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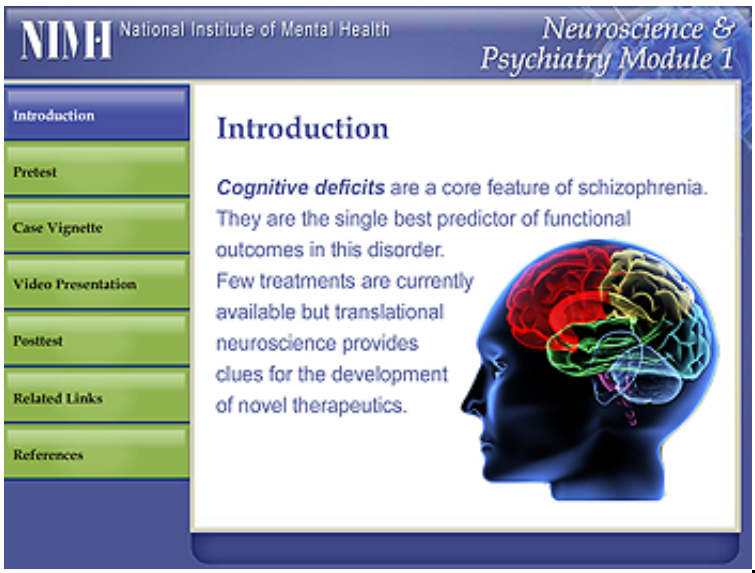
Neuroscience and Psychiatry Module 1: Translating Neural Circuits into Novel Therapeutics



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Neuroscience and Psychiatry video (http://www.nimh.nih.gov//neuroscience-and-psychiatry-module/index.html)

Introduction

Cognitive deficits are a core feature of schizophrenia. They are the single best predictor of functional outcomes in this disorder. Few treatments are currently available but translational neuroscience provides clues for the development of novel therapeutics.

Case Vignette

58 year old single white female with a 40 year history of paranoid schizophrenia. She is an attorney who was able to practice law for a period of time despite hallucinations beginning at age 18.

She has had multiple hospitalizations and symptoms have been variably controlled with medications and supportive therapy/reality testing.

Cognitive decline continued over the years and gradually she was unable to read her law books leading her to retire on disability. She then became unable to read fiction books, then newspapers and now she is only able to read headlines. She has to hire someone to pay her bills.

Extensive workup revealed neuropsychiatric abnormalities that are consistent with chronic schizophrenia but no other dementing process. Her inability to think or read is very distressing to her.

She retains enough function to live independently but is unable to tolerate being in public, cannot function even at a volunteer job and has become extremely socially isolated.

Video Presentation: Translating Neural Circuits into Novel Therapeutics

Can understanding the disease process free us from a dependence on serendipity in the development of pharmacological treatments of psychiatric disorders and lead us to a rational basis for novel therapeutics?

Dr. David Lewis and his group set out to answer this question in schizophrenia using the following strategy; understanding the pathological entity, linking it to the pathophysiology and the clinical syndrome and using this knowledge as a basis for treatment development. The clinical aspect of schizophrenia that Dr. Lewis and his group focused on is cognitive deficits.

Cognitive deficits are core features of schizophrenia. They are prevalent in patients with schizophrenia, precede the onset of psychosis, persist across the course of the illness and, importantly, predict long term functional outcomes. They are also present in a milder form in unaffected relatives. Treatment of cognitive deficits in schizophrenia remains a challenge.

One cognitive deficit that's been very extensively studied in schizophrenia is working memory. We know that patients with schizophrenia do not perform well on working memory tasks. Normally, working memory tasks lead to the activation of the dorso lateral prefrontal cortex or DLPFC. DLPFC activation is also impaired in schizophrenia.

What types of alterations in DLPFC circuitry contribute to these cognitive deficits in schizophrenia? There are two main groups of neurons in the cerebral cortex, pyramidal neurons and GABA neurons. Pyramidal neurons are the major excitatory cells in the cerebral cortex and most GABA neurons are inhibitory.

Pyramidal neurons are all pyramidal in shape and rather difficult to differentiate from each other. In contrast, GABA neurons are diverse in appearance, neurochemical content and electrophysiological properties and can be differentiated from each other.

Let’s focus on GABA neurons. What is GABA? GABA is an inhibitory neurotransmitter that is synthesized by an enzyme called glutamic acid decarboxylase or GAD_{67}. Once released in the synapse, GABA

produces its inhibitory effect.

GABA is then taken back up by the GABA membrane transporter GAT-1.

What does that have to do with cognitive deficits in schizophrenia? One of the most replicated findings in schizophrenia is a reduction in the expression of GAD_{67} and GAT-1 in the dorsolateral prefrontal cortex.

