**A Dartmouth study found that functional MRIs of patients with obsessive-compulsive disorder and of a control group show different patterns of brain activity during response inhibition tasks.**

# Patients opt for choice over coercion

The numbers are grim: Over 16 million American adults, about 1 in 17, live with severe mental illness. And studies show that 60% of them get no treatment and 35% get inadequate treatment, says DMS psychiatrist Robert Drake, M.D., Ph.D. Most of the 60% have been involved with the mental-health system but have "opted out," says Drake. "They're afraid of the coerciveness of the system, they don't find the system friendly or welcoming, they don't find that they get what they want from the system."

**Goal:** So Drake and his colleagues at the Dartmouth Psychiatric Research Center set a goal of making the system more patient- and family-friendly through shared decision-making—offering patients resources to help them develop their own treatment plans and take an active role in monitoring the results.

Very little research has been done on shared decision-making in the context of severe mental illness. And "with mental illness where decision impairment is part of the illness, there's a lot of skepticism that shared decision-making is even viable," says Jared Adams, Ph.D., an M.D.-Ph.D. student at Dartmouth.

So Drake, Adams, and psychologist George Wolford, Ph.D., conducted a pilot study of 30 clients of a New Hampshire community mental-health center; all had a severe mental illness—schizophrenia, bipolar disorder, or major depression.

The clients filled out questionnaires about their decision-making experiences and preferences regarding new medication, hospitalization (whether or not to be hospitalized for treatment), housing, finding and securing employment, and choosing a caregiver. Clients rated each area on a scale from "mostly my doctor's decision" (a passive role) to "mostly my decision" (a collaborative or autonomous role). They also completed a decision aid to help them articulate questions, benefits, and risks regarding their psychiatric care.

Most clients said they'd prefer greater participation in decisions about their psychiatric care. In choosing and managing new antipsychotic medications, for example, 23 clients (77%) indicated a preference for an autonomous or collaborative role, but only 11 (37%) rated their current experience as non-passive. The study participants were less likely to want a passive role in making medication decisions about their psychiatric care than their general medical care. The results were published in *Psychiatric Services*.

**Rank:** Adams, the paper's lead author, repeated the study with more subjects as part of his Ph.D. thesis, using computer decision aids he created to help clients rank and choose medications based on their side effects. "We need to treat people with respect and recognize that they have a right to make decisions about their own bodies, whether they're mentally ill or not," says Drake. He sees a need for "systems of care that are really patient-centered, so that people and their families can understand what their options are and what the evidence is and make reasonable choices."

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**Drake is a national leader in psychiatric research.**

## Looking for a coffee break

Epidemiological studies have suggested that long-term caffeine consumption reduces the risk of developing type 2 diabetes. But a small study in *Metabolism* by Todd MacKenzie, Ph.D., and other Dartmouth investigators showed that if healthy young adults consume 200 milligrams of caffeine (about a mug of coffee) twice a day for a week, it reduces insulin sensitivity—and thus *increases* the risk for type 2 diabetes. Further research is needed "to study longer-term effects," the authors noted, "and to clarify the differences between interventional studies such as ours" and epidemiological studies.

## Some skin in the game

Melanoma, which now accounts for 4% of all cancer cases, is on the rise worldwide. A team of DMS biochemists led by Constance Brinckerhoff, Ph.D., set out to explore the genetic underpinnings of metastatic melanoma, which is almost totally resistant to known therapies. In *Cancer Research*, they wrote that a gene called interstitial collagenase matrix metalloproteinase-1 (MMP-1), while not involved in primary tumor growth, "enhances tumor cell collegenase activity and tumor-induced angiogenesis," which are vital for the metastatic capability of melanoma cells. So "MMP-1 may be a therapeutic target in treating this disease."

