

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

Alzheimer's Proteins Team Up to Spur Decline

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FOR MORE than a century, scientists have struggled to define the relationship between the two brain abnormalities—amyloid plaques and neurofibrillary tangles—that Alois Alzheimer described in 1906 in the disease that bears his name. Researchers at Harvard Medical School recently described a direct link between the buildup of sticky plaques and the tangles of brain cell filaments, a finding that may help unlock the mystery of Alzheimer's and accelerate the steady movement toward prevention and treatment.

"For the past 15 years or so, there's been a bit of a 'religious war' in the Alzheimer's disease community about amyloid beta versus tau," says Dennis Selkoe, MD, the Vincent and Stella Coates Professor of Neurologic Diseases at HMS and Brigham and Women's Hospital (BWH) and senior author of the study, referring to the proteins that form plaques and tangles, respectively. Some researchers

believe that amyloid beta and tau attack the brain independently, while most scientists are convinced the two must somehow work in concert. "We have now shown that the buildup of amyloid beta protein and tau protein are not disparate events in the brain, but instead have a true mechanistic relationship. It's not an either/or. It's both."

A hallmark of Alzheimer's disease is the accumulation of amyloid plaques between nerve-cell junctions in the brain. Amyloid beta is actually a protein fragment snipped from a larger amyloid precursor protein, called APP. In healthy brains, these fragments are broken down and eliminated, but in brains diseased with Alzheimer's, the fragments gradually aggregate into insoluble plaques. Appearing with these plaques are neurofibrillary tangles, twisted strings inside the nerve cells that are made primarily of tau proteins. Tau normally functions as part of a microtubule, a cellular structure that provides scaffolding support for a cell and helps with the intracellular transport of nutrients and other substances.

Scientists don't know exactly how these plaques and tangles affect brain function, but the common belief is that they slowly wring the life out of nerve cells by short-circuiting communication among neurons and ultimately disrupting processes the cells need to survive. The dysfunction, and later death, of these nerve cells leads to memory failure, behavioral changes, and other symptoms associated with Alzheimer's disease.

A potent relationship

Selkoe's study, published April 5 in the *Proceedings of the National Academy of Sciences*, built on his previous work in which tau was genetically deleted from the brains of mice. The researchers found that mice lacking tau protein exhibited less severe behavioral abnormalities than did mice that had both the amyloid beta plaques and tau.

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Dennis J. Selkoe
Vincent and Stella Coates Professor of Neurologic Diseases,
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The Selkoe team chose to define these findings more precisely at the molecular level. They removed neurons from healthy rats, encouraged them to grow in a petri dish, and then exposed these cultured neurons to soluble pairs of amyloid beta molecules, called dimers, that had been isolated from the brains of deceased Alzheimer's patients.

“The amyloid beta and tau proteins work in concert to damage neurons. This degenerative effect, over the course of a decade or two, leads to the spectrum of debilitating signs and symptoms that characterize Alzheimer's disease.”

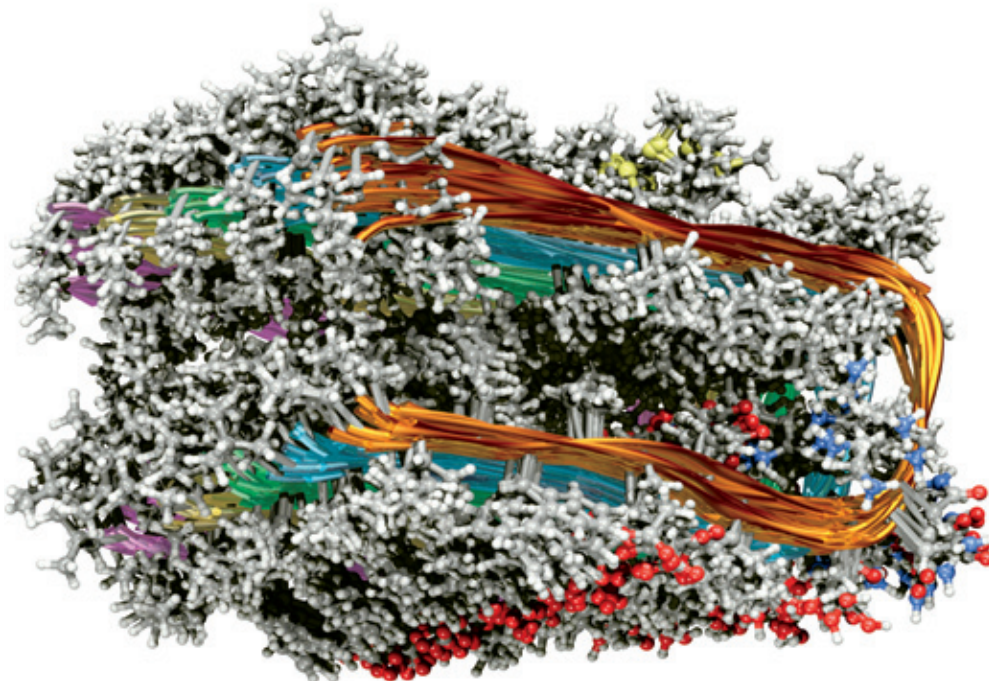
The results surprised Selkoe and his colleagues. The dimers of human amyloid beta protein had devastating effects on the tau proteins in the rat neurons: They collapsed the microtubules that formed the neurons' cytoskeletons and caused degeneration of the nerve cells' dendrites and axons, cell extensions that transmit information to and from the body of the neuron, respectively.