This decrease in the expression seems to be restricted to a subset of GABA neurons. These are the so-called parvalbumin containing neurons including a type of GABA cells called chandelier neurons.

The axon terminals of chandelier neurons synapse on the axon initial segment of pyramidal neurons where action potentials are generated.

Under certain circumstances and because of this critical location, chandelier axons can exhibit a powerful inhibitory effect on pyramidal neurons. In addition, each chandelier neuron synapses on the axon initial segment of ensembles of pyramidal neurons which helps synchronize their firing. Therefore, the reduction of GABA production in chandelier neurons can affect their inhibitory function AND the synchronization of firing of pyramidal cells.

In schizophrenia, because GABA production in chandelier neurons is reduced, the system attempts to compensate. There are findings in the DLPFC in schizophrenia that appear to be compensatory. The first such finding is a decrease in the expression of the GABA transporter GAT-1. GAT-1 removes GABA from the synapse after its release, it is essentially a recycling agent. When there is not enough release, keeping GABA in the synapse longer is one way of compensating. This can be achieved by decreasing the transporter.

Another finding in schizophrenia that can be interpreted as a compensatory change is the increase of a particular type of $GABA_A$ receptors on the postsynaptic side. There are several types of $GABA_A$ receptors, the one containing the alpha 2 subunit protein is particularly enriched at the axon initial segment of pyramidal neurons and is, interestingly, the type of $GABA_A$ receptor that is increased in schizophrenia presumably in order to enhance the postsynaptic effect of GABA in an attempt to compensate.

How can these findings at the level of neural circuits relate to abnormal cognitive function in schizophrenia?

As mentioned earlier, chandelier neurons help synchronize oscillatory activity of cortical pyramidal neurons.

This activity leads to the production of cortical network oscillations in the gamma band (30-80 Hz) range. Gamma band oscillations are an essential mechanism for cortical information processing during cognitive functions.

If a patient with schizophrenia is asked to perform a working memory task, not only is their performance impaired, gamma synchrony in the prefrontal cortex, measured by EEG, is also lower than in normal controls.

These findings are, therefore, consistent with the hypothesis that impaired GABA neurotransmission in chandelier neurons in the DLPFC contributes to deficits in gamma band power and to cognitive impairments in schizophrenia.

Clearly, the compensatory measures that the system produced, namely, decreasing GAT-1 expression and increasing $GABA_A$ receptors that contain the Alpha 2 subunit, are not sufficient. Can we use a pharmacological agent to boost the compensatory response?

One possibility is to use an agonist for $GABA_A$ Alpha 2 subunit receptors.

In a proof of concept clinical trial conducted in 2008, a GABA agonist was administered to patients with schizophrenia for four weeks. Other patients received placebo. Outcome measures included measures of working memory and tasks designed to increase the synchronous Gamma oscillations in the brain.

The investigators showed that patients with schizophrenia who received the agonist had an improved performance on the working memory tasks compared to those who received placebo. Moreover, they showed an increase in frontal Gamma band power during induced activity. The drug was well tolerated. This study is a preliminary study and further clinical testing of this drug is needed.

Nevertheless, the strategy used in developing this promising new drug for the treatment of cognitive dysfunction in schizophrenia can be summarized as follows: Understanding the pathological entity, in this case cell specific deficits in GABA neurotransmission in the DLPFC, linking it to the pathophysiology (reduced gamma band power) and to the clinical syndrome (impaired working memory) in order to develop rational treatment which can then undergo rigorous clinical testing.

If successful, the development of effective treatments for cognitive deficits in schizophrenia can significantly improve quality of life for the patient described in the clinical vignette and that of many patients with this devastating disorder.

References

Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci. 2006 Dec 26;103(52):19878-83. PMID: 17170134

Gonzalez-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. Curr Psychiatry Rep. 2010 Aug;12(4):335-44. PMID: 20556669

Lewis DA. Pharmacological Enhancement of Cognition in Individuals with Schizophrenia. Biol Psychiatry. 2011 Mar;69(5):397-8. PMID: 21316514

Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. Neuropsychopharmacology. 2010 Dec;35(13):2590-9. PMID: 20827271

Science News

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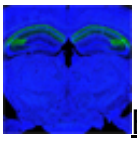
Middle Schoolers Field Day with the Brain (http://www.nimh.nih.gov//news/science-news/2014/nimh-scientists-help-students-learn-about-the-brain-at-nmhm.shtml)

-  Brain Region Singled Out for Social Memory (http://www.nimh.nih.gov//news/science-news/2014/brain-region-singled-out-for-social-memory-possible-therapeutic-target-for-select-brain-disorders.shtml)
-  When Kids Relocate, Who Suffers? (http://www.nimh.nih.gov//news/science-news/2014/girls-thrive-emotionally-boys-falter-after-move-to-better-neighborhood.shtml)

