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BRIEFINGS

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NEUROSCIENCE

The brain's nutrient sensor

CERTAIN BRAIN cells can respond not only to changing glucose levels, but also to mixtures of amino acids — the building blocks of proteins. This suggests that the brain can sense the body's nutrient status in addition to its energy needs.

Denis Burdakov at the University of Cambridge, UK, and his colleagues looked at cells in the brain's hypothalamus called orexin/hypocretin neurons, which regulate energy balance and feeding. Working with mice, they found that these cells were activated both *in vitro* and *in vivo* when exposed to nutritionally relevant amino-acid mixtures.

Glucose normally suppresses the activity of these neurons, but when the researchers exposed the cells to both glucose and amino acids, the amino acids excited the neurons and blocked the effect of glucose. The authors suggest that this boosts the signal from amino acids, which are typically at lower concentrations in the brain than glucose.

—Corie Lok, Nature

■ *Neuron* doi: 10.1016/j.neuron.2011.08.027 (2011)

PERCEPTION

Excitability modulates synaesthesia

SYNAESTHETES WHO experience colors when perceiving or representing numbers exhibit structural and functional differences in cortical areas that are involved in number and color processing compared to non-synaesthetes. Using transcranial magnetic stimulation or tran-

SUNNYBEACH/ISTOCKPHOTO

scranial direct current stimulation, D. B. Terhune *et al.* showed that in humans, grapheme-color synaesthesia is characterized by enhanced cortical excitability in the primary visual cortex and can be augmented or attenuated with cathodal or anodal stimulation, respectively.

—Monica Hoyos Flight, Nature Reviews Neuroscience

■ *Curr. Biol.* doi: 10.1016/j.cub.2011.10.032 (2011)

NEURONAL FUNCTION

A Doc uses calcium

EVOKED NEUROTRANSMITTER release consists of two Ca^{2+}-regulated phases: a fast synchronous phase essential for rapid communication with downstream neurons and a slow asynchronous phase that has been implicated in neural network activity. Synaptotagmin 1 (syt1) is the Ca^{2+} sensor of the fast phase, but the sensor of the second phase was unknown. To identify this component, Yao *et al.* focused on the Doc2 family of cytosolic proteins, which interact with membrane phospholipids in presynaptic terminals in response to Ca^{2+}. The authors found that Doc2 isoforms α and β have several features of a Ca^{2+} sensor: binding to and functional dependence on SNARE fusion proteins, binding to membranes in a Ca^{2+}-dependent fashion, regulating Ca^{2+}-triggered membrane fusion *in vitro* and dependence on the lipid phosphatidylserine. Compared to syt1, Doc2α and Doc2β bind to membranes with slower kinetics and disassemble from the membrane with much longer timescales. Knockdown of Doc2α or mutation of its Ca^{2+}-binding sites also supports a role for Doc2α in asynchronous release in cultured neurons. Finally, the authors showed that Doc2 has a role in the induction and maintenance of persistent reverberatory activity in neural networks, in which asynchronous release is known to be important. These results suggest that Doc2 is a Ca^{2+} sensor kinetically tuned to regulate the slow component of transmitter release.

—Mirella Bucci, Nature Chemical Biology

■ *Cell* doi: 10.1016/j.cell.2011.09.046 (2011)

ADDICTION

One thing leads to another

ADDICTION TO alcohol or nicotine often precedes the use of cocaine and other illegal substances. A recent study points to the possible neural basis of this phenomenon.

Amir Levine *et al.* pretreated mice with nicotine and found that it increased addiction-related behaviors such as conditioned place preference in response to cocaine. This effect was unidirectional; exposing the mice first to cocaine did not affect responses to nicotine.

Mechanistically, the authors found that nicotine enhanced the ability of cocaine to inhibit histone deacetylase, promoting histone acetylation in the nu-

MAC99/ISTOCKPHOTO

ON THE COVER

Beyond tasting the flavors in food, the brain may also sense the presence of amino acids and other nutrients present, according to one recent report. See page 2.

Credit: YouraPechkin/ iStockphoto

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cleus accumbens, a key component of the brain reward system. This priming magnified the effect of cocaine on synaptic plasticity in the accumbens. Indeed, pharmacologically or genetically manipulating histone acetylation correspondingly modified the effects of cocaine on plasticity.