“These amyloid beta dimers from Alzheimer's-affected brain tissue have a potent effect on the

outside of the neuron,” says Selkoe, who also runs the Center for Neurologic Diseases at BWH. “They trigger the addition of extra phosphate molecules to the tau proteins. We believe that these extra phosphates contribute to the cytoskeleton's collapse, as well as to the dendrite and axon abnormalities, causing neurons to become disconnected.”

What happened in the petri dish is similar to what Selkoe thinks happens in the brains of Alzheimer's patients: The amyloid beta and tau proteins work in concert to damage neurons. This degenerative effect, over the course of a decade or two, leads to the spectrum of debilitating signs and symptoms that characterize Alzheimer's disease.

The researchers also found that treating neurons with an antibody designed to grab and remove amyloid beta proteins prevented the ill effects that the amyloid beta dimers had on tau and the neuron's cytoskeleton. Although some potential therapeutic agents have failed to thwart amyloid beta's actions so far, Selkoe says, “it looks like this antibody has the right properties to diminish this process.” A humanized form of that antibody, called bapineuzumab, is now in Phase III clinical trials in several countries. These trials aim to measure the antibody's effectiveness in neutralizing the harmful effects of amyloid beta protein in Alzheimer's patients. Initial results should be available in the summer of 2012.



A molecular model of amyloid beta aggregation. According to Selkoe's research, the presence of amyloid beta aggregates together with tangles of tau proteins may signal the breakdown of neuronal function that marks Alzheimer's disease.

Attacking Alzheimer's early

The Selkoe lab's findings are timely. New biomarkers and new guidelines for defining Alzheimer's are helping doctors diagnose the disease well before advanced impairments set in.

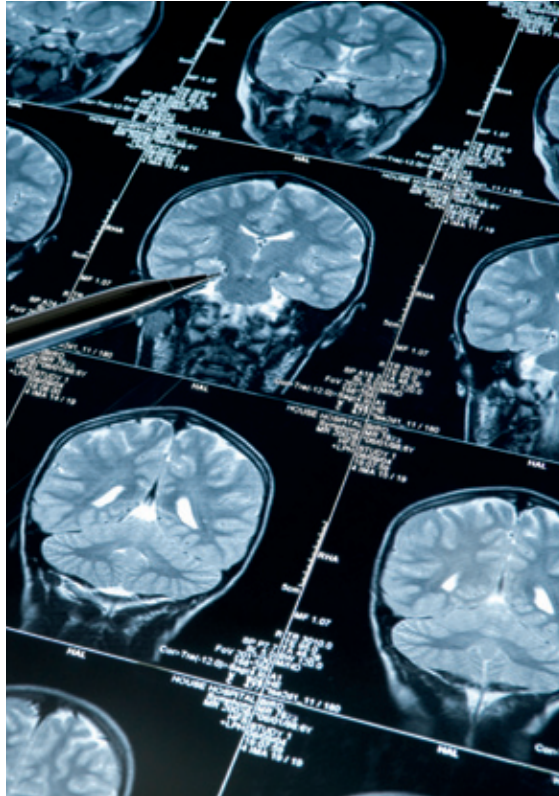
In April, the National Institute on Aging and the Alzheimer's Association jointly issued the first new guidelines for diagnosing Alzheimer's in almost 30 years. Previous criteria were associated with the middle and late stages of the disease, by which time symptoms are well advanced. The new guidelines instead parse Alzheimer's into three distinct stages, beginning with an early, preclinical stage in which patients may appear symptom-free even as their brains are becoming clogged with amyloid plaques, and threads of tau protein are beginning their twisted dance. Next is a stage called low-grade cognitive impairment, which is marked by mild memory problems that do not yet compromise a person's ability to function or live independently. The final stage, Alzheimer's dementia, refers to the period when a person's memory, behavior, and personality undergo increasingly severe changes that eventually prove lethal.