More (http://www.nimh.nih.gov//news/science-news/index.shtml)

Upcoming Events

- Brain Awareness Week
  March 10-16, 2014
- USA Science & Engineering Festival, Washington, DC
  April 24-27, 2014
- National Children's Mental Health Awareness Day
  May 8, 2014
- National Prevention Week 2014
  May 18-24, 2014

General Health Information from NIH

- MEDLINEPlus : Authoritative information from government agencies and health-related organizations, available in both English and Spanish (Español)
- ClinicalTrials.gov : Federally and privately supported research using human volunteers
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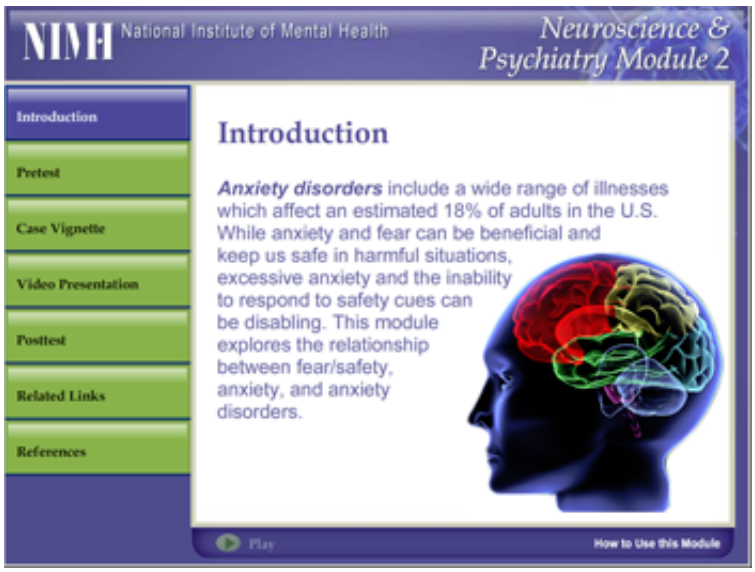
Neuroscience and Psychiatry Module 2: Fear/Safety, Anxiety, and Anxiety Disorders



Neuroscience and Psychiatry video

Introduction

Anxiety disorders include a wide range of illnesses which affect an estimated 18% of adults in the U.S. While anxiety and fear can be beneficial and keep us safe in harmful situations, excessive anxiety and the inability to respond to safety cues can be disabling. This module explores the relationship between fear/safety, anxiety, and anxiety disorders.

Case Vignette

62 year old Caucasian male veteran who experienced incredible horror in Viet Nam. He has had a long course of severe PTSD. He is getting married on a rainy day and is walking out of a church in Vermont in a white tuxedo, with his new bride on his arm, a car drives by and backfires. He dives into the muddy bushes for cover.

In the face of a stimulus that reminded him of past dangers, why did he disregard the safety signals?

40 years since Viet Nam - **now in a safe time**

In Vermont not Viet Nam - **now in a safe place**

In a white tuxedo, not battle fatigues, with his new bride next to him - **now in a safe context**

Is Post Traumatic Stress Disorder An Inability to Respond to Safety Signals?

Video Presentation: What is the Relationship Between Fear/Safety, Anxiety, and Anxiety Disorders?

Let's start with some definitions. What is fear? **Fear** is a feeling of disquiet that begins rapidly in the presence of danger and dissipates quickly once the threat is removed. It is generally adaptive.

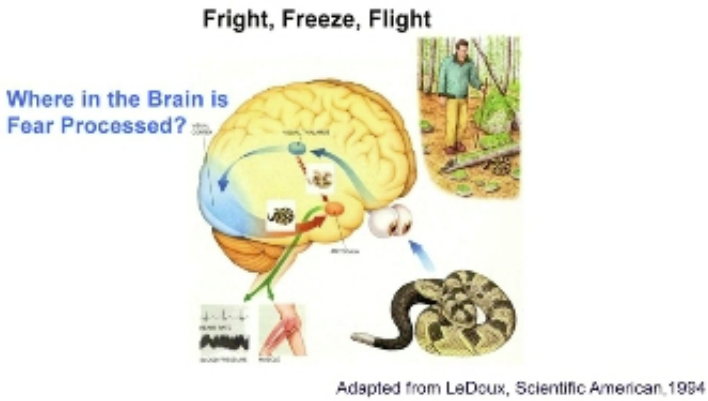
Anxiety, on the other hand, is uneasiness over the anticipation of less specific or predictable threats. It lasts longer than fear and can also be adaptive.

When fear and anxiety are greater than expected or last beyond what is adaptive, affecting well being and function, then an anxiety disorder is present.

