important feature of primate adaptive radiation. Large brains are a significant trait of *Homo sapiens*, and the relative sizes of different parts of the brain in different species may be more important than total relative brain size in terms of brain evolution. However, the conditions under which the diversification of brain shape occurs remain unclear. Leandro Aristide et al. investigated the role of ecological factors such as group size, diet composition, and locomotion strategy in the process of primate brain shape diversification. The authors used a sample of 179 adult skulls from a group of New World monkeys called platyrrhines. The sample included both sexes of 49 platyrrhine species belonging to 17 genera. Brain shape variation was quantified via virtual reconstruction and analyzed using evolutionary models. The results suggest the existence of separate bursts of brain evolution over the course of platyrrhine radiation, with brain shape convergence likely occurring at a late stage following earlier diversification. In particular, the relative enlargement of the neocortex that occurred in multiple groups may have evolved in response to the cognitive demands of life in increasingly large, complex social groups, according to the authors. — L.G.

"Brain shape convergence in the adaptive radiation of New World monkeys," by Leandro Aristide, et al.
[Abstract (/cgi/doi/10.1073/pnas.1514473113)]

Evolution

Evolutionary analysis of origin of cancer metastases



Evolutionary analysis can help uncover origin of metastatic lineages. Image courtesy of Wikimedia Commons/Mikael Häggström.

Many aspects of tumor formation remain poorly understood, including the origins of metastatic lineages. To study how metastases arise, Zi-Ming Zhao et al. used evolutionary biology tools to analyze exome sequences from 32 primary tumors and 139 metastatic sites from 40 volunteers. The authors' analysis supported a nonlinear model of cancer progression, in which metastatic tumors originate from divergent lineages within primary tumors rather than descending from a single departing primary tumor cell. The authors examined the timing of gene mutations and how the mutations contributed to tumor formation. The results suggest that a specific series of genetic changes are unlikely to be required to give rise to metastases, with heritable genetic and epigenetic events that occur early in tumor evolution likely only affecting the tendency toward metastasis. In addition, the authors found that metastatic lineages are produced stochastically and arise early in tumor development, sometimes well before diagnosis of the primary tumor. The study's analyses could help elucidate the timing of mutations in driver genes that occur early in cancer evolution. According to the authors, these mutations could serve as therapeutic targets against both primary tumors and metastases. — S.R.

"Early and multiple origins of metastatic lineages within primary tumors," by Zi-Ming Zhao, et al.
[Abstract (/cgi/doi/10.1073/pnas.1525677113)]

Evolution; Anthropology

Competition and extinction of Neanderthals

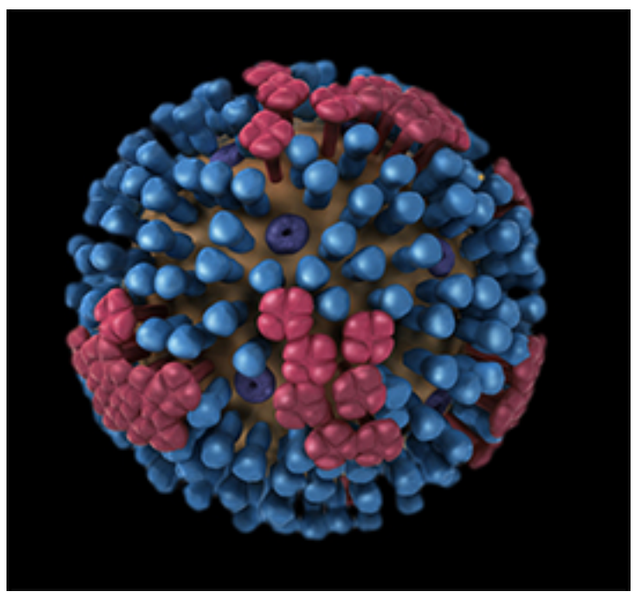
Reconstruction of Neanderthal man at the Neanderthal Museum in Germany. Image courtesy of Flickr/Erich Ferdinand.