"These guidelines no longer define Alzheimer's as just dementia," says Selkoe. "Instead it's a process that begins subtly, before we can see clinical symptoms."

According to the guidelines, it's too soon for most doctors in the community to rely on biomarkers to make a clinical diagnosis of Alzheimer's. Instead such tests, which include measuring abnormal levels of amyloid beta and tau proteins in spinal fluid and using positron emission tomography and functional MRI to scan the brain for plaque buildup, should be used for patients enrolled in clinical research studies and drug trials. Imaging scans may detect warning signs up to 20 years before symptoms begin.

Selkoe notes that although biomarkers can't definitively diagnose the disease alone, they are becoming vital detection tools. As an example, Selkoe points to spinal fluid assays, which can help clinicians determine who should receive agents that might help slow the decline that occurs with Alzheimer's.

"Our new findings play right into these predictive tests," he adds. "By measuring amyloid beta and tau protein levels in human spinal fluid,



"Imaging scans may detect warning signs up to 20 years before symptoms begin."

we can monitor when tau in particular is increasing. According to the findings of our study, elevated tau levels will tell us that amyloid beta protein has accumulated in the brain and is injuring neurons."

For more than three decades, Selkoe has helped set the pace for Alzheimer's disease research, with his early work including a method for isolating neurofibrillary tangles, the discovery that cells produce amyloid beta protein, and the formulation of the hypothesis that amyloid buildup was a key factor in precipitating Alzheimer's. These breakthroughs set the course for how the scientific and clinical communities now think about Alzheimer's disease. Selkoe hopes his laboratory's latest discovery, which connects the dots between dimers of amyloid beta protein, tau alteration, and neuronal disconnection, will edge researchers a step closer to treatments, and prevention, of this devastating neurodegenerative disease. ♥

Itch and the Brain

This article is part of a series on the internal and external forces that affect the brain.

AS MOST of us know, a good scratch can satisfy an itch. Yet the question of why we itch and scratch in the first place has baffled researchers for years. Recently, however, science has begun to enlighten us to the mechanisms at work in the itch-scratch cycle.

For years, the itch sensation was thought to travel along the same nerve pathway used by pain signals. Itch, in fact, was considered a weakened form of pain. Modern molecular, genetic, and anatomical studies now indicate that itch usually follows its own distinct course, says Qiufu Ma, PhD, an HMS professor of neurobiology who has studied the phenomenon. Itch runs along a neuronal interstate highway system that links the skin, the spinal cord, and the brain.

Itch and pain represent different sensations that evoke distinct behaviors. Place your hand on a hot burner and you instantly pull it away; the pain is intense. By contrast, when a piece of clothing brushes against your bare forearm, you scratch to quiet the irritation, giving little thought to the sensation and your reaction to it.



"These distinct behaviors likely developed to protect us against different types of threats," says Anne Louise Oaklander, MD, PhD, an associate professor of neurology at HMS who studies chronic pain and itch. "Pain is obvious and, without it, we wouldn't live long—there would be nothing to prevent us from putting our hand into a fire or onto that hot burner." She adds that the itch-scratch cycle most likely evolved to protect us from small, clinging threats—insects or plants—that can be avoided by withdrawal movements.

