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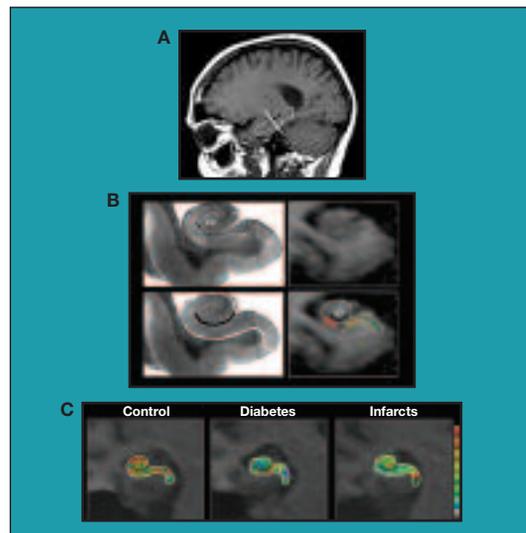
Glucose Levels Linked to Memory Decline

Normal changes in glucose handling that occur with age might be an underlying cause of age-related memory decline, a recent study by neurologist Scott A. Small, MD, and colleagues at NewYork-Presbyterian Hospital/Columbia University Medical Center suggests. “Blood glucose levels are less and less well regulated starting in the fourth decade, and through a mechanism yet to be defined, glucose targets the dentate gyrus, one of the hippocampal regions involved in fixing new memories,” said Dr. Small. He and his colleagues reported these findings in the December 2008 issue of the *Annals of Neurology*.

According to Dr. Small, the hippocampus’s several regions (the entorhinal cortex, dentate gyrus, CA1 subfield and subiculum) work together as a circuit in learning new memories—the name of someone you met recently, where you put your keys, a new software program. Each subregion contains a molecularly distinct population of neurons, which may explain why different physiologic processes such as aging, disease, and stroke appear to affect different regions of the hippocampus. Alzheimer’s disease, for example, affects the entorhinal cortex, and vascular disease affects the CA1 subfield and the subiculum, while normal cognitive aging targets the dentate gyrus. “The early stages of Alzheimer’s and normal aging look very similar using standard memory tasks, though, because they access the whole circuit,” Dr. Small noted. “It’s as though different parts of your computer are down, but the end result is the same, it’s not working.”

In this study, Dr. Small and his colleagues used high-resolution functional magnetic resonance imaging

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Functional maps of the hippocampal formation. (A) A sagittal scout image was used to identify the long axis of the hippocampal formation (demarcated by the solid line). High resolution T1-weighted images are acquired perpendicular to the hippocampal long axis (stippled line). (B) The general locales of four hippocampal subregions are shown in a post-mortem hippocampal slice (top left panel): the entorhinal cortex (EC), dentate gyrus (DG), CA1 subfield (CA1), and the subiculum (Sub). A single magnetic resonance imaging slice (top right panel) contains all four hippocampal subregions and provides sufficient anatomical information to parse the hippocampal formation. Specifically, by identifying the external morphology of the hippocampal formation (as demarcated by the white line in bottom left and right panels) and its internal architecture (as demarcated by the black line in the bottom left and right panels), regions of interest can be drawn in the entorhinal cortex (green), dentate gyrus (blue), CA1 subfield (red), and the subiculum (yellow). (C) Cerebral blood volume (CBV) maps are shown for an individual control subject and a subject with diabetes or infarcts. Maps are color coded such that warmer colors indicate greater CBV.

Early Nutrition Vital Following Brain Injury

Traumatic brain injury (TBI) is the leading cause of death and disability in people ages one to 44. Although care of these patients has improved dramatically since “best practice” guidelines were established in 1995, the treatments have focused on relieving intracranial pressure, hypotension, hypoxia, and avoiding steroids. The nutrients patients receive in the first

few days following their injury have never been considered as important. But a recent study by neurosurgeon Roger Härtl, MD, and colleagues at NewYork-Presbyterian Hospital/Weill Cornell Medical Center shows that providing early nutrition following a brain injury is vital.

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Dr. Härtl and his colleagues chanced upon the significance of nutrition as they were analyzing data from a New York State trauma center compliance study of TBI guidelines. As they sifted through six years of data from the care of 797 patients, this finding leapt out, Dr. Härtl said. “We found almost a linear relationship between nutrition and mortality.” In other words, patients who did not receive gastric feeding within the first five days of their injury were twice as likely to die from their brain injury, and those who did not receive feeding within seven days were four times as likely to die.

