ON THE BRAIN

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Anger and the Brain

continued from page 7

Perlis cautions that the success of anger management and CBT depends on the quality of the program—who designed it, who runs it, how intensive it is, and the individual's motivation. "You need to be motivated to change your behavior," he says. "When you get to the point that you recognize what the anger is doing to yourself and others, that's the time to get into an anger management program and when anger management is most successful."

Other avenues for treating anger include medications such as antidepressants and anti-convulsants, the latter of which help with impulsivity, and a class of drugs called serenics, which Dougherty says work primarily through dampening limbic system responses. Treating underlying mood disorders or depression can also help alleviate angry outbursts.

Perlis says it is important to remember, however, that "everyone gets angry; not everyone needs treatment."

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THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

Cognitive Neuroscience: Understanding Complex Human Behavior and the Brain

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CONTENTS

1 *Cognitive Neuroscience: Understanding Complex Human Behavior and the Brain*

3 *The Stress of Poverty Affects Childhood Brain Development*

5 *Small Amyloid Assemblies Provide New Target for Alzheimer's*

6 *Anger and the Brain*

Since the dawn of civilization, humankind has tried to answer vexing questions about the relationship between the body and the mind. In the last 20 years or so, the scientific and medical communities have made great strides in answering the question of how physical matter (the brain) relates to mental (cognitive) phenomena such as perception, memory, learning and attention. In large part, the study of that relationship resides in the relatively new field of cognitive neuroscience.

"Cognitive neuroscience is a discipline that merges psychology and basic neuroscience," says Dean F. Salisbury, PhD, an associate professor of psychiatry at Harvard Medical School and director of the Cognitive Neuroscience Laboratory at McLean Hospital. "We're trying to understand complex human behavior in the construct of plausible brain systems."

Taking a multidisciplinary approach to the study of the brain and human behavior, cognitive neuroscience involves the study of internal mental processes and the chemistry, physiology and anatomy of neurons and neural systems. It also examines theories that explain the relationship between the brain and behavior and compares neural systems across species.

A "cute idea"

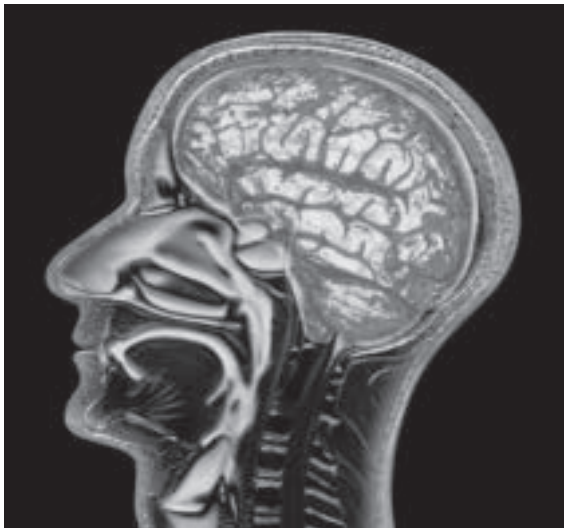
The roots of cognitive neuroscience lie in the same work as the now defunct field of phrenology in which personality traits were determined by "reading" bumps and fissures on an individual's skull. Developed by German physician Franz Joseph Gall around 1800, phrenology was based on the concept of localization; that is, that certain areas of the brain have specific, localized functions. Gall believed that the brain was made up of 27 different "organs" that created an individual's personality. These organs included affection and friendship, self-defense and courage, vanity, circumspection, sense of language, and kindness, among others. A person's capacity for a given personality trait was determined by the size of that "brain organ," and could be measured by the area of the skull that covered a given region of the brain in which the specific trait was thought to reside.

While some of the assumptions of phrenology are still valid (such as certain mental processes being localized in the brain), the shape of a person's skull is not a reliable predictor of personality.

"Gall and Spurzheim [Johann Gaspar Spurzheim was a German physician and chief proponent of phrenology] went overboard on localization," says Salisbury. "They said that when you have more of that personality trait, then that area of your brain is bigger. Looking at bumps on your head is a cute idea, but cognitive neuroscientists don't have lot in common with that extreme form of phrenology."