Archaeologists have hypothesized that competition between Neanderthals and modern humans led to the former's extinction, likely because of the competitive edge afforded by modern humans' advanced culture. William Gilpin et al. tested the plausibility of this hypothesis using a model of interspecies competition that incorporates differences in the competing species' levels of cultural development. According to the model, an initially small modern human population could completely displace a larger Neanderthal population, provided that the modern humans had a sufficiently large cultural advantage over the Neanderthals. The minimum modern human population that could displace the Neanderthals decreased with increasing cultural advantage and with a decrease in the rate of cultural change relative to population growth. This minimum population threshold also decreased when the authors introduced a positive feedback loop into the model, such that increasing the size of modern humans' cultural advantage increased the size of their competitive advantage, which in turn further increased their cultural advantage. The results support the hypothesis that competition with modern humans drove Neanderthals to extinction, likely due to competitive advantages tied to levels of cultural development, according to the authors. — B.D.

"Ecocultural model predicts Neanderthal extinction through competition with modern humans," by William Gilpin, Marcus W. Feldman, and Kenichi Aoki
[Abstract (/cgi/doi/10.1073/pnas.1524861113)] **OPEN ACCESS ARTICLE**

Immunology and Inflammation

Enhanced efficacy of adjuvanted influenza vaccine in children



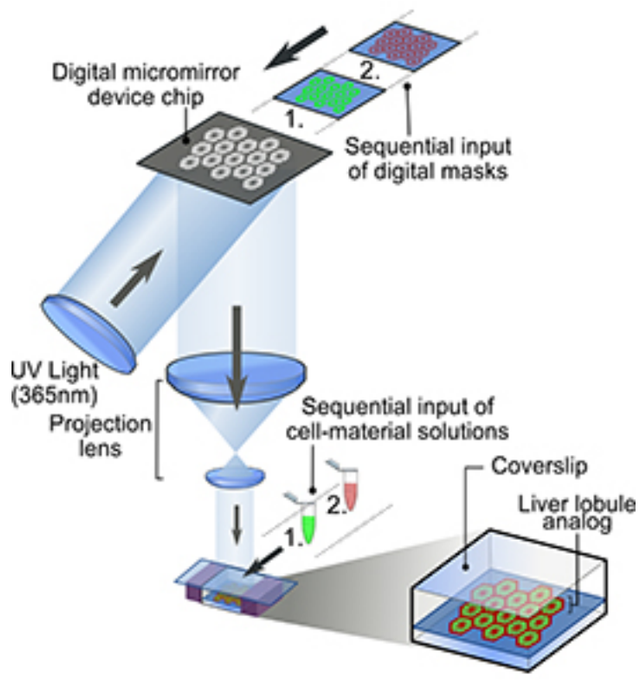
3D graphic of generic influenza virion ultrastructure. Image courtesy of Dan Higgins/CDC.

Clinical trials have revealed that the efficacy of the seasonal trivalent inactivated influenza vaccine (TIV) in 6- to 72-month-old children is improved by the addition of the squalene-based MF59 adjuvant. However, the precise molecular signatures of innate and adaptive immune response to the adjuvanted vaccine remain unclear. Helder Nakaya et al. conducted a phase II open-label, randomized controlled trial of adjuvanted and nonadjuvanted TIV in 90 healthy 14- to 24-month-old children during the winter of 2012–2013. Taking a systems biology approach, the authors measured the magnitude and kinetics of antibody generation, production of vaccine-specific $CD4^+$ T cells, and gene expression signatures in response to vaccination. Compared with TIV, the adjuvanted vaccine boosted serum antibody levels, immune response kinetics, and levels of $CD4^+$ T cells that secreted multiple cytokines, including TNF-α and IL-2, which are involved in antiviral immunity. Adding the adjuvant increased the consistency and robustness of gene expression tied to antigen presentation and antiviral immunity; the adjuvant also shifted vaccination-associated gene expression in the children to adult-like patterns. According to the authors, in addition to uncovering molecular correlates of vaccine-induced immunity in children, the findings underscore the role of the MF59 adjuvant in improving the efficacy of seasonal influenza vaccination in children. — P.N.