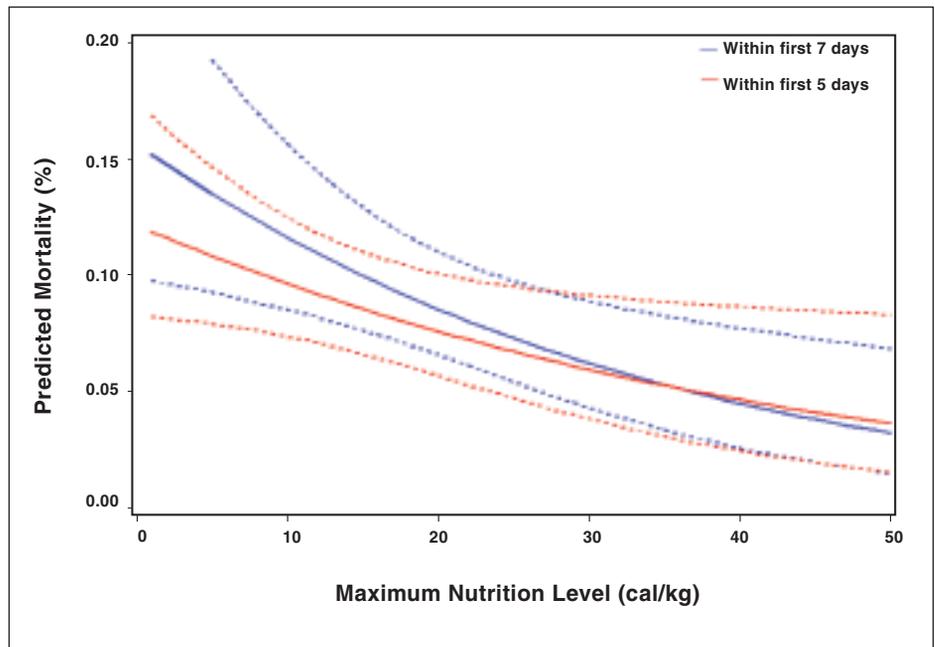
Previous nutrition recommendations said that patients should receive 140 percent of their normal caloric intake within seven days of the TBI (100 percent for patients who were paralyzed). Dr. Härtl’s study showed that, not only is it better to get nutrients into patients as early as possible, but also that the more nutrients they get the better. The best outcomes were in patients who received a minimum of 25kcal/kg each day. For every 10kcal/kg decrease in caloric intake, the mortality rate increased 30 to 40 percent.

“Reaching patients’ minimum caloric requirement is sometimes complicated,” said Dr. Härtl, “because the activity of their intestinal system may be so slowed. If you feed gastric or enteral nutrition to patients without peristalsis it’s just not being transported—you can’t really get it into them.” In these cases the trauma team stimulates peristalsis and gastric motility medically. “Sometimes you can circumvent this by giving parenteral, intravenous nutrition, and that is safe; however, there is some concern about infection,” he said.

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Brain in Overdrive

“PET and metabolic studies have shown that a severe traumatic injury sends the brain into a hypermetabolic state, a possible explanation for its dramatic energy requirements,” said Dr. Härtl. “Within the first few days of the injury everything is running full speed, but at the same time there appears to be a dysfunction of the mitochondria. So the brain’s disproportional increase in energy requirements



Line graph showing the predicted mortality as a function of maximum nutrition level. Regression models were adjusted for age, hypotension status on Day 1, pupil status (normal or abnormal) on Day 1, initial GCS score, and CT scan findings. Solid lines represent the maximum amount of nutritional support, and dashed lines indicate the 95% confidence interval.

may be due to the fact that it is not metabolizing the energy properly.”

“Any type of trauma to the body can also result in a posttraumatic stress response, which is associated with an increased rate of infection,” he said. Studies have shown that if patients with other types of trauma receive nutrients early on after their injury, the stress response is blocked and the infection and mortality rates both decrease as well.

Since the study was designed to look at compliance, Dr. Härtl and his colleagues were able to follow patients for only a short period following an injury; their endpoint was

survival at two weeks. “This is a very crude parameter of outcome obviously,” he said. “But studies have shown that if you do anything to decrease mortality—treat intracranial pressure very aggressively, avoid hypotension—you also improve outcome. So we’re not just shifting the patients who would have died into a vegetative state, but actually really increasing overall the quality of survival.”

Initial Transport Crucial

The database held another surprise, Dr. Härtl said, namely just how important the initial transport decision was. “If TBI patients were not brought directly to a Level 1 Trauma Center, but were brought to a community hospital first and to a trauma center later, they tended to have a poorer outcome. Level 1 Trauma Centers provide better care for TBI patients because they have neurosurgeons available around the clock; they have a CT scanner that’s functional around the clock, a trauma team, and a trauma bay. Patients are immediately greeted by the trauma team when they arrive.”

But not all trauma centers are equal in terms of the care they provide TBI patients, he added. “In New York City, we have 18 Level 1 Trauma Centers, and everyone takes care of head injury patients, and this is a big problem. The mortality within the trauma centers in the city is variable, and guideline compliance is also variable.” Dr. Härtl hopes to gather additional data to demonstrate that having a few trauma centers in New York City that are really well equipped and well trained to take care of head injury patients would be a much more efficient and effective approach.