While many cognitive neuroscientists still follow the theory of localization, the more modern

continued on page 2



continued from page 1

thinking is that behavior is governed by both local action and distributed networks throughout the brain.

Imaging drives science

Advances in imaging technology have driven modern-day cognitive neuroscience. In the last 20 years, in fact, modern imaging techniques have significantly contributed to the emergence of cognitive neuroscience as a discipline.

While a host of imaging methods are used, three techniques—EEG, functional MRI, and structural MRI—form the basis of much of the work done in cognitive neuroscience. The first, EEG (electroencephalography), measures the electrical activity produced by the brain. Abnormal EEG results can indicate irregular brain structures and can be a sign of attention problems, seizure disorders, or confusion. Salisbury says EEG and extraction of specific event-related brain activity from the EEG lets scientists see electrical activity changes "at the speed of thought."

Secondly, through advances in magnetic resonance imaging (MRI), researchers and clinicians can see brain activity while a person is performing certain functional tasks. Functional MRI (fMRI) is a relatively new procedure that uses MRI scans to measure metabolic changes that take place in an active part of the brain. This technology is used to examine the brain's anatomy to determine which areas are handling critical functions such as thought, speech, movement and sensation.

Thirdly, structural MRI maps the water volume inside the body. Because different tissues have different amounts of water in them, structural MRI gives a very detailed image of these tissues. Unlike X-rays or CT scans, structural MRI is not affected by the skull bone and thus gives an extremely fine picture of brain structure, with the greatest contrast between gray and white matter. Gray matter is akin to a computer, while white matter is like the cables connecting the different computer components to one another. By providing the highest resolution of brain anatomy, Salisbury says, structural MRI is valuable for cognitive neuroscientists because is allows for very precise measurement of brain volumes in specific areas.

"EEG has been large in cognitive neuroscience since the late 1960s, early 1970s," says Salisbury. "Other [technologies] that came along in the '90s have taken over." He adds that increasing numbers of cognitive neuroscientists and research psychiatrists are using the newer methods of MRI, which provide better spatial resolution of activity within the brain than earlier EEG-based tools.

Clarifying thought disorders through imaging

In the Cognitive Neuroscience Laboratory at McLean Hospital, Salisbury has spent the past 16 years studying brain structure and function, trying to determine what regions of the brain are abnormal in mental illnesses such as schizophrenia and bipolar disorder and what the brain looks like in the early courses of these diseases. Among other studies, he uses multimodal brain imaging to examine cognitive-level thought disturbances.

Thought disturbance is a cardinal symptom of schizophrenia, a mental disorder characterized by abnormalities in the perception and expression of reality. The disease typically includes auditory hallucinations, paranoid or bizarre behavior, or disorganized speech and thinking. Salisbury and his colleagues are combining behavioral measures and brain activity measures to clarify the nature of thought disorder and cognitive dysfunction in schizophrenia with respect to actual brain structure and function.

Until recently, it was thought that schizophrenia was caused by poor interpersonal relationships between the patients and their mothers. Better imaging techniques, says Salisbury, allow researchers and clinicians to identify changes in the brains of schizophrenics and develop interventions to halt the process and possibly cure the disease.

If a specific brain function is localized to a certain area, MRI can measure that area to see if varying gray matter volumes lead to different brainwave patterns. Bigger brain areas might not mean better performance, Salisbury says, but even subtle pathology in the these areas generally leads to functional consequences to which the brain waves are sensitive.

"If you believe the brain is important for human behavior," he says, "then cognitive neuroscience is relevant. It's important to think about human behavior and how it might be served by the brain. Cognitive neuroscience gives us information about the human condition based on plausible information about the brain. It helps us understand how we work and helps us design interventions based on the brain mechanisms involved."

A long way, indeed, from feeling a bump on someone's head.

The Stress of Poverty Affects Childhood Brain Development

The high prevalence of developmental difficulties among poor, disadvantaged children has been chronicled for years. We don't, says Jack P. Shonkoff, MD, need another study simply documenting that association.

"We've known for a very long time that there's a link between low income or low parent education and poor school achievement as well as increased risk for physical and mental health problems," says Shonkoff, the Julius B. Richmond FAMRI Professor of Child Health and Development and director of the Center on the Developing Child at Harvard University.