Fear can be innate or learned. Examples of innate fear include the fear of scorpions, snakes, or heights. Learned fear stimuli such as guns would not have been frightening to someone who lived in the 12th century, for example. Neither would images associated with man-made disasters or destruction such as a car accident or mushroom cloud.

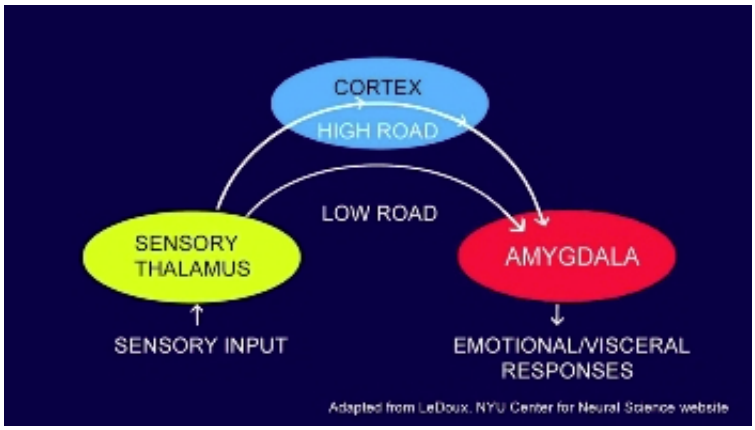
Fear is highly preserved across animal species, so many species exhibit fear conditioning.

We know that the classic fear response is "fright, freeze, flight" but where does that happen in the brain?



We learned from animal models of fear that the **amygdala** is central to the fear response. Sensory input reaches the sensory thalamus and then very quickly the amygdala which allows for a fear response, via the so called low road. This direct pathway to the amygdala is necessary but not sufficient, it cannot differentiate a snake from a stick.

The **cortex** is needed for conscious awareness, context, and perspective. That process is slower and occurs via the so called high road.



Here is a clinical example of how central the amygdala is to the fear response.

Patient SM has a very rare case of Urbach Wiethe disease, a congenital calcification of the amygdala bilaterally.

For many years, SM has repeatedly stated that she "hates" snakes and spiders. When asked to elaborate, SM reports that she simply does not like them and "tries to avoid them." In order to assess the validity of SM's claims, investigators took her to an exotic pet store that specializes in selling snakes and spiders.

Contrary to her verbally stated aversion to snakes and spiders, SM displayed a striking pattern of excessive approach-like behavior in concert with a lack of avoidance behavior; a pattern highly reminiscent of the behavior displayed by monkeys with focal amygdala lesions.

SM repeatedly approached all snakes, including holding and playing with a snake for over three minutes. She attempted to touch a tarantula, but had to be stopped due to the high risk of being bitten. She displayed a compulsive desire to want to "touch" and "poke" the store's larger and more dangerous snakes, even though the store employee repeatedly told her that these snakes were not safe and could potentially bite.

When asked why she would want to touch something that she knows is dangerous and claims to hate, SM consistently replied that she was overcome with curiosity.

Throughout all of this SM's reported experience of fear never surpassed a minimal level!

This case illustrates the essential role of the amygdala in fear, a human emotion.

Can We Use Animals to Model Human Emotions?

That may be difficult to do for some emotions.

But we can model fear in animals. This is useful because fear, anxiety, and anxiety disorders are likely to be biologically related. For example, neuroimaging studies show that there are brain circuits common to humans and animals that are involved in normal fear as well as anxiety disorders. And animals can learn to fear a neutral stimulus. Therefore animal models of fear are feasible and useful in informing our understanding of anxiety disorders in humans.

Let's begin by describing an animal model of fear developed by Dr. Michael Davis and his colleagues using fear potentiated startle.

Central to this model is fear conditioning or cue conditioning, which is essentially learning to associate a neutral stimulus such as a light with an aversive event, for example, an electric shock. One can conceive of that as learning about danger.

This animal model relies on the observation that animals and people startle more when they are afraid. For example, if the phone rings suddenly, you may startle a bit. If you are alone at night watching a scary movie and the phone rings suddenly, you would startle far more severely. So how is this applied to animals.

The experimental device consists of a box with a grid that is capable of delivering an electric shock.