Contributing faculty for this article:
Roger Härtl, MD

Chronic Fatigue Syndrome Tied to High Lactate Levels in Brain

Chronic fatigue syndrome, a condition that was not long ago dismissed as the “yuppie flu,” is now accepted as a legitimate diagnosis. The diagnostic criteria developed by the Centers for Disease Control (CDC) in 1994 have been widely disseminated, and the CDC now tracks chronic fatigue syndrome (CFS) and reports that between 1 and 4 million Americans suffer from the illness. But arriving at a definitive diagnosis of CFS remains difficult as there is no gold standard diagnostic test and because CFS shares symptoms with several other medical and psychiatric conditions such as diabetes, thyroid disease, depression, anxiety, and substance abuse. A recent brain scanning study by Dikoma C. Shungu, PhD, Professor of Physics in Radiology, Psychiatry, and Physiology and Biophysics, and colleagues at NewYork-Presbyterian Hospital/Weill Cornell Medical Center may help open the way to diagnostic clarity. The study showed that a diagnosis of CFS is linked to elevated levels of lactate in the cerebrospinal fluid.

The Centers for Disease Control now tracks chronic fatigue syndrome (CFS) and reports that between 1 and 4 million Americans suffer from the illness.

Dr. Shungu discovered the brain abnormality in CFS while using magnetic resonance spectroscopy (MRS) to research dysregulated brain function in people with mitochondrial diseases. “After doing metabolic workups in several people we discovered something surprising: several people who had been referred to us as having CFS or were suspected to have CFS turned out to have had elevated lactate in their cerebrospinal fluid,” said Dr. Shungu.

With a grant from the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America, Dr. Shungu further explored the link between lactate and CFS. His study, published in the April 2009 edition of *NMR in Biomedicine*, found that more than 50 percent of the CFS patients studied had cerebrospinal fluid lactate levels up to 348 percent higher than the healthy controls.

With collaborators Sanjay J. Mathew, MD, from Mount Sinai School of Medicine, and Benjamin H. Natelson, MD, from University of Medicine & Dentistry of New Jersey, Dr. Shungu is now embarking on a new study to look at the mechanisms that may lead to the elevated lactate in CFS. They will compare patients with CFS with those with anxious depression, and with healthy controls.

Immune Reaction Sparks CFS

“Chronic fatigue syndrome often develops on the heels of an initiating event such as flu-like illness,” said Dr. Shungu. “The patient does not really recover from the illness—they remain sick and start feeling very, very tired. Elevated levels of lactate may be the end result of a chain of events: The immune reaction to the infection leads to a build up of free radicals, which accumulate in such numbers that

they create oxidative stress. Oxidative stress almost invariably attacks or destroys the mitochondria, which then become dysfunctional. When that happens glycolysis kicks in to give us more energy. The end product of glycolysis is lactate, also called lactic acid, which we’re detecting.”

“Increased brain lactate might also be caused by decreased oxygenation in the brain,” Dr. Shungu said. “Mitochondria require oxygen to operate. If oxygen levels are too low due to decreased blood flow, mitochondrial energy is not produced efficiently so glycolysis kicks in, and lactate, the end-product, is produced.”

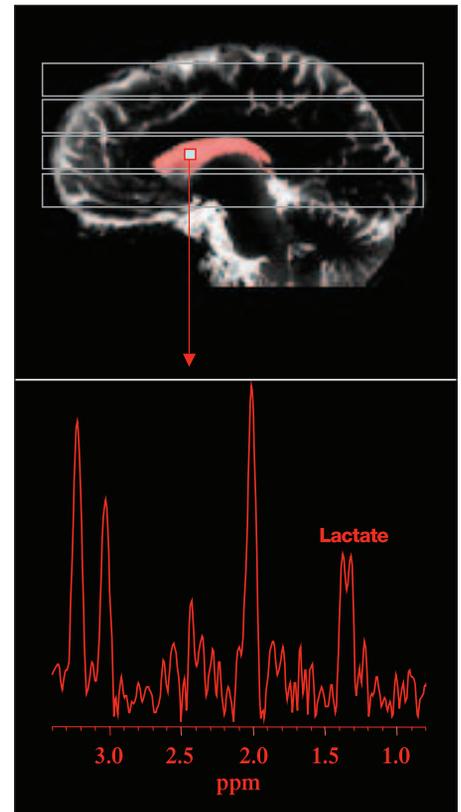
“After doing metabolic workups in several people we discovered something surprising: Many of those who had been referred to us as having CFS or were suspected to have CFS had elevated lactate in their cerebrospinal fluid.”