"Systems biology of immunity to MF59-adjuvanted versus nonadjuvanted trivalent seasonal influenza vaccines in early childhood," by Helder I. Nakaya, et al. [Abstract (/cgi/doi/10.1073/pnas.1519690113)] **OPEN ACCESS ARTICLE**

Medical Sciences

3D model of human liver



Schematic of 3D bioprinting of a hydrogel-based hepatic construct.

In vitro models of the liver fail to precisely recapitulate the complex structures of hepatic lobules, which consist of diverse cell types in which hepatocytes develop and function. However, the development of light-assisted 3D bioprinting has enabled the design of digital masks that allow distinct cell types to be assembled in precise tissue architecture. Xuanyi Ma et al. used such a method to build a 3D triculture model of the human liver in which hepatic progenitor cells derived from human induced pluripotent stem cell (hiPSC) are localized to hexagonal lobules within a photopolymerizable gel matrix using one mask, followed by localization of two types of supporting cells to the surrounding spaces using a second mask. The hiPSC-derived hepatic progenitor cells (hiPSC-HPCs) grown in 3D triculture expressed hepatic markers at higher levels than those grown in either 2D triculture or 3D hiPSC-HPC monoculture, suggesting that 3D triculture enabled greater hepatocyte maturation than the two other methods. Cells grown in 3D triculture also secreted relatively greater amounts of albumin and urea and

expressed higher levels of key cytochrome P450 enzymes, which metabolize drugs in the liver. According to the authors, the triculture model has potential applications for personalized medicine, drug screening, and translational studies. — C.B.

"Deterministically patterned biomimetic human iPSC-derived hepatic model via rapid 3D bioprinting," by Xuanyi Ma, et al.
[Abstract (/cgi/doi/10.1073/pnas.1524510113)]