**Teens shown evidence of skin damage from sun exposure, found DMS's Ardis Olson, M.D., were more likely than a control group (59% versus 35%) to say they'd use sunscreen in the future.**

# Seeking subtle differences in skin cancer risk

"If we can figure out why people get cancer, then we stand a chance of learning how to prevent it," says Dartmouth epidemiologist Margaret Karagas, Ph.D. She investigates the subtle differences that may make people more or less susceptible to certain cancer risk factors. In a recent study, she and her collaborators showed that exposure to radiation increased people's risk of getting two common types of skin cancer. They went on to show that the risk is increased in those exposed to radiation at an early age and those with a sun-sensitive skin type.

**Link:** The first link between radiation and cancer was made in the early 1900s, when it was reported that radiologists working with x-rays developed skin cancer. Since then, it has been well established that radiation is carcinogenic. Of course radiation is still commonly used for diagnostic and treatment purposes, notes Karagas, although the doses are lower than those that early radiologists were exposed to. She explains that radiation is used not only in x-rays and cancer treatments but also in imaging techniques such as fluoroscopy and CT scans.

What are the implications of exposure to these levels of radiation? And are there additional risk factors that make some people more prone to getting skin cancer from radiation? These are some of the questions that Karagas, who is the associate director of Dartmouth's Center for Environmental Health Sciences, has been looking at. Her recent paper was published in the journal *Epidemiology*.

**Cell:** The study examined basal cell and squamous cell carcinomas, the two most common types of skin cancer. With treatment, they are rarely life-threatening, though the ability of squamous cell carcinoma to metastasize makes it slightly more dangerous. Through a collaboration with the New Hampshire Society for Dermatology, the researchers collected a wide range of information on over 1,000 people with basal cell carcinoma and over 800 people with squamous cell carcinoma. This information included the individuals' history of radiation exposure and sun exposure, as well as their sun-sensitivity, or tendency to sunburn. The same information was also gathered from a similar collection of control subjects.

**Skin:** The team found a strong association between radiation exposure and basal cell carcinoma—something many previous studies have shown. But the association between radiation exposure and squamous cell carcinoma had not been previously established. In this study, Karagas identified that association primarily in people with a sun-sensitive skin type, as determined by the individual's tendency to sunburn. Subjects who had experienced radiation exposure when they were less than 20 years old also showed an increased risk for both types of skin cancer.

While radiation exposure appears to elevate the risk of getting skin cancer, the benefits of such treatments may well outweigh that risk. So, Karagas emphasizes, "we don't want to scare people off from treatment they need—we just want people to be mindful that there are risks associated with radiation." KRISTEN GARNER

JON GILBERT FOX

**Karagas is shining the light of day on skin cancer.**

## A raft of results

Ta-Yuan Chang, Ph.D., reported in the *Journal of Biochemistry* that plasma membrane (PM) lipid rafts, cholesterol-rich areas of cell membranes, play a key role in cholesterol metabolism. Scientists knew that mammalian cells synthesize sterols, as well as cholesterol, in the endoplasmic reticulum (ER). Sterols move to the PM, then back to the ER, for processing to cholesterol. But no one understood how. Chang's lab determined that rafts complete cholesterol biosynthesis "by participating in the retrograde movement of precursor sterols back to the ER."

## Coverage for veterans

Medicare data helps VA planners analyze older veterans' use of health-care services, but it's harder to determine where younger VA enrollees get their care or how it's funded. A DMS team used three hospitalization datasets to compare payers for younger and older enrollees and found that most younger vets use private insurance more often than the VA or other coverage. "Veterans of the current Middle East conflict are likely to need extensive care, which will challenge the VA system," the team wrote in *Medical Care*. "Understanding younger veterans' health-care needs, service utilization, and payment options may require synthesizing data from multiple sources."

DMS's James Sargent, M.D., recently showed that exposure to smoking in movies is more likely not only to make teens take up smoking but also to make them established smokers.

# Celebrating cellular and scientific flexibility

Was it good luck or brilliant insight? That's what Chuck Cole, Ph.D., a professor of biochemistry at Dartmouth Medical School, wonders about a recent discovery in his lab. He and former DMS graduate student Jack Scarcelli, Ph.D., started down one scientific path but ended up making an important, unexpected discovery that brought them onto a very different avenue. They identified a gene that plays a role in allowing the membrane surrounding the cell nucleus to stay flexible. And they showed that this flexibility is very important in the assembly of passageways that allow cellular messages to get in and out of the nucleus.