The big question, he says, is why? What is it about poverty and low parent education that leads to children having more problems in school and in life? Shonkoff and his colleagues at the Center on the Developing Child are among those who are trying to understand the causal mechanisms that link highly stressful experiences with later problems in learning, behavior and health.

According to the National Poverty Center at the University of Michigan, children represent a disproportionate percentage of the poor in the United States. Children make up nearly one-quarter of the total U.S. population, but account for 35 percent of the poor. In 2007, 13.3 million children, more than 17 percent of the children in the country, lived in poverty.

The developing brain

At the time of birth, the architecture of the human brain is underdeveloped. The brain, as it grows, is constantly wiring and refining the connections among its trillions of nerve cells and the synapses through which messages are sent throughout the brain. In early childhood, the brain is genetically programmed to develop many more synapses than it will ever use, with different circuits being formed in different areas of the brain at different times. This brain circuitry is influenced by a blend of genetics and experience.

"The brain expects the environment to influence its evolving circuitry," says Shonkoff. "These circuits are literally shaped by personal experience."

This process of circuit building results in what some scientists call biological embedding; that is, experience gets built into our bodies and has physiological effects on the brain as well as other developing organ systems. Stable, predictable relationships and a nurturing environment, he adds, may create stronger brain circuits. Likewise, sound circuits for learning may require an environment with plentiful opportunities for interaction and safe exploration.

Parents who are preoccupied with the daily struggle of putting food on the table and shelter over their family's head often don't have the resources, education or time necessary to provide the kinds of experiences that could be required to facilitate healthy brain circuit development in their children. Shonkoff says that in poor, less educated families there is reduced language interaction between parents and children, and the stresses associated with poverty can produce physiological responses that derail the healthy development of brain circuitry.

According to The Ounce of Prevention Fund, an organization dedicated to helping children in low-income families overcome the challenges

continued on page 4

"The brain expects the environment to influence its evolving circuitry," says Shonkoff.

"These circuits are literally shaped by personal experience."

—Jack P. Shonkoff, MD

continued from page 3

of poverty and prepare for successful schooling, "Infants and children who are rarely spoken to, who are exposed to few toys, and who have little opportunity to explore and experiment with their environment may fail to fully develop the neural connections and pathways that facilitate later learning. Despite their normal genetic endowment, these children are at a significant intellectual disadvantage."

'Toxic stress' alters brain circuitry

Significant and continuing stress can have a negative impact on early brain development. The day-to-day adversity of severe poverty and parental mental health problems such as maternal depression, which has a higher prevalence among poor women, can compromise parent-child interaction. The resulting lack of responsiveness—as well as violence, abuse, drugs and alcohol—is incredibly stressful for children, says Shonkoff.

Unrelenting stress in the absence of supportive relationships with adults—referred to as "toxic stress"—causes a prolonged activation of the body's stress response system, which includes the release of stress hormones such as cortisol. Released by the adrenal gland, cortisol circulates in the brain during the body's fight-or-flight response to stress. Under normal circumstances, cortisol has short-term benefits that help protect us from danger. When the cortisol system is repeatedly activated, however, levels of cortisol remain high and can actually damage the brain.

"The area of the brain most sensitive to elevated cortisol is the hippocampus," says Shonkoff, "the region of the brain where basic memory and early learning circuits are developing. High levels of cortisol can kill brain cells and disrupt circuit development in this region."

Constant adversity also produces what scientists call allostatic load, or the physiological costs of chronic stress, which include high blood pressure, increased heart rate, and elevated blood sugar and cortisol levels. Shonkoff says this may help explain why rates of hypertension, diabetes and heart disease are higher in low-income populations. "Chronic activation of the stress response system precipitated by deep poverty," he says, "causes physiological changes that can affect the cardiovascular system, brain circuits that influence learning and memory, and other metabolic systems."

High quality programming to help the brain develop

The principles of neuroscience inform "reasonably good" guidelines for clinicians and policymakers who want to promote healthy brain development in poor children, says Shonkoff. An environment of stable, nurturing relationships and varied opportunities for learning produce positive effects. Healthy brain development can also be promoted by protecting children from chronic adversity. Exactly how to do this in the most effective way, however, has been a public policy challenge for decades.