Medical Sciences

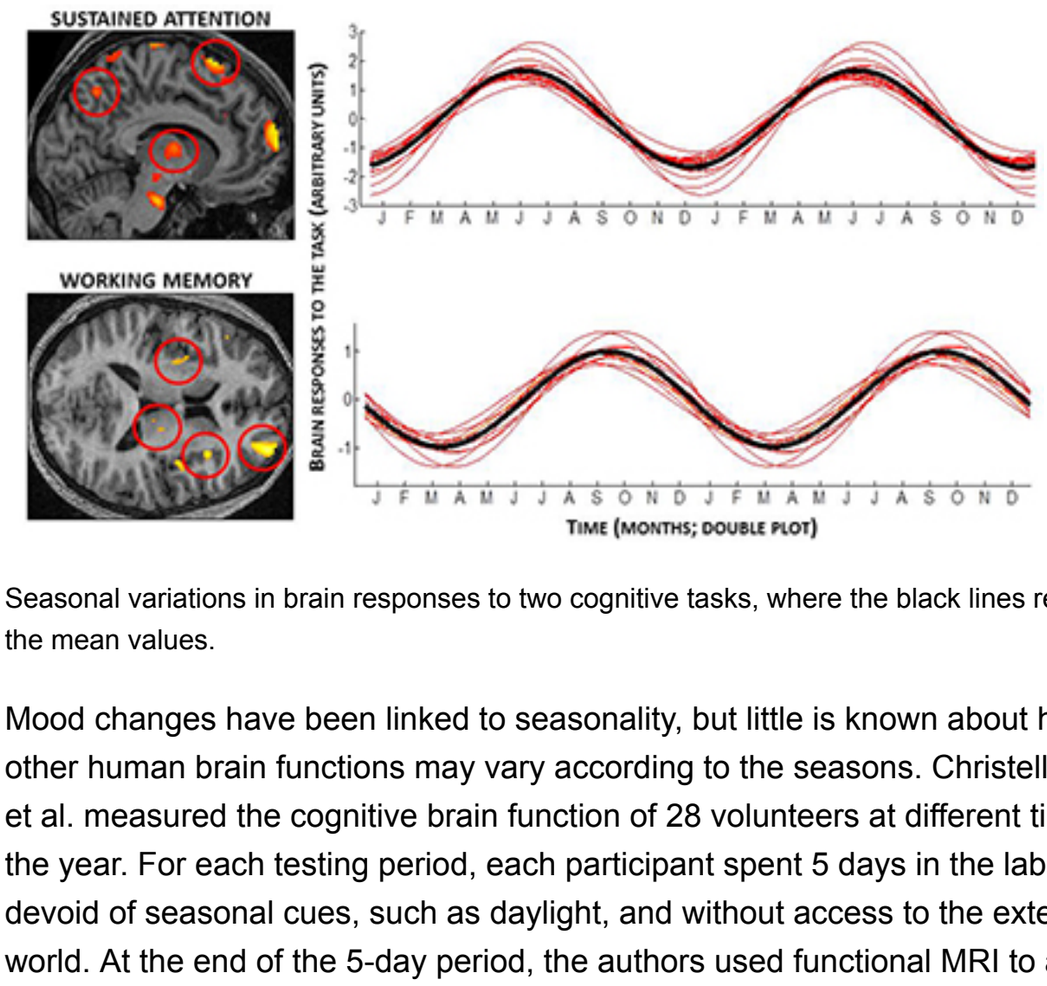
Cellular model of insulin resistance

Obesity increases the risk of type 2 diabetes and cardiovascular disease through defective cellular responses to insulin. Insulin resistance is a growing public health concern, but the development of effective interventions has been limited by an incomplete understanding of the underlying molecular mechanisms. Salvatore Iovino et al. developed a cellular model of insulin resistance in skeletal muscle tissue, which is affected during early stages of type 2 diabetes. The authors obtained skin cells from four healthy individuals and four patients with Donohue syndrome, which causes insulin resistance through mutations in the insulin receptor. Next, the authors genetically reprogrammed the skin cells into induced pluripotent stem (iPS) cells, which are capable of turning into multiple cell types. Upon exposure to a specific combination of chemicals, the iPS cells transformed into skeletal muscle fibers known as myotubes. Compared with myotubes derived from healthy individuals, the patient-derived myotubes showed not only a 90% reduction in levels of the insulin receptor but also impaired insulin signaling. Moreover, insulin treatment failed to trigger an increase in the activity of genes that regulate metabolism and growth in patient-derived myotubes. According to the authors, the iPS model of insulin resistance could help identify new therapies for type 2 diabetes and related diseases. — J.W.

"Myotubes derived from human-induced pluripotent stem cells mirror in vivo insulin resistance," by Salvatore Iovino, Alison M. Burkart, Laura Warren, Mary Elizabeth Patti, and C. Ronald Kahn
[Abstract (/cgi/doi/10.1073/pnas.1525665113)] **OPEN ACCESS ARTICLE**

Neuroscience

Seasonality in brain function



Seasonal variations in brain responses to two cognitive tasks, where the black lines represent the mean values.

Mood changes have been linked to seasonality, but little is known about how other human brain functions may vary according to the seasons. Christelle Meyer et al. measured the cognitive brain function of 28 volunteers at different times of the year. For each testing period, each participant spent 5 days in the laboratory, devoid of seasonal cues, such as daylight, and without access to the external world. At the end of the 5-day period, the authors used functional MRI to assess sustained attention and higher executive function in two separate tasks. Performance on both tasks remained constant, but the brain resources used to complete each task changed with the seasons. Brain activity related to sustained attention peaked in June near the summer solstice and was lowest near the winter solstice. In contrast, working memory-related brain activity, a higher-order task, peaked in fall and was lower near the spring equinox. The authors report that these results did not correlate with endocrine measures, such as melatonin, or neurophysiological measures of alertness and sleep. According to the authors, in addition to daily circadian rhythms, certain brain functions may be more seasonal than previously appreciated and that seasonal rhythmicity may be specific to the cognitive process. — T.H.D.