These passageways, nuclear pore complexes (NPCs), are tunnels made of proteins through the nuclear membrane. NPCs are important because, says Scarcelli, messenger RNA (mRNA), which encodes the proteins that carry out many of the functions of the cell, is made from DNA within the nucleus—but the cellular machinery that makes the proteins is out in the cell's cytoplasm.

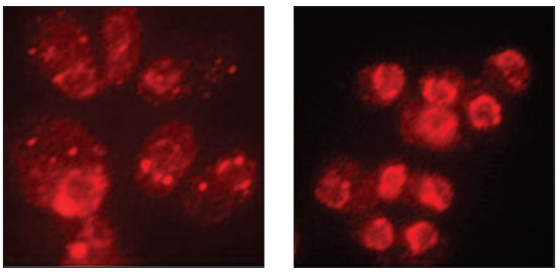
"In science," says Cole, "you have to follow the interesting results."

**Studies:** The discovery began with studies of how mRNA gets in and out of the cell—something Cole's lab has long been interested in. Scarcelli used robotics to do a large-scale experiment to identify genes in yeast cells that, when missing, cause a defect in the export of mRNA. From this screen, several genes were shown to affect mRNA export, including Apq12. At first the researchers thought Apq12 was directly involved in mRNA export, perhaps as part of the NPC. What they found, however, was quite different.

**Hypothesis:** When Cole and Scarcelli looked closely at Apq12's role, they saw that, in cells lacking it, NPCs could not be assembled correctly at low temperatures. At lower temperatures, cells adjust the makeup of the nuclear membrane to maintain its fluidity and flexibility. So the researchers hypothesized that yeast cells that lacked Apq12 no longer had the ability to alter the membrane's composition. To test the idea, they treated the cells with benzyl alcohol, a chemical that loosens up the membrane. After the membrane's flexibility had been restored with benzyl alcohol, the NPCs could then be assembled correctly, even in the Apq12 mutants.

So a project that began with mRNA export ended with a discovery in nuclear membrane biophysics—a discovery that has garnered quite a bit of attention. The paper was published in the *Journal of Cell Biology* and featured in *Cell*'s "Leading Edge" section. The researchers still don't know exactly how Apq12 changes the nuclear membrane's flexibility, but that's their next step.

"In science," says Cole, "you have to follow the interesting results that you get." Clearly, his and Scarcelli's ability to switch gears and follow unexpected findings has paid off. Instead of good luck or brilliant insight, maybe this finding is a credit to their ability to remain flexible. KRISTEN GARNER



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Nuclear pore complexes (NPCs) are passageways through which cellular messages move. Researchers stained these NPCs to show that those lacking a protein called Apq12 (on the left) could not assemble the passageways the way normal cells can (on the right).

## A hearty endorsement

A DMS team led by cardiologist Michael Simons, M.D., has genetically engineered adult mice to grow new blood vessels around their hearts. Within three weeks, the animals' vasculature had grown 50% percent, and by six weeks their hearts were 50% larger. "This study demonstrates that an increase in the size of the vascular bed in the normal heart leads to increased cardiac mass and myocardial hypertrophy paralleled by increased cardiac performance," the researchers wrote in the *Journal of Clinical Investigation*. The findings may lead to new approaches for treating heart disease.

## Looking to stem leukemia

A blood formation gene called mixed lineage leukemia (MLL)—which is essential for the development of embryonic blood stem cells and is involved in a type of childhood leukemia—also plays an unexpected role in the adult blood-forming system, according to a recent study in *Cell Stem Cell*. DMS geneticist Patricia Ernst, Ph.D, and colleagues found that in mice, MLL acts on bone marrow stem cells and controls key aspects of their growth to generate mature blood cells. If it's disrupted, it cannot work properly and leukemia can ensue. The researchers hope that their discovery may one day lead to new anticancer treatments. ■