A scratch for every itch

Previously, few studies focused on the neural mechanisms associated with itch, but several recently have succeeded in identifying a neural component to the itch sensation and its scratch

response. In 2009, neuroscientists at the University of Minnesota identified part of the mechanism by which scratch relieves an itch. They showed that relief takes place deep within the spinal cord along the spinothalamic tract. The STT transmits information about sensations, such as pain, temperature, touch—and, it turns out, itch—to the thalamus, deep within the brain. This relays the information to the brain's center for perceptual awareness, the sensory cortex.

In their study, the researchers monitored spinal nerve activity in monkeys whose lower limbs had been exposed to itch-inducing histamine. With each exposure, the monkeys' STT neurons went wild. But when the scientists used a device that mimics monkey fingers to scratch the itchy limbs, they saw a dramatic drop in STT neuronal activity. This sudden drop suggests that the act of scratching calmed the STT neurons.

In a recent study published in the journal *Neuron*, Ma identified a neural component necessary for the pain sensation *and* itch suppression that also may help answer the "why do we itch?" question. This component is VGLUT2-dependent synaptic glutamate, a molecule that is released from certain sensory neurons and that serves as a transport for glutamate, the most abundant neurotransmitter in the brain. Ma came across this pain-itch dualism unexpectedly, while monitoring the behavior of mice that had been genetically altered to lose the action of VGLUT2 in a group of peripheral sensory neurons. He discovered VGLUT2-deficient mice developed itch disorders as severe as those found in humans with chronic itch disorders. Essentially, Ma's research team had created a mouse model that mimics some types of chronic itch in human patients.

"Removing VGLUT2 from pain-related sensory neurons in these mice weakened their responses to acute and chronic pain and caused the sensitization of multiple itch pathways," says Ma. "The mice began to scratch until they developed skin lesions."

The VGLUT2 pathway, says Ma, likely quells excessive itching by activating certain inhibitory neurons in the spinal cord or brain.

Insatiable itch

Common itches brought on by a chemical or mechanical stimulus—think mosquito bites and poison ivy—can be treated readily with agents that counteract histamine, a chemical the body produces to fight allergic reactions. A mosquito bite causes the body to release histamine in the area of the bite, turning the skin red and itchy. An

antihistamine relieves the itch sensation by preventing histamine from binding to itch-instigating receptors in the skin.

Widespread itch, by contrast, is often caused by diseases of internal organs. More than 80 percent of chronic kidney disease patients have chronic, widespread itch, and some patients with liver disease and non-Hodgkin's lymphoma also suffer from severe itch. Certain pain medications, such as opiates, can also trigger itching.

Neuropathic itch is a different kind of chronic itch caused by a malfunction of nerve cells. It appears in many of the same conditions that can cause chronic neuropathic pain, including shingles, a very common viral infection. The complications of shingles are a focus of study for Oaklander in her laboratory at the Nerve Injury Unit of Massachusetts General Hospital. Other conditions that can spur neuropathic itch include spinal cord lesions, brain tumors, and phantom limb syndrome.

"Neuropathic itch is ultimately caused by inappropriate firing of itch neurons in the central nervous system," says Oaklander. "People with chronic itch often feel as if insects are crawling all over them."

Few remedies are available for generalized or neuropathic itch. A new drug on the market, Remitch (nalfurafine), was developed to reduce itching in hemodialysis patients, and may also prove effective for other types of chronic itch that don't respond to antihistamines. This treatment is based on paradoxical clinical observations: Morphine, which triggers a response in certain opioid receptors in the brain, suppresses pain but causes itch, while nalfurafine, which triggers action in another set of opioid receptors, suppresses itch. It is conceivable that a combination of morphine and nalfurafine might relieve pain without causing itch side effects. And, if scientists manage to develop compounds that activate the inhibitory pathway discovered by Ma and his colleagues, "we would have a completely novel strategy to treat itch," he says.

"Scratching," said the sixteenth-century French essayist Montaigne, "is one of the sweetest gratifications of nature and as ready at hand as any. But repentance follows too annoyingly close at its heels."