"Seasonality in human cognitive brain responses," by Christelle Meyer, et al.
[Abstract (/cgi/doi/10.1073/pnas.1518129113)]

Neuroscience; Physics

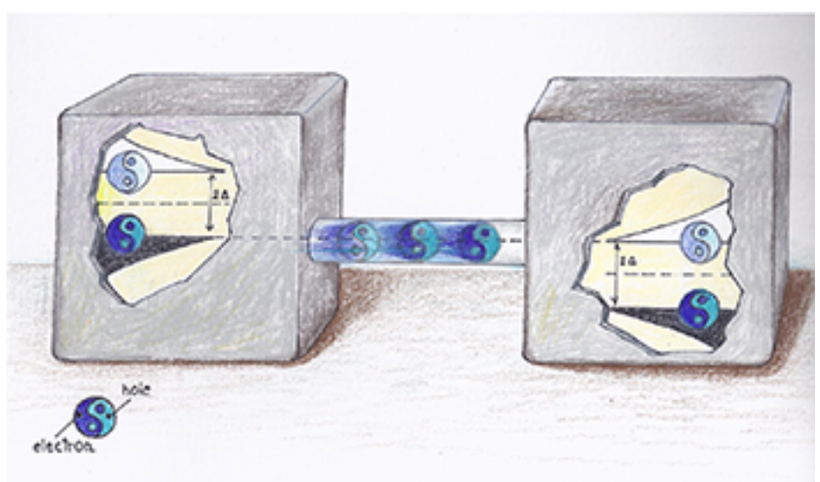
Recording whole-brain activity in moving animals

The ability to use sensory information from the environment to decide which movements to make is critical for survival. To fully understand this complex process, brainwide neural activity must be monitored as an animal responds to environmental changes. Vivek Venkatachalam et al. developed an imaging setup and analysis pipeline to track and simultaneously record the activity of approximately 80 neurons at single-cell resolution in crawling nematodes exposed to fluctuating environmental conditions. The authors used genetic techniques to make neurons in the nematode brain emit fluorescence when activated, and then built a customized microscope to continuously track the movements of crawling nematodes and record neural activity across the brain. Image analysis algorithms filtered out motion artifacts from the animals' movements and identified individual neurons based on unique, local patterns of fluorescent signals from constellations of nearby neurons. Using this imaging pipeline, the authors identified specific sensory and motor neurons whose activities were modulated by the nematodes' forward and backward movements in response to temperature fluctuations. According to the authors, the imaging system could be used in transparent, moving animals to uncover insights into the neural circuits that transform sensory information into behavioral decisions. — J.W.

"Pan-neuronal imaging in roaming *Caenorhabditis elegans*," by Vivek Venkatachalam, et al.
[Abstract (/cgi/doi/10.1073/pnas.1507109113)]

Physics

Quasiparticle charge measurement in a Josephson junction



Quasiparticle transport across a Josephson junction.