—Dikoma C. Shungu, PhD

Brain Blood Flow Decreased in CFS

In their new study, Dr. Shungu and colleagues will use MRS to observe markers of oxidative stress, mitochondrial dysfunction and cerebral blood flow. “Preliminary studies have shown that brain blood flow is decreased in CFS compared to the other groups, which might be a cause for the increased lactate,” said Dr. Shungu. “We want to know why the blood flow is decreased. To find out, we’re going to see if the markers of oxidative stress are elevated, which could cause vasoconstriction.”

Dr. Shungu’s recent study showed levels of lactate that varied considerably among the CFS patients in the study. “We actually had a



Top panel: An MRI of the brain with the ventricular space that contains CSF in which we measured the lactate is highlighted in red. **Bottom panel:** A magnetic resonance spectroscopy trace, also called a spectrum, showing the presence of lactate from single-volume element (voxel) in the CSF highlighted in the top panel.

very big spread—more than half of them had significantly increased lactate, but there were also patients who didn’t have increased lactate. But that’s very telling because it’s consistent with the disease — it’s a very, very heterogeneous condition and it’s multisystem,” noted Dr. Shungu. The researchers have tightened the inclusion criteria in the new study so that they will be looking at a more homogeneous population of CFS patients. “We’re going to accept a group of patients who are quite similar in terms of symptoms, because if there is a spread in symptoms then there could be a lot of confusion.”

Contributing faculty for this article:
Dikoma C. Shungu, PhD

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(fMRI), a variant of fMRI, to map cerebral blood volume (CBV) in the subregions of the hippocampus. CBV has a high correlation with other basal measures of brain function such as cerebral blood flow (as measured with MRI) or glucose uptake (as measured with positron emission tomography).

“High-resolution fMRI had several advantages for this study,” explained Dr. Small. “High-resolution fMRI has some relatively unique features—one is that it has very high spatial resolution so it enables us to look at the different parts of the hippocampus, which are very tiny. The second is that we can use this same imaging technique across species, a big advantage in this study since subjects included rhesus monkeys and mice, as well as humans.”

High Glucose and Poor Cognition

In the first phase of the study the researchers generated high-resolution fMRI snapshots of the hippocampal formation in 240 nondemented elders (mean age 79.7 years). Among the analyses they performed was an examination of the relationship between blood glucose, insulin, and hippocampal CBV to determine whether glucose and insulin underlie dentate gyrus dysfunction. They found that blood glucose levels were inversely correlated with dentate gyrus CBV, and were also

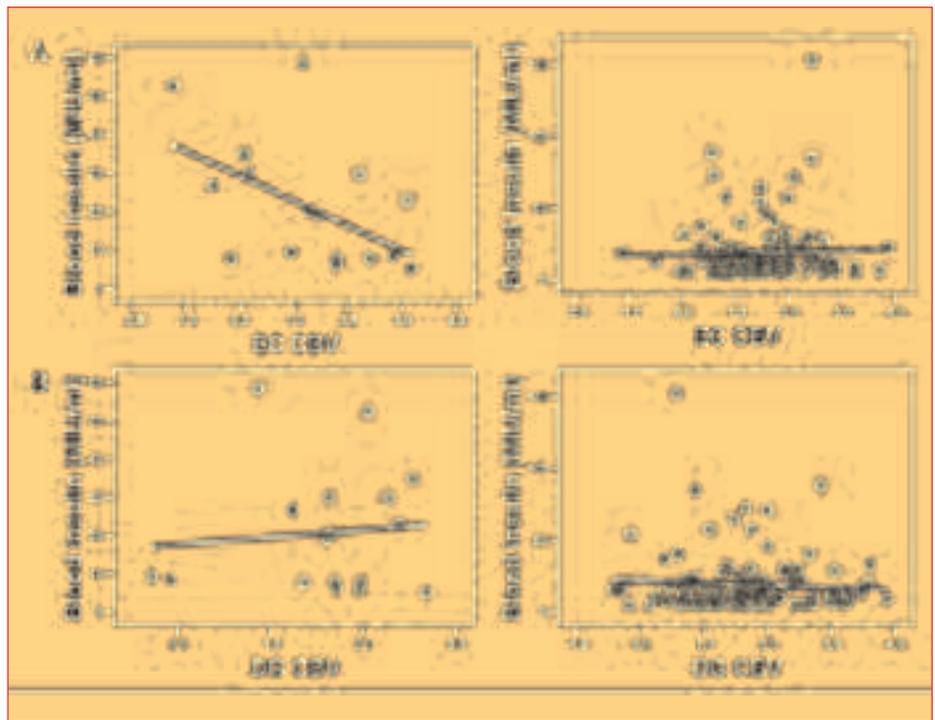
“As we age, we gradually have a harder time absorbing sugars that we eat.”

—Scott A. Small, MD

inversely correlated with total recall on the Selective Reminding Test, a cognitive measure of hippocampal function.