Now that the scientific community's view of itch has evolved to the point where it's considered a bona fide and potentially serious clinical condition, people who suffer as Montaigne did—his eczema caused him to scratch incessantly—may finally find some relief. ♥



Baby Blues: Mental Illness at the Start of Life

FOR CENTURIES, medical science recited litanies of what a baby's brain could not do. It couldn't focus, it couldn't reason, and it couldn't process emotions or language. It was, more or less, an empty organ waiting to develop. Today, we know that a baby's brain is actually a welter of activity, capable of learning vast amounts of information and mastering complex skills, such as walking and talking, in a relatively short period of time. Neuroscientists and psychiatric professionals are also learning that something more insidious—and more "adult"—may be occurring in the brains of infants and children: mental illness.

A 2010 study by Columbia University researchers found that the number of children age two to five with bipolar disorder who are also being treated with psychiatric medications has doubled in the past decade. In their study, more than half of the preschool children had received a mental health assessment or therapy visit. According to Zero to Three, a national advocacy group dedicated to promoting the health and development of infants and toddlers, one of every ten toddlers appears to suffer some form of mental illness, about the same percentage found in adults.

According to Charles A. Nelson, PhD, an HMS professor of pediatrics and the Richard David Scott Chair in Pediatric Developmental Medicine at Children's Hospital Boston, many young children diagnosed with mental disorders haven't yet developed a strong connection between the brain's prefrontal cortex and the amygdala. The prefrontal

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cortex is responsible for planning complex cognitive behaviors, expressing personality, and moderating social behavior appropriately. The amygdala, an almond-shaped mass of cells deep in the brain, processes emotional reactions, especially fear, and directs affect, the outward expression of emotion. Studies have shown that when the link between the prefrontal cortex and the amygdala is weak, excessive anxiety and other psychological disorders may result.

“Signs of depression in young children can mirror those in adults: A child may cry a lot and be listless, or may develop stomach problems. Refusing to attend school or go to day care could signal depression as well.”

Diagnostic challenges

While the psychopathology of mental illness is different in children and adults, diagnosing these problems in the very young can be tricky. Children experience many physical, emotional and mental changes as they develop, and what is considered normal falls within a wide range of behaviors.

How would you know a two-year-old is suffering from a mental illness? While her appearance or actions might differ in troubling ways from others in her age group, she’s not yet able to articulate how or what she’s feeling. So clinicians must assess a child’s behavioral expression. A day-care provider, for example, may observe a three-year-old sexually groping another child. The first thought might be that the child is sexually abused, at home or elsewhere, or has seen other children abused. While either may be true, says Nelson, it could instead be that the behavior has been triggered by some abnormal brain process.

“We diagnose young children in an informal way, paying close attention to deviations from the norm,” says Nelson. “We look at patterns of behavior and the context in which they occur. It’s normal for a two-year-old to be apprehensive around strangers, but what if that child acts that way with all adults, including his or her grandparents? That’s not normal.”

Signs of depression in young children can mirror those in adults: A child may cry a lot and be listless, or may develop stomach problems. Refusing to attend school or to go to day care could signal depression as well. Each behavior may

indicate a mental disturbance or simply a stage of development from which the child will mature.

In 1994, Zero to Three published *DC: 0–3*, a pediatric diagnostic manual that classifies mental health and developmental disorders. Its guidelines have been used by medical professionals and clinicians to sort out the differences between normal infant behavior, such as sleeping 20 or more hours a day or trembling while crying, and behavior that suggests a depressive or anxiety disorder.

A lifetime of hurt

While statistics show that mental illnesses are on the rise in children, it’s less clear why such disorders might emerge at such tender ages. Genes have some role: Mental illnesses, especially anxiety disorders and depression, tend to run in families. Physiology also may play a part. Neurotransmitters, chemicals found in the brain, may become disrupted, interfering with messages transmitted between nerve cells. Psychological trauma, such as physical, emotional, or sexual abuse, and environmental stressors (a death, divorce, or dysfunctional family life) may also trigger mental illnesses in vulnerable infants and toddlers.

“A lot depends on the nature of a child’s experiences, how many they’ve had, and when they’ve had them,” says Nelson.

In a study of Romanian preschool children, Nelson and his colleagues found a high prevalence of mental health issues—depression, anxiety, and attention-deficit disorders—in children who were institutionalized, while kids in stable foster homes had less than half the rates of depression and anxiety. Many of the institutionalized children suffered neglect and abuse, strong triggers for mental illness. Nelson says that profound neglect is “almost a guaranteed pathway” to mental health problems.