Quasiparticles are excited energy states in solids, a conceptual framework that exploits the equivalency of matter and energy to simplify complex quantum interactions among electrons. Condensed matter physicists study quasiparticle properties to better understand superconductivity; however, charge has proven difficult to measure because quasiparticles coalesce into pairs that increase and distort the charge density around them. Yuval Ronen et al. investigated quasiparticle charge using a superconductor–insulator–superconductor (SIS) Josephson junction—two superconductors separated by a gated nanowire semiconductor—and highly sensitive measurements of time-dependent, low-frequency current fluctuations known as quantum shot noise. By observing shot noise over a wide energy regime, the authors detected charge in quantized multiples of an electron's charge in tunneling current across the SIS junction. Further measurements revealed a relatively low value at the edge of the superconducting energy gap, which the authors attribute to the charge of a tunneling quasiparticle. This subelectron value aligns with theoretical predictions of Bogoliubov quasiparticles, a superposition of electrons and holes that should exhibit charges less than that of an electron. Though the findings are preliminary, the approach may help investigate quasiparticle charge in other superconductors, according to the authors. — T.J.

"Charge of a quasiparticle in a superconductor," by Yuval Ronen, et al.
[Abstract (/cgi/doi/10.1073/pnas.1515173113)]

Physiology

Circadian misalignment and heart disease predictors

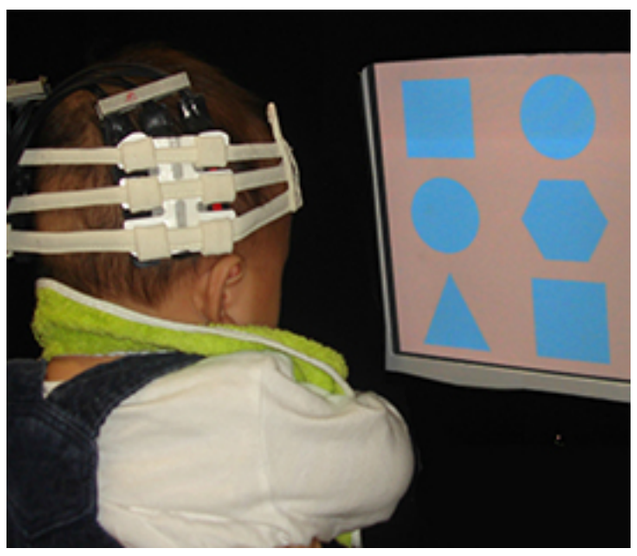
Circadian misalignment increases heart disease risk. Image courtesy of Image courtesy of Henk Stoffels and Frank A. J. L. Scheer.

Shift work is associated with increased blood pressure and inflammation, which can lead to cardiovascular disease. Because shift work results in inversion of sleep/wake cycles and circadian clock misalignments, Christopher Morris et al. measured blood pressure, inflammatory markers, and indicators of autonomic nervous system activity in healthy participants during controlled sleep studies. The authors monitored 14 adult volunteers for two experimental periods of 8 days each. During one of the 8-day periods, the volunteers, who were given a controlled diet, maintained normal sleep patterns. During the other test period, the volunteers maintained normal sleep patterns for the first three nights and were then shifted to 11:00 AM–7:00 PM sleep periods. During these periods of circadian misalignment, inflammatory marker levels rose and blood pressure increased, especially during sleep. Both effects are known to be strong predictors of cardiovascular disease. According to the authors, despite the small size and short duration of the study, the results merit further investigation to identify countermeasures, such as dietary changes or timing of exercise, for the adverse effects of circadian misalignment on cardiovascular health. — T.H.D.

"Circadian misalignment increases cardiovascular disease risk factors in humans," by Christopher J. Morris, Taylor E. Purvis, Kun Hu, and Frank A. J. L. Scheer
[Abstract (/cgi/doi/10.1073/pnas.1516953113)]

Psychological and Cognitive Sciences

Categorical color perception and language acquisition



Brain activity in infants distinguishes color categories.