Analyzing epidemiological data, Levine *et al.* showed that cocaine use often occurs in smokers. Moreover, people who initiate cocaine use after they become smokers are most likely to develop cocaine dependence. Decreasing smoking rates might therefore lead to a decrease in cocaine addiction.

—Juan Carlos López, Nature Medicine

■ *Sci. Trans. Med.* doi: 10.1126/scitranslmed.3003062 (2011)

ANIMAL BEHAVIOUR

Rats rescue others in distress

PRIMATES SHOW signs of empathy, but can other mammals sense and respond to emotional distress in another individual? Yes, say Peggy Mason and her coworkers at the University of Chicago in Illinois, who report that rats will liberate a trapped individual even when they do not receive a reward for doing so.

NIKOLAY SUSLOV/ISTOCKPHOTO

In the experiments, one rat was trapped inside a container within a larger arena in which another rat roamed free. By day six or seven, on average, the roaming rat learned to free the trapped one. When a container holding chocolate was added to the arena, the liberators took roughly the same amount of time to free a trapped rat as to access the treat.

Distressed rats typically freeze in response to another distressed rat. The fact that the creatures can control such urges to help another shows that empathy can motivate behavior in animals other than primates, the authors suggest.

—Virginia Gewin, Nature

■ *Science* doi: 10.1126/science.1210789 (2011)

EVOLUTION AND DEVELOPMENT

How the brain became human

HUMANS' EVOLUTION of big brains and unique cognitive abilities may be down to key regulators that control gene expression during development.

Philipp Khaitovich and Svante Pääbo at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and their colleagues compared gene-expression patterns in the brains of dozens of humans, chimpanzees and rhesus macaques of different ages. Relative to those of chimps and macaques, human brains showed many more differences in gene-expression patterns as newborns developed into adults, particularly in a region involved in cognition called the prefrontal cortex (PFC). Genes that encode microRNAs, which regulate the activity of many other genes, were among those whose developmental expression patterns varied most between the PFCs of humans and other primates.

MADSABILDGAARD/ISTOCKPHOTO

The authors suggest that a small number of microRNAs and proteins controlling brain development could have driven the evolution of the human brain.

—Ewen Callaway, Nature

■ *PLoS Biol.* doi: 10.1371/journal.pbio.1001214 (2011)

ALZHEIMER'S DISEASE

Amyloid-targeting antibody performs well in phase II trial

THE FULLY human monoclonal antibody gantenerumab, which targets amyloid-β plaques, seems to cause a dose-dependent decrease in brain amyloid levels, according to a clinical trial involving 18 patients with mild to moderate Alzheimer disease (AD).

Accumulation of toxic amyloid plaques is a hallmark of the AD brain, and targeting of this process is a therapeutic strategy under investigation. In the current multicenter study, published in *Archives of Neurology*, patients were randomly assigned to receive placebo or monthly intravenous doses of gantenerumab (60 mg or 200 mg), which were administered for 2–7 months. PET scanning for the tracer carbon-11-labeled Pitts-

burgh compound B (^{11}C-PIB) was performed to measure regional brain amyloid levels at baseline and at the end of treatment.

Patients in the placebo group (n = 4) showed a mean 11 percent increase in cortical ^{11}C-PIB signal during the study. By contrast, the signal increased by an average of only 2.1 percent in patients receiving 60 mg gantenerumab (n = 6), and declined by 9.4 percent in patients in the 200-mg group (n = 6). The therapeutic antibody seems, therefore, to produce a dose-dependent reduction in plaque burden, although the small sample sizes preclude firm conclusions from being drawn.

In an *ex vivo* phagocytosis assay, live-cell imaging revealed that the drug dose-dependently increased microglial uptake of amyloid plaques within hours.

Future research should address whether targeting of amyloid levels translates into clinical benefit, and whether mild to moderate AD is a sufficiently early time point for starting treatment.