In the study’s second phase Dr. Small tested the hypothesis that an increase in blood glucose is differentially linked to the dentate gyrus by mapping hippocampal CBV in aging rhesus monkeys. “We found that the monkeys with elevated blood glucose were more likely to have dysfunction in the dentate gyrus than in the other subregions,” he said, adding that, “The first two studies confirmed each other, but they’re correlational.”

In the final phase the researchers induced elevations in blood glucose in mice to observe the effects of systematic increases. The mice were treated with streptozosin at three and six months of age, killing the insulin producing cells of the pancreas, which resulted in an



Blood insulin selectively targets the entorhinal cortex in a stroke-dependent manner. (A) Blood insulin levels are inversely correlated with entorhinal cortex (EC) cerebral blood volume (CBV) in subjects with infarcts in the hippocampal vascular territory (left scatterplot) but not in subjects without infarcts (right scatterplot). (B) Blood insulin levels are not correlated with dentate gyrus (DG) CBV in subjects with infarcts in the hippocampal vascular territory (left scatterplot) or in subjects without infarcts (right scatterplot).

abnormal increase in blood glucose. Using fMRI the researchers found significant dysfunction in the dentate gyrus, confirming their earlier findings.

“An increase in blood glucose is a natural and inevitable aspect of aging,” said Dr. Small. “As we age, we gradually have a harder time absorbing sugars that we eat. Starting in our 30s, we all begin to experience spikes in blood glucose levels, particularly after meals, and as a result our brains are exposed to higher and higher levels of blood glucose over time. The major reason for this is that we all become gradually and subtly insulin insensitive. The mechanisms by which insulin enables the body to ‘sponge up’ blood glucose work less and less well with age, so we don’t take up the glucose as well.”

Although Dr. Small and his colleagues have identified glucose as a likely factor in memory decline, they do not understand its role. “This study really framed that question,” he said. “Now, we really need to figure out what it does.”

Exercise is Beneficial

“This research suggests that any manipulation—behavioral or pharmacological—that reduces glucose could potentially ameliorate age-related memory decline,” said Dr. Small. He noted that these results clarified the findings

of a previous study he and his colleagues published in *Proceedings of the National Academy of Sciences* (PNAS 2007 104:5638-5643). In that study, physical exercise (in humans and mice) preferentially benefited the dentate gyrus. “We didn’t clearly understand why at the time, but this latest finding does give a very plausible mechanism. As you exercise, your muscles start expressing a glucose transporter, allowing muscles to be spongier to glucose. This suggests that physical exercise benefits the dentate gyrus because it allowed subjects to have better glucose handling. It may also account for other findings in which physical exercise is actually beneficial to cognition. That’s one of the things we’re very keen on trying to pin down.”

Dr. Small noted that large-scale epidemiological studies often produce conflicting results regarding recommendations on foods or vitamins that are beneficial to your health. “However, in all of the studies of aging and disease, exercise always proves to be of value.”

“At this point, there is nothing else to recommend.” Dr. Small added that he is working with colleagues to develop a number of compounds derived from food that might imitate the benefits of exercise, “but that’s into the future.”

Contributing faculty for this article:
Scott A. Small, MD

Borderline Personality Disorder – Perspectives on Treatment

NewYork-Presbyterian Hospital doctors presented two different approaches to treating patients with borderline personality disorder (BPD) at the American Psychiatric Association meeting in San Francisco in May. Frank E. Yeomans, MD, discussed transference focused psychotherapy for BPD in a talk entitled: “Aiming for Change in Personality Structure.” Barbara H. Stanley, PhD, presented “Dialectical Behavior Therapy and Beyond: Strategies and Interventions for Suicidal Individuals with Borderline Personality Disorder,” with an emphasis on the use of safety plans.

“BPD is a multi-faceted syndrome whose main characteristics include extreme and rapid shifts from one intense emotion to another, very chaotic and stormy interpersonal relationships, and dramatic impulsive behaviors such as wrist cutting, suicide attempts, and overdoses,” said Dr. Yeomans. “In the past 15 to 20 years, researchers have developed a number of specialized treatments for BPD such as transference focused therapy, dialectical behavioral psychotherapy, supportive psychodynamic therapy, and mentalization based treatment, which are each based on somewhat different views of the core pathology in BPD.”

Dr. Stanley notes that, “In recent years, mentalization based treatment, a psychodynamic psychotherapy that focuses on attachment, has shown efficacy for BPD.”

Safety Planning in Suicidal Patients with BPD

Suicide attempts are common in people diagnosed with BPD: Between 60 to 70 percent of patients with BPD attempt suicide, and 8 to 10 percent of those attempts succeed. Risk factors for suicide in BPD include a history of multiple suicide attempts and significant, persistent substance use.