Humans can distinguish thousands of colors, but individuals across cultures use relatively few words to describe a continuous color space. Past studies have suggested not only that language could influence the perceptual grouping of colors into a few discrete categories, but also that categorical color perception may develop independently of language. Jiale Yang et al. examined neuronal responses associated with color perception in 12 5- to 7-month-old prelinguistic infants and six adults. In each 10-second trial, the participants saw a three-by-three array of nine geometric shapes that alternated in color every second. In the between-category condition, the color of the shapes alternated between blue and green, whereas the within-category condition contained shapes that alternated between different shades of green. Brain imaging through near-infrared spectroscopy revealed that visual regions in the brain's occipitotemporal cortex in both infants and adults responded to the between-category condition, but not to the within-category condition. The findings suggest that the visual system can support the perception of color categories prior to language acquisition. According to the authors, categorical color distinctions might arise before the development of linguistic abilities, but are later shaped by language learning. — J.W.

"Cortical response to categorical color perception in infants investigated by near-infrared spectroscopy," by Jiale Yang, So Kanazawa, Masami K. Yamaguchi, and Ichiro Kuriki
[Abstract (/cgi/doi/10.1073/pnas.1512044113)] **OPEN ACCESS ARTICLE**

Psychological and Cognitive Sciences

Restful REM sleep, depression, and anxiety

Insomnia is a common sleep disorder associated with depression, anxiety, and posttraumatic stress disorder. The development of effective treatments for these disorders has been limited by incomplete understanding of the causes of physiological hyperarousal, which is a key characteristic of insomnia. Rick Wassing et al. recorded two nights of brain activity, eye movements, and other physiological measures in 32 people, who also completed a questionnaire about nocturnal thoughts. The findings validated that restless rapid-eye-movement (REM) sleep, which is commonly associated with insomnia, could be approximated by the abundance of nocturnal thoughts—a variable measurable in a sufficiently large sample of people. The authors then evaluated the frequency of nocturnal thoughts in 1,199 participants who also completed questionnaires measuring the severity of hyperarousal and insomnia as well as the duration of distress after personal distressing experiences. The more people showed signs of restless REM sleep, the less a night of sleep helped to dissolve the distress from such experiences. The resulting distress accumulation, in turn, contributed to the development of chronic hyperarousal. According to the authors, targeted interventions promoting restful REM sleep may benefit patients suffering from significant emotional distress and sleep disturbances. — J.W.

"Slow dissolving of emotional distress contributes to hyperarousal," by Rick Wassing, et al.
[Abstract (/cgi/doi/10.1073/pnas.1522520113)] **OPEN ACCESS ARTICLE**

Psychological and Cognitive Sciences

Brain size and problem solving among carnivores

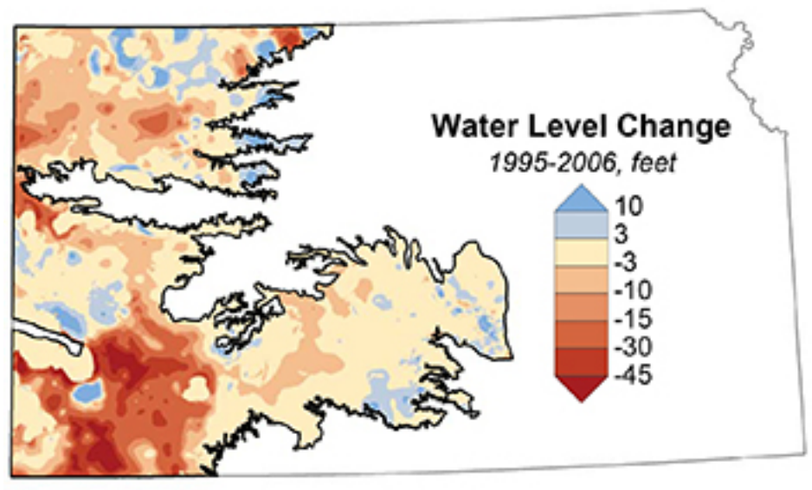
Spotted hyena standing by puzzle box.