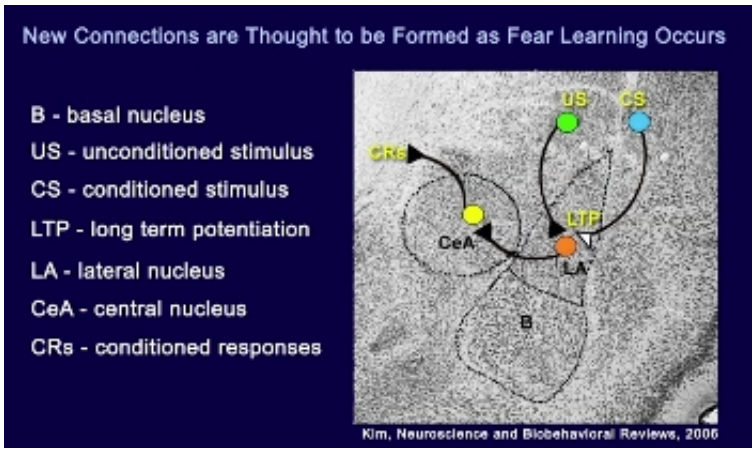
During training, a light is paired repeatedly with an electric shock such that the animal learns that the light will be always followed by a shock and becomes afraid of the light. That is classical conditioning.

In the testing phase, the animal is startled by a noise while the light is off. No more shocks are given. The extent of the startle is measured by how high the animal jumps.

The light is then turned on which induces fear in the animal. The animal is then startled by the same noise. Because it is afraid, the animal startles much more, and jumps higher. The difference in the height of the jump between startle when the light is off and when it's on is a measure of fear potentiated startle.

So what happens in the brain as conditioned fear is acquired?

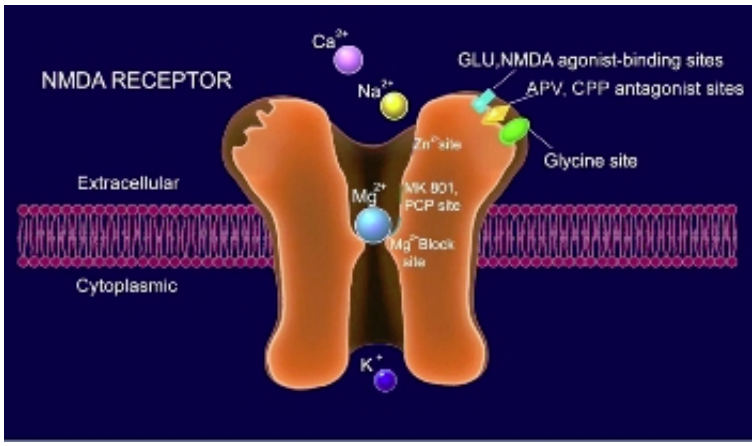
New excitatory connections are thought to be formed within the amygdala as fear learning takes place through long term potentiation. These connections are formed between the lateral nucleus of the amygdala and the central nucleus of the amygdala which is thought to be the main amygdaloid output structure sending projections subcortically.



Therefore, fear producing cues through the basal nucleus and the central nucleus of the amygdala activate multiple brain regions that then produce a variety of signs and symptoms of fear and anxiety.

For example, activation of the lateral hypothalamus can lead to changes in blood pressure and heart rate, and sweating. Activation of the parabrachial nucleus can lead to panting and respiratory distress, and so on.

The neurochemistry of fear learning has been elucidated using animal models. It is known that glutamate acting at the NMDA receptor is critically involved in learning and memory as well as in fear learning. For example, blockade of NMDA receptors in the amygdala interferes with the acquisition of conditioned fear.



Animals can also learn to respond to safety signals.

If a light is consistently followed by a shock, the light becomes a danger signal. If a light is repeatedly not followed by a shock, the light becomes a safety signal.

Can this animal model be adapted to humans?

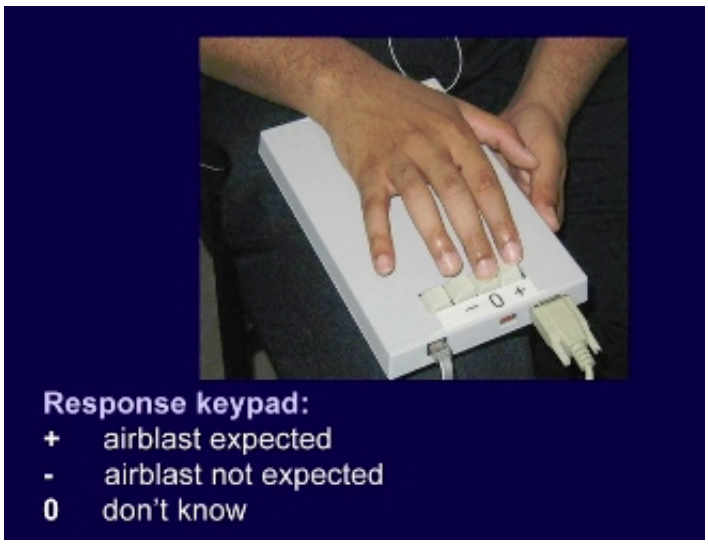
Dr. Davis and his group were able to devise a fear potentiated startle paradigm in humans to study safety signal learning based on the animal model.