“BPD patients who attempt suicide are typically either hospitalized,” said Dr. Stanley, “or we keep our fingers crossed and hope that they come back safe for their follow-up appointment with the therapist.” With Gregory K. Brown, PhD, at the University of Pennsylvania, Dr. Stanley developed a technique to bridge the gap between hospitalization and a future appointment with a doctor. In this approach the patient and therapist work together to develop a written document called a safety plan. This technique is one of several that Dr. Stanley developed based on principles of dialectical behavior therapy (DBT) and cognitive therapy (CT), which clinicians can use in their general psychiatric practices even if they do not practice DBT or CT. “The idea behind this is that suicidal urges ebb and flow, and the plan can help patients get through the peak of their urge. The plan also includes ‘means restriction,’ an effort to remove means such as medication or a gun that people can use to kill themselves,” she said. “This gives people time for their urges to subside.”

Each plan is highly individualized. “Working together with the patient we figure out what they consider a strongly distracting activity that will take their mind off their urges for a time,” noted Dr. Stanley. “For some people this will be surfing the web, for others listening to music, going for a run, or taking a shower. The patient and therapist also identify social places where the patient can go and be around other people such as a local coffee shop or church, and identify



people who can take the patient’s mind off of the urge and get outside themselves.”

When patients recognize that they are in crisis they follow the plan, step by step. If step 2 does not decrease the suicidal urge, they move on to step 3, and so forth. The basic components of the safety plan include:

1. Recognizing the warning signs of an impending suicidal crisis
2. Identifying and employing internal coping strategies on their own
3. Contacting other people in healthy social settings to distract themselves from suicidal thoughts
4. Contacting family members or friends who can help them resolve the crisis and with whom they can discuss their suicidal urges
5. Contacting mental health professionals or agencies

Drs. Stanley and Brown developed this approach for adolescent boys and girls. According to Dr. Stanley, it has also been adopted by the Veterans Health Administration and is now used by every veteran who is at risk for suicide.

Dr. Stanley is testing other approaches to bridging the gap between the ER and the doctor’s visit through a series of studies in the Emergency Department at NewYork-Presbyterian Hospital/Columbia University Medical Center. “Suicidal individuals often do not stay in treatment,” she said. “As many as 38 percent of people who attempt suicide and are hospitalized for three months do not engage in outpatient treatment after discharge, and 73 percent of people who attempt suicide are not in treatment one year after their suicide attempt.”

Through two pilot studies, Dr. Stanley is researching ways to increase the likelihood that suicidal patients seen in the ER will engage in treatment in the three months after their visit to the ER to decrease their risk of suicidal thoughts and behavior in that time period. In one study the researchers are assessing the effectiveness of a problem-solving interview and in the other of a brief motivational interview.

Transference Focused Psychotherapy

Transference focused psychotherapy (TFP) is a modified form of psychodynamic psychotherapy developed by clinician-researchers under the leadership of Otto F. Kernberg, MD, at NewYork-Presbyterian Hospital/Weill Cornell Medical Center’s Personality Disorders Institute. “TFP is based on the concept that people with BPD have an underlying identity disturbance,” said Dr. Yeomans. “They lack a coherent sense of self, which, combined with temperamental vulnerability, leads to the behavioral manifestations of BPD. While other therapeutic approaches tend to focus on behaviors and cognition, TFP works in the area of identity integration and its impact on affects and cognitions.”

Dr. Yeomans explained that emotions can be seen as the expression of an internal object representation. “In the course of every infant’s early development, mind and identity are built up gradually under the influence of internalized dyadic experiences of self and other (important caretakers) marked by intense emotion. Some internalized experiences are marked by positive affect—warmth, love, happiness, and satisfaction, while others are experiences of extremely negative

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Neuroimaging Reveals Deficits in Impulse Control Among Patients with Bulimia Nervosa

“I hate the way that I’ve lost control. Food has taken over my life,” Emma wrote about her binge-eating and vomiting on the University of California at Davis website devoted to eating disorders. “I have lost friends, family, and my life because of this. The sad thing is, though, that I enjoy doing it. I want to stop but I can’t, and half of me won’t. Bingeing does something to me, which I can’t explain. Whether it’s control, relief, or power I’m not sure.”

Many patients with bulimia nervosa, a disorder characterized by recurring episodes of binge eating followed by self-induced vomiting or the use of laxatives to avoid weight gain, describe their experience this way. “Patients report feeling a kind of out-of-body experience, they’ve totally lost control over themselves and their eating, in particular,” said Rachel Marsh, PhD, a Columbia University psychologist.

Bulimia typically affects females and although the mean age of onset is reported to be approximately age 18, the binge-eating and purging behaviors often begin as early as age 13. In most patients, the impulsivity is not just focused on food—they also have higher levels of substance abuse, shoplifting, and self-destructive behaviors such as cutting. “Patients report feeling an ‘internal urge’ that they need to express somehow,” Dr. Marsh said. It turns out that this loss of impulse control has

a neural basis, according to the results of a new study done by Dr. Marsh and her colleagues.