The place to start is to think about how communities support families with young children, says Shonkoff. Many times parents are not aware of how their interactions affect their children's development. This includes talking and playing with them or reading to them at an early age. In situations where parents can't provide what children need, due to extreme poverty, substance abuse, mental illness, or violent relationships, interventions targeting the source of the stress as well as the needs of the family and children are essential.

Universal access to prenatal and primary health-care services is also essential, so all children can benefit from early diagnosis and preventive measures, and affordable, accessible, high-quality childcare programs can provide nurturing environments that promote learning. In a study in the late 1990s, the National Center for Early Development and Early Learning found that, because childcare providers are often poorly trained, a majority of children in lower quality daycare programs "do not have the opportunity to form the kind of comfortable, secure relationships with a caregiver who will promote their healthy emotional development."

Shonkoff says that childcare and educational programs for low-income children can be organized "based on what the brain needs to develop in a healthy way." The quality of these programs—in terms of staff training and stability, a language-rich environment, high ratio of adults to children, and safety, among other aspects—is essential.

"We know the characteristics of good quality programs," he says, "and if a program has those features, we know it will be more successful in helping children develop."

Small Amyloid Assemblies Provide New Target for Alzheimer's

In the early 1990s, Dennis Selkoe, the Vincent and Stella Coates Professor of Neurological Diseases at Harvard Medical School and neurologist at Brigham and Women's Hospital, made a discovery that provided an important clue to the development of Alzheimer's disease. He and a group of researchers found that even normal brain cells produce soluble forms of amyloid beta-peptide (Abeta), the protein found in the plaques of patients with the disease, raising the possibility—since confirmed—that Alzheimer's might actually be a direct consequence of Abeta over-production. Selkoe and his colleagues soon showed that when mutant forms of certain genes are present in Alzheimer's patients, the cellular production of Abeta is doubled, or more.

Now, Selkoe and his coworkers have taken that knowledge a step further. Using extracts of human brain tissue obtained from patients who died of Alzheimer's, Selkoe has found that dimers of Abeta, the smallest possible assembly of the protein, can lead to the dysfunction and loss of synapses that are the hallmark of early Alzheimer's disease. A synapse is the point of connection between two nerve cells through which chemical signals travel.

"Like most things with Alzheimer's, these dimers [so-called because they consist of two small molecules that bond together] appear very early in the disease process, even many years before clinical symptoms," says Selkoe. "We don't know precisely how they induce synaptic dysfunction, but we speculate it is because they bind to neuronal membranes and perturb important proteins within them."

Selkoe says the findings are significant because this is the first time Abeta assemblies have been isolated from the brains of actual Alzheimer's patients and their effects established. "Others have studied Abeta effects in genetically engineered mice or with synthetic Abeta in cell culture," he says, "but not from a human host. We feel this is the real significance of the study."

Plaques, tangles are culprits in Alzheimer's

Alzheimer's disease is a progressive, fatal disease that destroys brain cells, causing problems with memory, thinking, and behavior severe enough to interfere with daily life. According to the Alzheimer's Association, the disease affects nearly 5 million Americans and begins its development in the hippocampus, the part of the brain responsible for memory. From there, it appears to spread to the cerebral cortex, the brain's outer layer, which plays a key role in memory, attention, language and perceptual awareness.

Two abnormal structures—plaques and tangles—are the primary culprits that cause damage to nerve cells in the brains of Alzheimer's patients. Plaques, which build up between nerve cells (including outside the synapses), contain large, insoluble fibers of Abeta protein. Tangles are twisted fibers of another protein, called tau, that form inside some nerve cells. Scientists have long debated what roles plaques and tangles play in Alzheimer's, but they now believe that plaques precede tangles and that the two lesions act in concert to block communication among nerve cells and disrupt the activities required for neurons to survive.

The early stages of Alzheimer's occur when memory begins to diminish, although the patient usually needs little or no assistance with daily routines at that point. After diagnosis, patients gradually progress beyond early-stage disease, reaching a more advanced stage that is associated with confusion, irritability, aggression, mood swings, and long-term memory loss for which there is currently no cure. Eventually, bodily functions are lost, ultimately leading to death.