As you see in this picture, the acoustic startle probe is delivered through headphones. The EMG recordings of the eye blink muscle contraction are used as a measure of the startle response. The unconditioned stimulus is a puff of air to the throat which is mildly noxious. The conditioned stimulus is the viewing of a colored square.

During the habituation phase, the acoustic startle probe or the noise is delivered and startle reactivity is measured.

During conditioning, the conditioned stimulus or fear signal, in this case a green square is shown along with a neutral stimulus or yellow square and followed by an air puff.

Using the response key pad the subject indicates whether he is expecting an airblast, no airblast or does not know.



The safety signal pink square is shown along with a neutral stimulus or yellow square and never followed by an air puff. Using the response key pad the subject responds.

The danger signal is then shown. Paired with the safety signal.

In this paradigm, several questions were asked:

Can fear potentiated startle be detected in people using this model?

Can subjects learn to respond not only to a fear signal but also to a safety signal?

Is the ability to respond to either fear or safety signals impaired in PTSD?

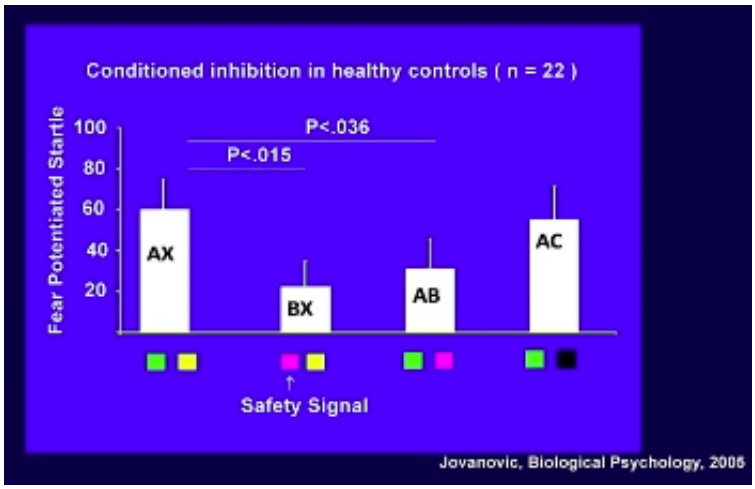
Here are the results in healthy controls. A, refers to the green square which represents danger and X refers

to the yellow square which is neutral. Clearly the subjects show a fear potentiated startle response to the danger signal.

In contrast, the safety signal does not induce such a response. B refers to the pink square which represents safety.

When the danger and safety signal are shown together AB the response is intermediate. This indicates an ability to generalize or transfer the safety signal.

Finally, when the subjects are presented with the green square representing danger along with a black square or C - a neutral signal never before seen - they react to the danger signal as they have before. This is a controlled condition.

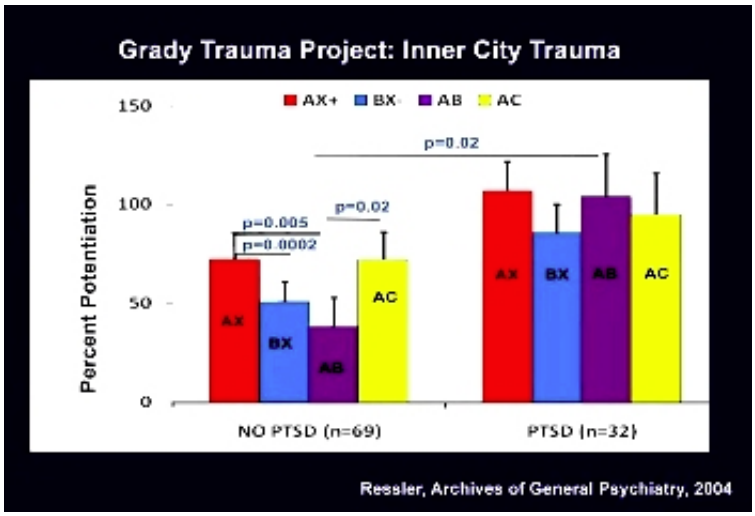


Veterans of the Croatian war who do not suffer from PTSD showed the same results as healthy controls. However, veterans of the Croatian war who suffer from PTSD, showed a different set of responses.

They responded to the danger signal and the safety signal in the same way but responded to the mixed signal in the same way they responded to the danger signal. What that suggests is that the subjects were not able to generalize or transfer the safety signal.

This same experiment was repeated by Dr. Kerry Ressler and his colleagues in the Grady Trauma Project. This is an entirely different group of civilians from inner-city Atlanta who have experienced multiple traumas. Some suffer from PTSD and some do not.

In this graph, the purple column shows the response to the combined danger and safety signals. Subjects with PTSD responded to it in the same way they did the danger signal while subjects without PTSD were able to transfer or generalize the safety learning to the combined state.