To find out what is happening in the brain of a bulimic, Dr. Marsh and her colleagues

appear on each side of a computer screen and had to identify the direction the arrows were pointing. When an arrow on the left side points to the left or one on the right points to

“Nobody has studied eating disordered patients without using symptom-related material. We showed that they’re not just impulsive in terms of their binge-eating behavior, they’re impulsive in terms of their general cognition and brain activation.”

— Rachel Marsh, PhD

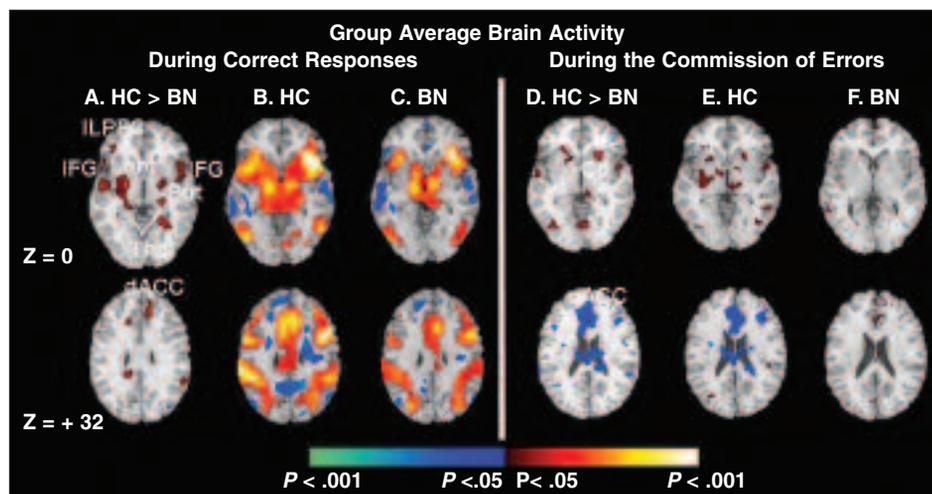
designed an experiment that would examine the impulse-control mechanism at work. Using functional MRI, she compared brain activity in 20 women with bulimia nervosa and 20 healthy controls while they performed a self-regulatory control task, called a Simon task. The subjects watched a series of arrows

the right the task is easy. When an arrow on the right points left, though, or vice versa, it gets more difficult.

Healthy adults activate brain processes that prevent them from automatically responding and allow them to focus on resolving the conflicting information. “To do well on the task you need to hold back and engage control,” said Dr. Marsh. “The patients with bulimia, however, responded a lot faster, more impulsively, and made many more errors. In addition, in the patients’ frontal-striatal brain regions that mediate self-regulatory control, processes were activated much less than they were in the controls. The patients performed more impulsively on this task and didn’t engage the brain circuitry that’s needed to perform correctly on the task.” Patients with the most severe bulimic episodes or symptoms—the greatest number of binge eating episodes, the highest ratings of preoccupation with shape and weight engaged these circuits even less.

Because this study did not rely on the subjects’ responses to pictures of food, it provided new information. “Nobody has studied eating disordered patients without using symptom-related material. We showed that they’re not just impulsive in terms of their binge-eating behavior, they’re impulsive in terms of their general cognition and brain activation.”

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(A) Group-by-stimulus (congruent vs. incongruent) interactions were detected in frontostriatal regions (red). Activations were greater in healthy (B) than in BN participants (C). Increases in signal during correct incongruent relative to correct congruent trials in red, decreases in blue. (D) Group-by-response (incorrect vs. correct) interactions were detected in frontostriatal brain areas. fMRI signal associated with incorrect versus correct responding on incongruent trials was greater in the healthy (E) compared with the BN participants in (F) the striatum (red). Increased activity in the patients was most prominent in dACC (blue). Increases in signal during incorrect incongruent relative to incorrect congruent trials are shown in red, and decreases in blue. BN, Bulimia Nervosa participants; HC, healthy controls; dACC, dorsal anterior cingulate cortex; ILPFC, inferolateral prefrontal cortex; IFG, inferior frontal gyrus; Lent, lenticular nucleus; Put, putamen; Cd, caudate nucleus; Thal, thalamus; STG, superior temporal gyrus.

continued from **Bulimia Nervosa**, page 6

Current treatments—selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) in which patients are retaught how to feed themselves in a structured intensive outpatient or inpatient setting—are fairly effective, said Dr. Marsh, and

Dr. Marsh has already embarked on a study of younger women with bulimia to see if frontal-striatal abnormalities and impulse control problems exist before the onset of the disorder or predict its course.

are most effective together. The results of this study suggest therapies that target patients' general impulsiveness could also be helpful.

Dr. Marsh has already embarked on a study of younger women with bulimia to see if frontal-striatal abnormalities and impulse control problems exist before the onset of the disorder or predict its course. But she has encountered a few difficulties in enrollment. "A lot of adolescents don't seek treatment," she said. "They don't meet full criteria for the disorder so they're not usually eligible for insurance. And a lot of girls who see my flyers and call because they do want to participate hang up the phone as soon as they find out that their parents need to know about it. It's very messy out there."