Destructive dimers

In their study, published in *Nature Medicine* in June 2008, Selkoe and his team, which included Ganesh Shankar, Shaomin Li and Bernardo Sabatini, all of Harvard Medical School, tested extracts of cerebral cortex taken from the brains of people who died of Alzheimer's or other dementias, as well as those without dementia. They found significant amounts of soluble Abeta in the brains of Alzheimer's patients and little in any of the others.

Previous postmortem brain studies showed that soluble forms of Abeta correlate most strongly with the cognitive symptoms of Alzheimer's. The researchers found that small soluble Abeta assemblies taken from patients' cortices inhibited long-term potentiation (LTP) and encouraged long-term synaptic depression. LTP is an electrical correlate of the strengthening of the connection between two neurons and is commonly regarded as a surrogate for the cellular basis of memory. Long-term synaptic depression is the selective weakening of neuronal synapses.

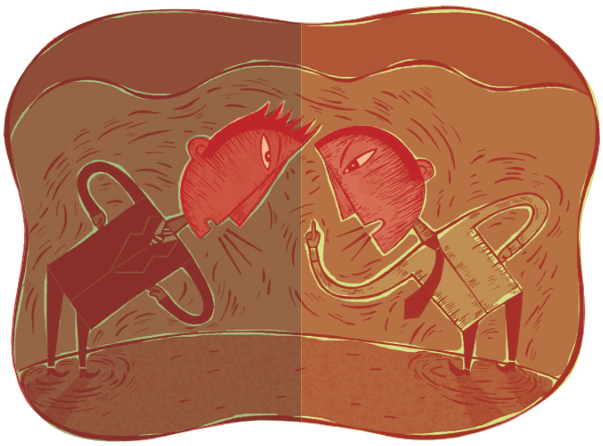
"We're not certain why these dimers are so destructive," says Selkoe. "We think small is bad because the dimers are easily diffusible and can go

continued on page 7

Anger and the Brain

This is the first in a series of articles on how internal and external forces affect the brain.

The physical signs of anger are unmistakable. Our heart rate increases, sometimes climbing from a normal 80 beats per minute to more than 180; our blood pressure elevates to often dangerously high levels. Breathing becomes more rapid as we try to get additional oxygen into our bodies, the muscles used for the fight-or-flight reaction tighten, and the energy outburst can cause a deficiency in our blood sugar that makes us literally "shake" from anger. But, what is going on in our brain when we get angry?



"A lot goes into anger," says Roy Perlis, MD, an assistant professor of psychiatry at Harvard Medical School who studies anger and the brain. "There's the physical: the pounding heart, sweating, gestures: and the mental: thinking about why you're angry and what you're going to do about it. So, as far as the brain is concerned, anger is both cortical [higher cognitive aspects] and subcortical [physiological aspects]."

Imaging studies have shown that in normal individuals (those without underlying mental or physical illnesses), there is increased activity in the orbitofrontal cortex (OFC), the area of the brain behind the forehead that controls reasoning and other higher cognitive functions. At the same time, blood flow to the amygdala, the almond-shaped region deep in the brain that controls emotions, also increases its activity. Angry emotions in the amgydala are thus cooled by activity in the OFC, inhibiting our thoughts of rage.

But, why then, do we not fly into a fit of rage every time we become angry?

"Our, and others', hypothesis is that the OFC plays a crucial role as a brake when our limbic system [which includes the amygdala] is active; that is, when we are emotional," says Darin Dougherty, MD, a psychiatrist at Massachusetts General Hospital and associate professor at HMS. "Most people have intact, functional OFCs, so they are able to avoid frequent bouts of rage. Of course, our findings are that patients who *do* have frequent bouts of rage, *do not* activate their OFCs to the degree that healthy volunteers do."

Perlis, whose work focuses on regions of the brain influenced by genetics, says there is likely a genetic component that influences how we respond to anger, either controlling our own or responding to others who are angry. Some studies suggest that twins are more likely to act similarly to hostility and anger than are unrelated people.

"There is some inherited factor [that predisposes one to angry outbursts]," he says. "There's some normal variation in the population, so we know it's not pathological, just like we know there are some people who are 6 feet tall and others who are 5'9"."

Psychiatric disorders, including depression and bipolar disorder, influence how prone one is to anger. More than half of those with major depression report significant problems with irritability, says Perlis, so "as often as depression is about sadness, it can also be an angry state." Bipolar disorder is also tied to anger, with irritability often being a primary feature of the illness. In addition, substance abuse has a strong effect on anger and its consequences.