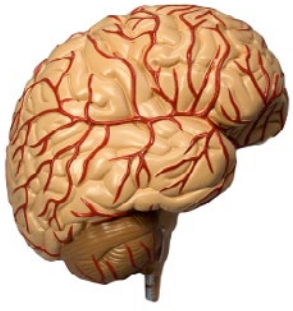
—Katie Kingwell, Nature Reviews Neurology

- *Arch. Neurol.* doi: 10.1001/archneurol.2011.1538 (2011)

NEUROIMMUNOLOGY

A boost to the brain's barrier

A BIOCHEMICAL pathway involved in development also maintains a physiological brain-defense system that is implicated in the autoimmune disease multiple sclerosis (MS).



ANDREAS ODERSKY/ISTOCKPHOTO

The blood–brain barrier (BBB) protects the brain by preventing cells and many molecules from entering it, and is disrupted in MS. Signaling between brain cells called atrocities through the Hedgehog pathway promotes the maturation of cells lining the brain's blood vessels and formation of the BBB.

Alexandre Prat at the University of Montreal in Canada and his group found that inhibiting this pathway in an animal model of MS boosted immune-cell invasion of the brain and increased demyelination — loss of neurons' protective sheath, the hallmark of MS. Stimulating Hedgehog signaling in cultured human cells caused fewer inflammatory T cells to interact with and migrate across blood-vessel cells.

Many patients with MS experience cyclical inflammatory attacks of the brain, and they also have higher levels of Hedgehog signaling. The authors think that this pathway may be involved in rebalancing the immune response after each attack.

—Susan Young, Nature

- *Science* doi: 10.1126/science.1206936 (2011)

NEUROSCIENCE

Sleep calms the emotions

A GOOD night's sleep is restful for the amygdala, the brain's emotional centre. People who had recently awoken from sleep showed a decrease in reactivity in the amygdala after viewing emotional pictures, whereas those who had remained awake showed an increase.

Matthew Walker and his colleagues at the University of California, Berkeley, scanned the brains of volunteers as they looked at the pictures and rated the images' emotional intensity. The tests were repeated 12 hours later, after either a night of sleep

MARK BOWDEN/ISTOCKPHOTO

or a wakeful daytime period. The most intense emotional ratings decreased among those who had slept, but not in those who had not slept. These decreases in amygdala reactivity and emotional ratings correlated with declines in electrical activity in the brain during rapid eye movement (REM) sleep.

The findings could explain why people with anxiety disorders, who often have abnormal REM sleep, are more emotionally reactive.

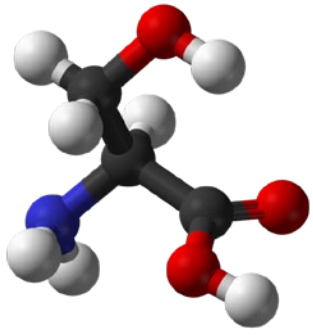
—Corie Lok, Nature

- *Curr. Biol.* doi: 10.1016/j.cub.2011.10.052 (2011)

NEUROLOGICAL DISORDERS

Serine to the rescue

NO EFFECTIVE treatments exist for individuals with hereditary neuropathies. On the basis of recent progress in understanding the cause of one such disorder, hereditary sensory and autonomic neuropathy type 1 (HSAN1), K. Garofalo *et al.* provide initial promising results for



EPHEMERONIUM/BEN MILLS/WIKIMEDIA COMMONS

L-serine.

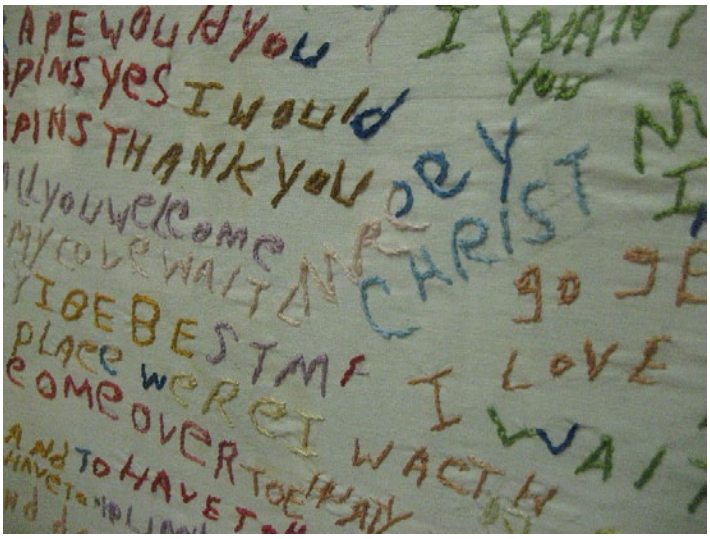
a mechanism-based therapy for this rare disease: dietary supplementation with L-serine.