Dr. Marsh has some preliminary findings from studying adolescents, though, and these results show that they also fail to activate these self-regulatory control circuits appropriately—evidence that these abnormalities arise early in the course of the illness. "What's needed is a longitudinal study looking at the progression of symptoms in these girls, along with the progression of these brain abnormalities," said Dr. Marsh. "It could be that these circuits do not mature appropriately in them. Maybe once they start engaging in impulsive behaviors it's rewiring their brains in some way. Or it could be that the impulse control problems and frontal-striatal abnormalities come first and predict whether they will go on to develop a disorder. We'd like to figure that out."

Contributing faculty for this article:
Rachel Marsh, PhD

Advances in Neuroscience: Psychiatry, Neurology and Neurosurgery

is a publication of the Neuroscience Centers and the Departments of Psychiatry of New York-Presbyterian Hospital. The Neuroscience Centers are at the forefront of research and practice in the diagnosis, treatment, and rehabilitation of neurologic disease. The Neuroscience Centers include the Neurological Institute of New York at New York-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Neuroscience Institute at New York-Presbyterian Hospital/Weill Cornell Medical Center. The Departments of Psychiatry pursue groundbreaking research and provide comprehensive care of children, adolescents and adults with psychiatric diseases. The Neuroscience Centers and the Departments of Psychiatry are affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College. The Department of Psychiatry at New York-Presbyterian/Columbia is also affiliated with the New York State Psychiatric Institute.

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Important news from the Neuroscience Centers and the Departments of Psychiatry of NewYork-Presbyterian Hospital. Current research projects, clinical trials, and advances in the diagnosis and treatment of patients with neurological and psychiatric diseases.

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ADVANCES IN NEUROSCIENCE AND PSYCHIATRY

continued from **Borderline Personality Disorder**, page 5
affect—fear, anxiety, anger, and hatred. Early in an individual's development these emotionally-charged representations of oneself and others are segregated into two camps: either all-positive or all-negative.

"In the course of normal development these negative and positive affective extremes become integrated and more nuanced over time – corresponding better to the complexity of life," he said. "We hypothesize that, in BPD, the negative and positive extremes are not integrated, resulting in highly polarized black and white thinking—things are either all good or all bad. This is related to corresponding internal representations of oneself as all good or all bad or others as all good or all bad, and explains the chaotic relationships and the extreme shifts from one intense affect to another."

TFP is based on a here-and-now analysis of how the patient is experiencing the relationship with the "other," who, in the therapeutic context, is the therapist. "In TFP, we combine the immediate activated emotion and the engagement of a cognitive capacity to observe what is going on in the moment. We feel that you've got to observe, discuss, and reflect upon the affect as it's being experienced in relation to the other."

In 2007, Drs. Otto Kernberg and John Clarkin, PhD, directed a study that randomized 90 patients to one of three treatments: transference focused psychotherapy (TFP), dialectical behavioral therapy (DBT), and supportive psychodynamic therapy (SPT) for a one-year course of treatment (Clarkin et al, *American Journal of Psychiatry*, 164, p. 922-928). The primary outcome domains they measured were suicidality, anger/aggression, and impulsivity; secondary outcome domains were social adjustment, depression, anxiety, and irritability. The researchers also studied a hypothesized mechanism of change, a mental function called reflective function. Each group showed overall

positive change, but in the DBT group, while there was significant change in suicidality, anxiety, depression, and social adjustment, there was not change in anger/aggression or impulsivity. In SPT there was significant positive change in all but suicidality. In all six domains there was significant positive change in the TFP group.

Dr. Yeomans and his colleagues hypothesize that the mechanism of change is linked to reflective function, which is closely correlated to

"Transference focused psychotherapy is based on the concept that people with borderline personality disorder have underlying identity disturbance."

—Frank E. Yeomans, MD

mentalization, the capacity to accurately perceive and understand one's own internal states of mind and those of others. Reflective function (RF) is measured on a scale from minus one to nine. "A person who is minus one has a grossly distorted, overly concrete, and unintegrated sense of self and of others, while a rating of nine on the RF scale reflects someone who has unusually complex, elaborate, or original reasoning about one's mental states and those of others, with five being considered average RF." In the Cornell clinical trial (Levy et al, *Journal of Consulting and Clinical Psychology*, 74, pp.1027-1040), there was a significant difference between the treatment groups, with TFP the only one that showed a significant increase in reflective functioning (from 2.9 to 4.1). "By encouraging this constant reflection on feelings in the moment, TFP offers a deep level of internal psychological change and enables the person to develop a more complex sense of the entirety of their emotional self and that of others," Dr. Yeomans said.

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