In general, Perlis adds, anger is a normal, sometimes even healthy, emotion. "People shouldn't be afraid to get angry," he says. "We worry about it when it impacts the individual's or others' lives or becomes pervasive."

Emotion and control

In 2004, Dougherty and his colleagues published findings in the *Archives of General Psychiatry*, showing that people suffering from major depressive disorder (MDD) and anger attacks have decreased blood flow to the OFC and amygdala, which reduces their ability to control impulsive acts and the feelings about the consequences of their actions. Thus, they suffer both a lack of emotion and a lack of control. Dougherty's team found significantly less activation of the OFC in patients with MDD with anger attacks when compared to a control group, but did not find a difference in amygdala activation between the groups. The amygdala came into play when they looked at areas of the brain that correlated with OFC activation. In normal patients, they found a healthy inverse reciprocal relationship in function between the two structures, whereas

this relationship was exactly the opposite in MDD patients with anger attacks (with MDD patients without anger attacks falling in the middle).

"We don't know that the underlying neurobiology of frequent rage attacks in patients with major depression with anger attacks is any different than that in other populations who have frequent rage attacks," says Dougherty. "In fact, studies of patients with borderline personality disorder (BPD) or intermittent explosive disorder (IED) exhibit results very similar to ours. We chose patients with major depression with anger attacks as a convenient vehicle for studying rage attacks, whereas others have studied BPD and IED."

Harvard researchers, including Ronald Kessler, PhD, a professor of health-care policy at HMS, found that IED, a disorder characterized by frequent bouts of angry and potentially violent outbursts, affects nearly 16 million adults and may predispose them to other mental illnesses and substance abuse.

Changing the way we think, feel, act

While it is hard to change a habitual behavior such as anger, formal anger management programs that focus on reducing both emotional feelings and the physiological arousal that contributes to anger can help individuals control their reactions. Perlis says that anger management programs that are based on cognitive behavioral therapy, or CBT, are often the most successful.

CBT is an umbrella term for several types of therapies. These are all based on the idea that our thoughts, not external things like other people, situations and events, cause our feelings and behaviors. The benefit of this is that we can change the way we think, feel and act even if the situation doesn't change.

"The approach to anger would be to either lessen the limbic response, strengthen the brakes in the OFC, or a combination of the two," says Dougherty. "CBT utilizes cortical regions, such as the OFC and other prefrontal areas, and strengthens them so they are better able to suppress limbic responses."

continued on page 8

Small Amyloid Assemblies Provide New Target for Alzheimer's

continued from page 5

into the synaptic cleft, bind to membranes, and cause local damage."

The HMS team also collaborated with scientists at University College Dublin to test human Abeta's effect on behavior. They injected soluble Abeta dimers isolated from patients' brains into the brains of adult rats and found that the dimers induced certain characteristics of Alzheimer's in the rats, specifically disrupting the memories of newly learned behaviors. The dimers, they further determined, acted directly on synapses, damaging the connections that are essential for neuron-to-neuron communication.

Neutralizing Abeta

The findings provide a potential new target for anti-Alzheimer's drugs, including antibodies that effectively neutralize Abeta dimers, says Selkoe. His team found that antibodies that target the first amino acid at the beginning of the Abeta protein worked best at neutralizing the protein.

Four related clinical trials are currently being conducted in the United States and Europe to determine if an N-terminus antibody can neutralize the adverse effects of Abeta dimers in Alzheimer's patients. Unpublished results of a Phase II study, conducted by Elan Corporation and Wyeth Pharmaceuticals, showed some encouraging results in patients with mild to moderate stages of Alzheimer's.

The HMS research has implications beyond Alzheimer's disease. The same Abeta process that causes Alzheimer's, Selkoe says, can also contribute to age-related mild memory loss. "There are other reasons [for age-related memory loss] than Abeta," he says, "but some percentage is represented by Abeta attacks on neuronal synapses."

Selkoe says the next step in the research is to fully purify Abeta dimers and trimers from patients' brains, label them with radioactive chemicals, and bind them to slices of mouse brain to determine which specific neuronal receptors are impaired by human Abeta. These receptors may provide additional targets to attack with drugs.