Correlations between brain size and advanced cognitive skills, such as innovation and self-control, among animal species have recently emerged. However, the difficulty of comparing animals with unique behavioral adaptations to their environments, among other factors, has hampered an understanding of whether species with larger brains than others have superior cognitive abilities. Sarah Benson-Amram et al. compared the ability of 140 zoo-reared carnivorous mammals from 39 species and 9 families to retrieve a food reward by opening a steel mesh puzzle box, the size of which was scaled to each species' body size. Species with large brains relative to body mass, such as those from the bear and raccoon families, were more successful at the problemsolving task than species with small brains relative to body mass, such as those from the mongoose family; performance improved with experience and was unrelated to manual dexterity. Social species, with large average group sizes, such as banded mongooses, had no advantage over solitary species, such as black bears or wolverines, in opening the puzzle box. Incorporating volume information from virtual endocasts of four major brain regions of some species improved the ability of a model to predict the species' performance in the puzzle-box trials, compared with a model that included total brain volume. Relative brain size might thus help predict animals' problem-solving abilities, according to the authors. — P.N.

"Brain size predicts problem-solving ability in mammalian carnivores," by Sarah Benson-Amram, Ben Dantzer, Gregory Stricker, Eli M. Swanson, and Kay E. Holekamp
[Abstract (/cgi/doi/10.1073/pnas.1505913113)]

Sustainability Science

Measuring real-world value of natural capital



Water volume declines in the Kansas section of the High Plains Aquifer between 1996 and 2005.

The term “natural capital” refers to all the natural resources that humans can use to support life on Earth. Economists have long attempted to assess the value of Earth’s natural capital within the context of established financial accounting practices and economic capital theory. Eli Fenichel et al. describe a framework for quantifying natural capital with prices that can be compared directly with traditional assets such as real estate, factory machinery, and inventory. Conforming with neoclassical economic capital theory, the framework incorporates the dynamics of changing ecosystems and human behavior to account for income derived from nature. As an example, the authors applied their approach to groundwater in the Kansas High Plains Aquifer, a declining source of agricultural water for western Kansas. The case study revealed that groundwater extraction reduced the state’s wealth by approximately $110 million per year, in 2005 US dollars, roughly equivalent to the state’s budget surplus for that year. According to the authors, implementation of effective groundwater management policies and prudent investment strategies could potentially offset such economic losses. — T.J.

"Measuring the value of groundwater and other forms of natural capital," by Eli P. Fenichel, et al.
[Abstract (/cgi/doi/10.1073/pnas.1513779113)]

Systems Biology

Screening platform for drug discovery

Complex human diseases such as cancer can arise from defects in multiple molecular pathways. Despite the need for new combination therapies that simultaneously target multiple disrupted gene networks, previous techniques for discovering disease-related gene combinations have been expensive, labor-intensive, and challenging to scale. Alan Wong et al. developed a simple, efficient screening platform to identify gene pairs that act synergistically to regulate disease-related cellular processes. The authors used a recently developed approach called combinatorial genetics en masse (CombiGEM) to rapidly create a library of 23,409 pairwise combinations of guide-RNAs (gRNAs). The gRNA molecules form a complex with the Cas9 enzyme to generate mutations at specific genomic sites. Leveraging this genome-editing approach, known as the CRISPR-Cas9 system, the authors delivered gRNA pairs into human ovarian cancer cells, thereby simultaneously generating mutations in gene pairs. The CombiGEM-CRISPR screening platform revealed several gene pairs that acted synergistically to regulate cancer cell growth. For example, gRNA pairs that simultaneously targeted the *KDM4C* and *BRD4* genes reduced cancer cell growth to a greater extent than individual gRNAs that targeted only one of these genes. According to the authors, the CombiGEM-CRISPR platform could facilitate the discovery of synergistic drug combinations for complex human diseases. — J.W.

"Multiplexed barcoded CRISPR-Cas9 screening enabled by CombiGEM," by Alan S. L. Wong, et al.
[Abstract (/cgi/doi/10.1073/pnas.1517883113)] **OPEN ACCESS ARTICLE**

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