HSAN1 is caused by mutations in genes that encode subunits of serine palmitoyltransferase, which catalyzes the first step in sphingolipid biosynthesis. These mutations loosen the substrate specificity of the enzyme, allowing it to use alanine or glycine rather than serine. This change in substrate results in the production of deoxysphingolipids, which may be neurotoxic. Proceeding from this mechanistic framework, the researchers hypothesized that increasing serine levels might be beneficial. Indeed, dietary supplementation with L-serine in a mouse model of HSAN1 decreased plasma deoxysphingolipid levels and decreased neuropathic symptoms. In 14 individuals with HSAN1, L-serine dietary supplementation also reduced plasma deoxysphingolipid levels.

In view of the short 10-week course of L-serine supplementation, neurological symptoms were not examined in the treated individuals with HSAN1. A larger and longer-term clinical trial will now be needed to test the safety and efficacy of this therapy.

—Michael Basson, Nature Medicine

■ *J. Clin. Invest.* doi: 10.1172/JCI57549 (2011)



COMETSTARMOON/FLICKR

Embroidery by a patient with schizophrenia.

PSYCHIATRIC DISORDERS

Multiple pathways to DISC1-related disease?

THE SCAFFOLDING protein disrupted in schizophrenia 1 (DISC1) has multiple roles in neurodevelopment. Both rare and common variants of this protein may influence psychiatric phenotypes, although it remains unclear how DISC1 is mechanistically linked to disease. Now, two studies provide evidence for possible DISC1-mediated pathophysiological pathways.

Tsai and colleagues examined the functional significance of three common DISC1 variants (R264Q, L607F and S704C DISC1) and one rare variant (A83V DISC1), which they identified from a group of healthy individuals and patients with psychiatric disorders.

DISC1 can bind glycogen synthase kinase 3β (GSK3β), activating canonical WNT signaling. Using *in vitro* assays, the authors showed that A83V, R264Q and L607F DISC1, unlike wild-type and S704C DISC1, were unable to stimulate WNT-induced transcription and proliferation (a process regulated by WNT signaling) in murine neuroblastoma cells, and that the absence of such effects was due to a reduction in the variant's GSK3β-binding capacity. They also showed that expression of S704C DISC1 but not the other variants rescued neural progenitor proliferation defects in embryonic mouse brain following knockdown of DISC1 and that transcription assays involving human-derived lymphoblast cell-lines yielded results that were in line with the previous data.

Thus, the R264Q, L607F and A83V DISC1 variants may increase the risk of psychiatric disease through impairment of canonical WNT signaling and neurodevelopment. Interestingly, S704C DISC1 may impair neurodevelopment through a different pathway, as the authors found that this variant — unlike R264Q, L607F and A83V DISC1 — was unable to rescue WNT-independent neuronal migration deficits in mouse embryonic cortex following knockdown of DISC1 expression.

In the second study, Ming and colleagues examined the role of DISC1 in the development of adult-born neurons, focusing their attention on the previously reported interactions of DISC1 with two proteins implicated in neural developmental processes: nuclear distribution protein nudE-like 1 (NDEL1) and fasciculation and elongation protein-ζ1 (FEZ1). They found that knockdown of FEZ1 expression in the dentate gyrus accelerated dendritic growth and caused an increase in soma size in newly born neurons. Moreover, simultaneous knockdown of DISC1 and FEZ1 further accelerated dendritic growth, suggesting

that in adult-born neurons, both proteins regulate dendrite development.

In contrast to the phenotypes observed with FEZ1 knockdown, knockdown of NDEL1 expression caused the formation of ectopic dendrites in adult-born dentate granule cells and the abnormal positioning of these cells in granule cell layers. Such phenotypes are also observed following knockdown of DISC1 expression, suggesting that FEZ1 and NDEL1 regulate adult-born neuron development through parallel pathways involving DISC1. Supporting this assertion, the simultaneous knockdown of NDEL1 and FEZ1 did not elicit any synergistic effects on newly born neurons, and a series of immunoprecipitation experiments showed that NDEL1 and FEZ1 did not directly interact; rather, they both bound DISC1.