These experiments demonstrate that it is possible to have an objective measure of safety signal learning not only in animals, but also in humans. And, as illustrated in the case vignette, people with post-traumatic stress disorder do not respond to safety signals in the same way as healthy controls.

How can we use this information to help us develop novel treatments for this disorder?

Currently, selective serotonin reuptake inhibitors are the mainstay of long-term pharmacological treatments of anxiety disorders and benzodiazepines are useful for short-term relief. While SSRIs have demonstrated efficacy in controlled clinical trials of PTSD, their universal effectiveness in the real world has been questioned. Novel therapies are needed, particularly ones that do not have to be administered indefinitely and that have fewer side effects.

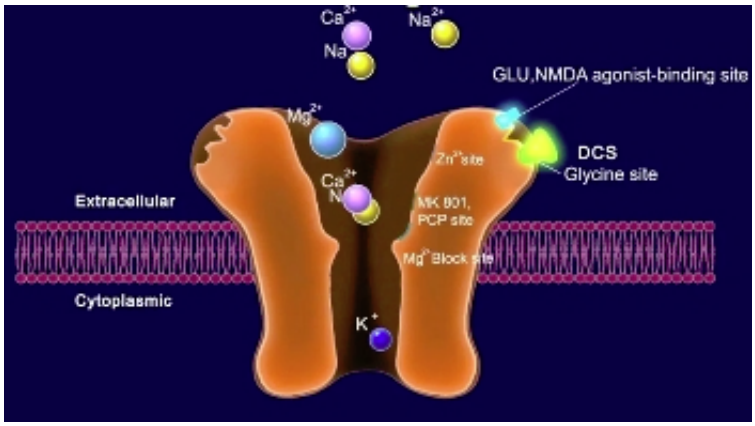
In addition to pharmacological interventions, **Cognitive Behavioral Therapy, or** CBT is an effective treatment approach for anxiety disorders and a first-line treatment for PTSD. **Exposure therapy** is a CBT approach that is thought to lead to extinction of fear.

In exposure therapy, a patient is repeatedly exposed for increasing periods of time to a feared object or situation in the company of a supportive therapist. The lack of aversive consequences leads to **extinction**. This is thought to be due to new learning.

In turn, this new learning allows the patient to face feared cues or situations with **less fear and avoidance**.

NMDA receptors are known to play a role in fear learning and fear extinction. NMDA receptor antagonists impair extinction in rodent models and NMDA agonists facilitate it.

D-cycloserine is a compound that indirectly activates the NMDA receptor.



A **single** dose of D-cycloserine given 2-4 hours prior to the therapy session, produced an enhanced decrease of fear at 2 weeks and 3 months after this single treatment.

This was tested in a virtual reality model for people with acrophobia, or fear of heights, where they wear goggles and they feel that they are in a three-dimensional space.

They can virtually walk out on ledges of increasing height and look down.

The first observation in this placebo controlled study is that D-cycloserine did not increase or decrease anxiety by itself indicating that it is **not** an anxiolytic.

After only two doses of DCS each administered before an exposure session, the DCS group showed a significantly greater decrease in anxiety than the placebo group, and that change persisted at follow-up after three months, with no additional DCS given.

Since it is not an anxiolytic this data suggest that it worked by enhancing extinction.

In addition, three months after the treatment, the DCS group reported exposing themselves to heights significantly more than the placebo group, indicating that the treatment altered behavior in the real world.

DCS is not approved for clinical use, but remains a research finding. In addition to simple phobias, the enhancement of cognitive behavioral therapy with DCS has been shown to be effective in studies on panic disorder, obsessive compulsive disorder, and social anxiety. However, it is not clear whether DCS will enhance CBT in PTSD. Recruitment of subjects for PTSD clinical trials is underway at multiple centers.

Take Home Messages

Animal models of fear and safety learning are feasible and highly informative.

It is possible to have an objective measure of safety learning in animals and humans.

People with post-traumatic stress disorder do not respond appropriately to safety signals.

In research studies, D-cycloserine facilitates fear extinction and may play a role in enhancing the effects of CBT.

Understanding the neurobiology of fear and safety circuits can help us develop novel treatments.

Here is our newly wed PTSD patient describing his symptoms and their triggers.

"I can't get the memories out of my mind! The images come flooding back in such vivid detail, and they're

triggered by the most inconsequential things, like a door slamming or the smell of stir-fried pork."

"Last night, I went to bed and I was having a good night's sleep for a change. And then in the early morning the storm-front passes through, there's this big bolt of crackling thunder. I woke up instantly, frozen in fear."

"And I'm right back in Viet Nam, I'm in the middle of the monsoon season at my guard post. And I am sure that I'll get hit in the next volley and I'm convinced I will die."