What Nelson’s study also showed, and what underscores its insight for mental health professionals, pediatricians, and early-childhood educators working with toddlers, is that early intervention is key. Parents, too, need to be educated to recognize risk factors and red-flag behaviors that might warn of a potential mental illness. And mental health consultations need to be integrated into regular well-child visits.

The receptiveness of a young child’s brain to learning means early interventions can be successful. That’s important, says Nelson, because research also has shown that mental disorders that start early, and go untreated, will likely trouble a life for decades to come. ♥

Restoring Calm in Classrooms Touched by Violence

ON A SPRING DAY IN 1999, two young men walked into Columbine High School armed and ready to kill. To the horror of a nation, they did.

The events of that April day in Colorado are etched in the minds of millions of Americans: terrified teenagers fleeing mayhem and death, 12 students and a teacher killed, 24 others wounded, and a suburban community forever changed.

In the United States, wrenching, life-taking, school-based violence has upended the world of students more than 200 times since 1966, a year shaken by the infamous University of Texas–Austin “tower massacre” in which 16 students, faculty, and bystanders perished under a sniper’s aim.

While experts often disagree on the best approach for getting students back on track psychologically and emotionally after a shooting, most agree that calming the classroom is an essential first step.

A school classroom is supposed to be a safe haven, a comfort zone of learning, growth, and creativity. But when it becomes a theater for horror, getting back to normal can seem impossible.

“Creating a calming environment,” says Gil G. Noam, PhD, an HMS associate professor of psychiatry at McLean Hospital, “can simply mean engaging in small changes that, taken together, temper student anxiety. Teachers might, for example, work to keep their voices low or at least avoid raising them. They should also avoid escalating speculation about the incident or dwelling on the traumatic experience. Instead, teachers should help kids regain their focus on their school work and on their ability to do their best.” Noam also directs McLean’s Program in Education, Afterschool & Resiliency, or PEAR.

According to the U.S. Centers for Disease Control and Prevention, students who witness school shootings can suffer myriad cognitive problems, such as memory loss, confusion, and concentration difficulties, as well as psychological disturbances, including feelings of helplessness, mood swings, and anxiety, all impediments to learning. A study of a 2001 shooting at Santana High School in Santee, California, found that more than a quarter of the students directly exposed to that violence suffered post-traumatic stress disorder to some degree up to nine months after the incident.

Through PEAR, Noam develops school-based trauma interventions as well as programs that build resiliency and prevent high-risk behavior among youth. The goal, he says, is to create an environment in which students build strong bonds with teachers, guidance counselors, and school administrators.

Resilience, Noam says, refers to an individual’s capacity to cope with and recover from stress and adverse events. This coping mechanism, which allows a person to bounce back to normal levels of emotional, cognitive, and psychological function, takes center stage in many trauma interventions.

Back to normal

The classroom, says Noam, is a natural place for healing to occur because it’s a comfort space for most children. Classrooms mean structure and focus, places where kids feel connected to people they trust. Recognizing this school–student bond, a team led by Mary Harvey, PhD, an HMS associate clinical professor of psychology and founding director of Cambridge Health Alliance’s Victims of Violence program, designed a community–intervention model. Rather than relying on outside experts to take charge of the healing process, the model mobilizes the creativity and resilience of people directly involved.



“Kids are familiar with their parents and teachers,” Harvey says. “They know them and trust them. Why would they trust more someone from the outside, someone they don’t know?”

A growing number of school systems have protocols in place to deal with potential tragedies, says Harvey. Some plans are as simple as bringing the students together in an assembly hall—

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a familiar space found in most schools—where talk is safe but mediated. Such assemblies allow students to discuss the incident, share their feelings about it, and get updates from administrators. By contrast, Noam represents another school of expert thought that argues that traumatized students are not particularly helped by discussing the incident because that can stimulate a traumatic response.

Many experts say classrooms are incubators for resilience, places where students learn to set goals and develop high expectations for achievement despite the adversities life may hand them. Building resilience helps students develop a sense of belonging and involvement and can decrease feelings of alienation and disengagement, both of which can develop after traumatic events. Together with a calm environment, say experts, this resilience—this connection—provides a sort of protective armor, giving students hope and the strength to recover and move on. ♥

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