Alongside their studies in mice, Ming and colleagues undertook a genetic association study of *FEZ1* with schizophrenia, from which they uncovered an epistatic interaction between a *FEZ1* polymorphism and the allele encoding S704C DISC1. This finding is consistent with the synergistic effect of knocking down the expression of FEZ1 and DISC1 in newly born neurons and shows how polymorphisms in *DISC1* and associated genes may combine to increase the risk of disease.

Taken together, these studies suggest pathways whereby DISC1 variants impair neurodevelopment and increase susceptibility to schizophrenia. Moreover, they highlight how mechanistic insights into psychiatric disease may be garnered from complex genetic findings.

—Darran Yates,
Nature Reviews Neuroscience

■ *Neuron* doi: 10.1016/j.neuron.2011.09.030 (2011)
Neuron doi: 10.1016/j.neuron.2011.09.032 (2011)

BEHAVIORAL NEUROSCIENCE

Curbing sweet cravings

AGNIESZKA KIRINICI/ANOW/ISTOCKPHOTO

A. I. Domingos *et al.* examined the reward value of sweeteners in mice by assessing the animals' preferences for sweeteners compared to lick-induced optogenetic activation of midbrain dopaminergic neurons. They found that mice preferred optogenetic stimulation to the artificial sweetener sucralose, but not to sucrose. Interestingly, following a period of food restriction, the reward value of sucrose increased, whereas after administration of leptin it decreased. These results highlight the postingestive effects of fat metabolism on nutrient preference.

—Monica Hoyos Flight,
Nature Reviews Neuroscience

■ *Nature Neurosci.* doi: 10.1038/nn.2977 (2011)

NEURODEVELOPMENTAL DISORDERS

A fragile synaptic balance

A NUMBER of specific gene mutations are associated with intellectual disability and autism, providing hope that understanding common downstream effects might shed light on the pathophysiology of autism spectrum disorders. Bear and colleagues now show that mutations in fragile X mental retardation 1 (*FMR1*) and tuberous sclerosis 2 (*TSC2*), which are associated with similar behavioral impairments, have opposing effects on metabotropic glutamate receptor 5 (mGluR5) function and synaptic protein synthesis.

In fragile X syndrome (FXS), silencing of *FMR1* increases mRNA translation downstream of mGluR5 activation, leading to increased long-term depression (LTD) at mGluR5-expressing synapses. The mutations in *TSC1* or *TSC2* that cause tuberous sclerosis are also thought to influence mRNA translation and synaptic function, suggesting that similar mechanisms might be involved. The authors were therefore surprised to observe that mGluR5-LTD in the hippocampal CA1 area was suppressed, rather than increased, in a mouse model of tuberous sclerosis ($Tsc2^{+/-}$ mice) and that there was a corresponding decrease in the synthesis of LTD-related proteins.

In animal models of FXS, reducing mGluR5 signaling can correct the abnormalities in protein synthesis and LTD. Here the authors found that a positive allosteric modulator (PAM) that boosts mGluR5 signaling returned both protein synthesis and LTD to wild-type levels in $Tsc2^{+/-}$ mice. Furthermore, the mGluR5 PAM was able to restore performance in a context discrimination task in which $Tsc2^{+/-}$ mice were impaired.

ANTHONY ROSENBERG/ISTOCKPHOTO

These results suggest that *FMR1* and *TSC2* mutations have opposing effects on protein synthesis and mGluR5 function. Indeed, their effects appear to cancel each other: the authors found that mGluR-LTD, protein synthesis and context discrimination were normal in mice carrying both mutations.

The behavioral characteristics of FXS and tuberous sclerosis are similar, suggesting that mutations that shift the balance of mGluR5 signaling in either direction have similar effects on cognitive function. The findings confirm the restoration of synaptic function to be a key target in the development of therapeutic strategies for autism spectrum disorders; however, they also suggest that such treatments will need to take into account the specific deficits present in each case.