"My hands are freezing, yet sweat is pouring from my entire body. I feel each hair on the back of my neck standing on end. I can't catch my breath, my heart is pounding. And I smell a damp sulfur smell. The next bolt of lightning and clap of thunder makes me jump so much that I fall to the floor."

Several Questions Remain

Will this treatment work for PTSD?

Will our newly wed PTSD patient learn to generalize the safety signal:

Safe time, safe place, safe context despite the complexity of triggers that bring back his fear response?

References

Adolphs R, Tranel D, Damasio H, Damasio A. 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372:669 - 672.

Davis M, Ressler K, Rothbaum BO, Richardson R. 2006. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. Biol Psychiatry, 60(4):369-375.

Ekman P, Friesen WV. Pictures of Facial Affect. Consulting Psychologists Press, Palo Alto, CA, 1976.

Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR. 2008. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry, 63(6):544-549.

Jovanovic T, Keyes M, Fiallos A, Myers KM, Davis M, Duncan, EJ. 2005. Fear potentiation and fear inhibition in a human fear-potentiated startle paradigm. Biol Psychiatry, 57(12):1559-1564.

Jovanovic T, Norrholm SD, Blanding NW, Davis M, Duncan E, Bradley B, Ressler KJ. 2010. Impaired fear inhibition is a biomarker of PTSD but not depression. Depression and Anxiety, 27(3):244-251.

Jovanovic T, Norrholm SD, Myers KM, Davis M, Duncan EJ. 2011. Conditioned inhibition in healthy veterans in Croatia. Manuscript in preparation.

Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of General Psychiatry, 2005 Jun;62(6):617-27.

Kim JJ, Jung MW 2006. Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. Neuroscience and Biobehavioral Reviews, 30:188-202.

Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, McCabe J, Peterson J, Foa EB. 2007. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry,

62(8):835-838.

LeDoux JE. 1994. Adapted from: Emotion, Memory, and the Brain. Scientific American, 270(6):50-57. Retrieved August 25, 2011 from New York University Center for Neural Science Web site: http://www.cns.nyu.edu/home/ledoux/ .

LeDoux JE. Memory and Emotion. Retrieved August 25, 2011 from New York University Center for Neural Science Web site: http://www.cns.nyu.edu/corefaculty/LeDoux.php.

Myers KM, Davis M. 2007. Adapted from: Mechanisms of fear extinction. Mol Psychiatry, 12(2):120-150.

Nestler, Eric. Adaptation of illustration.

Norrholm SD, Jovanovic T, Olin IW, Sands LA, Karapanou I, Bradley B, Ressler KJ. 2011. Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. Biol Psychiatry, 69(6):556-563.

Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, Hofmann SG, Eisenmenger K, Krystal JH, Pollack MH. 2010. Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiatry, 67(4):365-370.

Phelps EA ,LeDoux JE. 2005. Adapted from: Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron, 48(2):175-187.

Ressler K, Jovanovic T, Blanding, Norrholm S, Duncan E. Grady Trauma Project. Unpublished manuscript.

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, Hodges L, Davis M. 2004. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry, 61(11):1136-1144.

Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, Cannistraro P, Jenike MA, Rauch SL. 2008. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. Am J Psychiatry, 165(3):335-341.

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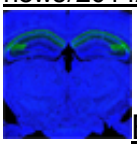
Rat brain image courtesy of Miles Herkenham, NIMH. Stock photos from iStockPhoto.

-  Middle Schoolers Field Day with the Brain (http://www.nimh.nih.gov//news/science-news/2014/nimh-scientists-help-students-learn-about-the-brain-at-nmhm.shtml)
-  Brain Region Singled Out for Social Memory (http://www.nimh.nih.gov//news/science-news/2014/brain-region-singled-out-for-social-memory-possible-therapeutic-target-for-select-brain-disorders.shtml)
-  When Kids Relocate, Who Suffers? (http://www.nimh.nih.gov//news/science-news/2014/girls-thrive-emotionally-boys-falter-after-move-to-better-neighborhood.shtml)

More (http://www.nimh.nih.gov//news/science-news/index.shtml)

Upcoming Events

- Brain Awareness Week
  March 10-16, 2014
- USA Science & Engineering Festival, Washington, DC
  April 24-27, 2014
- National Children's Mental Health Awareness Day
  May 8, 2014
- National Prevention Week 2014
  May 18-24, 2014

General Health Information from NIH

- MEDLINEPlus : Authoritative information from government agencies and health-related organizations, available in both English and Spanish (Español)
- ClinicalTrials.gov : Federally and privately supported research using human volunteers
- PubMed Central: An archive of life sciences journals
- NIH Research Fact Sheets
- NIH Office of Science Education : Resources for science educators
- Pillbox: How to identify unknown pills from the National Library of Medicine