—Katherine Whalley, Nature Reviews Neuroscience

■ Nature doi: 10.1038/nature10658 (2011)

LEARNING AND MEMORY

Channeling spatial information

GRID CELLS in the entorhinal cortex provide a two-dimensional metric of the spatial environment. Together with head direction cells and conjunctive cells, they integrate information about a moving animal's trajectory (*pictured*) and convey this information to place cells in the hippocampal CA1 and CA3 subregions. Two complementary papers now show that the size and stability of grid and place cells is regulated by HCN1 channels.

HCN1 channels — which generate the hyperpolarization-activated cation current I_h and thereby have a role in regulating oscillatory neuronal activity — are highly expressed in entorhinal grid cells and CA1 place cells, but to a lesser extent in CA3 place cells. A previous study showed that mice lacking HCN1 in the forebrain (*Hcn1*$^{-/-}$ mice) perform better in spatial learning tests. Giocomo *et al.* and Hussaini *et al.* therefore assessed the effect of deleting forebrain HCN1 channels on the firing of grid cells and place cells, respectively.

TECHNOTR/ISTOCKPHOTO

Grid cells in the cortex help to interpret how things move through space.

In both studies, the authors recorded from grid cells or place cells in mice that were running through square or longitudinal enclosures. Giocomo *et al.* found that in *Hcn1*$^{-/-}$ mice, the size and spacing of grid fields were larger than in control mice, but the previously described dorsal-to-ventral gradient in grid field size and spacing within the entorhinal cortex remained intact. Hussaini *et al.* found that *Hcn1* deletion also increased the size of place fields by roughly 50 percent in CA1 and by roughly 25 percent in CA3.

The larger grid and place fields would be expected to provide less spatial precision — so why do *Hcn1*$^{-/-}$ mice have enhanced spatial learning and memory? The authors compared grid field and place field maps from mice running through the same enclosure in two sessions. Place fields and grid fields in *Hcn1*$^{-/-}$ mice showed a higher cross-correlation between sessions than did those in control mice, indicating greater stability of place and grid cells in *Hcn1*$^{-/-}$ mice and, presumably, a more stable representation of the environment.

Previous studies suggested that increases in grid size and spacing may result from changes in intrinsic oscillations. Indeed, forebrain *Hcn1* deletion resulted in longer interspike intervals and thus reduced intrinsic activity in individual theta-modulated grid cells and place cells. In addition, Giocomo *et al.* showed that the frequency of the ongoing theta rhythm in the entorhinal electroencephalography signal was less strongly regulated by running speed in *Hcn1*$^{-/-}$ mice than in control mice. Moreover, Hussaini *et al.* showed increased theta power in the CA1 — but not CA3 — local field potential in *Hcn1*$^{-/-}$ mice compared with control mice. These studies suggest that I_h has a role in transforming self-motion signals into the localized firing patterns of grid and place cells.

The finding that an absence of HCN1 channels increases the size and stability of grid and place fields suggests that I_h contributes to the dorso-ventral gradient in grid and place field scaling in the entorhinal cortex and the hippocampus, respectively. As HCN1 is highly expressed in the entorhinal cortex

and CA1, I_h currents may directly influence field scaling in these areas. By contrast, the weak expression of HCN1 in CA3 suggests that place field scaling in this area may reflect input from entorhinal grid cells.

—Leonie Welberg, Nature Reviews Neuroscience

- *Cell* doi: 10.1016/j.cell.2011.08.051 (2011) *Neuron* doi: 10.1016/j.neuron.2011.09.007 (2011)

ADDICTION

NR2B — a target for preventing drug relapse?

THE PROPENSITY for drug relapse has been associated with cognitive impairments in the prefrontal cortex. H. Shen *et al.* examined changes in synaptic plasticity during relapse in a rat model of heroin addiction. They found that there was an increase in the long-term potentiation-like synaptic strength of prefrontal projection neurons that project to the nucleus accumbens, and that this increase was dependent on the recruitment of NR2B-containing NMDA receptors to the cell surface. Furthermore, they found that treatment of addicted rats with the NMDA receptor inhibitor ifenprodil prevented heroin relapse. These findings suggest that NR2B-containing NMDA receptors could represent a novel therapeutic target for addiction.

—Monica Hoyos Flight, Nature Reviews Neuroscience

- *Proc. Natl Acad. Sci. USA* doi: 10.1073/pnas.1112052108 (2011)

ENCKLC/ISTOCKPHOTO