Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Webinar Series

June 26, 2014, 1-2:30 p.m. (EDT)

"The Limits of Adaptive Coping: Neurobiology of Extreme Stress"

Welcome and thank you for standing by. All participants are in a listen-only mode for the duration of today's conference. Today's conference is being recorded. If you have any objections you may disconnect at this time. I would now like to turn today's meeting over to Captain Anthony Arita. You may begin.

Good afternoon and thank you for joining us today for the DCoE June Psychological Health webinar. My name is Captain Anthony Arita and I am the director of the Deployment Health Clinical Center in Bethesda, Maryland. I will be your moderator for today's webinar.

Before we begin, let us review some webinar details. Live closed captioning is available through Federal Relay Conference Captioning. Please see the pod beneath the presentation slides. Defense Connect Online and Adobe Connect Online are the technical platforms hosting today's webinar. Should you experience technical difficulties, please visit dcoe.mil/webinars and click on the "Troubleshooting" link under the "Monthly Webinars" heading.

There may be an audio delay as we advance the slides in this presentation. Please be patients as the connection catches up with the speaker's comments. At any time during the webinar, please submit technical or content-related questions via the question box. The event planning team will address your technical questions as soon as possible.

Our presenter and I will answer content-related questions during the last 30 minutes of the webinar. While we encourage you to identify yourself to the other attendees via the chat box, and will leave the chat box open for additional networking opportunities ten minutes after the webinar has concluded, please refrain from marketing your organization or product. Today's presentation and resource list are available for download from the "Files" pod below.

If you pre-registered for this webinar and want to obtain continuing education certificate or a certificate of attendance you must complete the online CE post-test and evaluation. After the webinar, please visit continuingeducation.dcri.duke.edu to complete the online CE post-test and evaluation, and then you can download your CE certificate or certificate of attendance. The Duke Medicine website online CE post-test and evaluation will be open through Thursday, July 3rd, 2014 until 11:59 p.m., that's Eastern Daylight Time.

Throughout the webinar you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. Please do not submit technical or content-related questions

via the chat pod. The Q&A pod is monitored during the webinar and questions will be forwarded to our presenter for response during the question-and-answer session of the webinar. Participants may also chat amongst each other during the webinar using the chat pod. We will keep the chat function open ten minutes after the conclusion of the webinar.

I will now move on to today's webinar topic, "The Limits of Adaptive Coping: Neurobiology of Extreme Stress." Despite unprecedented efforts over the course of this 13-year war in American history, existing programs in the Departments of Defense and Veterans Affairs to prevent, identify, and treat stress disorders among military service members, veterans, and their families remain hampered by factors that limit their effectiveness. Research studies indicate that stigma as a barrier to care remains high in the military community. One limitation of existing psychological health programs, including those designed to reduce stigma, may be their exclusion of emerging scientific perspectives on the role of central nervous system in extreme stress.

This webinar will examine the evidence that stress disorders are fundamentally neurobiological, as well as psychosocial, and will provide an overview of select CNS neurotransmitter systems and neuronal pathways implicated in normal and pathological stress states. Discussions will include biologically-informed approaches for psycho-education to reduce stigma and for prevention and treatment in both clinical and non-clinical settings. During this webinar, participants will learn to identify CNS neurotransmitter systems and pathways implicated in persistent adverse stress outcomes such as posttraumatic stress disorder; acute and chronic stress-induced changes in the functioning of CNS neurotransmitter systems with persistent changes in cognition, emotions, and behavior; summarize clinical and non-clinical approaches to addressing stress-induced neurobiological dysfunction.

I would now like to introduce our presenter, Dr. William Nash. Dr. Nash is a psychiatric researcher, educator, and consultant for posttraumatic stress disorder prevention and treatment for the Defense Department and Veterans Affairs. He holds academic appointments at the University of California, San Diego, and at Virginia Commonwealth University. Dr. Nash chairs the Military Committee of the Group for the Advancement of Psychiatry. He led the development of a Navy and Marine Corps Combat Operational Stress Control Doctrine. While on active duty, Dr. Nash provided far-forward psychological health services to the 1st Marine Division. Dr. Nash has also authored numerous journal articles and book chapters, and co-edited the recent book "Combat Stress Injury: Theory, Research, and Management." Thank you for joining us and welcome, Dr. William Nash.

Thank you, Tony, for that awesome introduction. And I want to thank DCoE for giving me this opportunity to speak to you all on this topic, which is very important to me. I just want to say I'm just really excited about how the DCoE webinar series has taken off. I think it's one of the best products DCoE has come up with. You guys deserve a lot of credit for that. My disclosures are up on the slide. You can read that. Next slide.

An additional disclosure I want to make is I'm not a neuroscientist. I don't play one on TV and I didn't even sleep at a Holiday Inn last night. What I am though, or try to be, is a translational scientist. Actually, that's something we're all involved in, and that's the process of taking the stovepipe models, theories, and findings from research in a laboratory, in clinical settings, in various sciences, and try and integrate them into coherent models that can inform programs that actually make a difference. Next slide.

In the behavioral health arena, look at the contributing sciences that we have to choose from, I mean, the list is way too long. This is only five. I chose five to put on this slide: neuroscience; stress and coping, which is a very important set of models and interventions; learning theory, of course, is important for fear conditioning and other things; health psychology; resource theory, but there's also positive psychology, there's spiritual components. So there's a universe of different models, theories, and datasets to choose from to help us understand what happens to people under stress and how do we protect them, prevent adverse outcomes, and then how do we help them heal and recover.

So the biggest challenge for this, I think, is deciding which of these findings and models to choose, because I don't think -- we may never get to the point where we have a theory of everything. I know physics is still trying to work on its theory of everything, trying to integrate quantum mechanics with relativity. And if they can't do it with just two theories, you know, how are we going to do it with a thousand or however many we have that contribute to this. So you have to pick and choose. And so the first question is which ones? Next slide.

Well, I'm here to make the case that neuroscience is the one indispensable behavioral stress science. First of all, if you doubt that you could have no cognition or behavior without a central nervous system -- sorry for the double negative -- I invite you to spend an hour with me when I do telesite consulting at skilled nursing facilities. All you have to do is talk to someone who has one of the many different kinds of dementia, degenerative changes in the brain, to see how all of these functions, of coping, of control of emotions and cognitions and memory, are deconstructed as the brain degenerates. So, clearly, each one of these things is in the brain.

We're learning more about brain science, and eventually we're going to get to the point where we can make more coherent models and create interventions from them, but that doesn't mean we don't know enough to at least try. The other thing I think, without neuroscience I don't that we're ever going to be able to explain heterogeneities and comorbidities. PTSD is not just one thing; anyone who works with it clinically knows that. There are many different subtypes, dissociative, there's complex from, you know, repeated trauma, which I think is way more common in military and veteran populations than we realize.

And comorbidities, that's huge. You know, you're never going to see, in a clinical setting, a patient with PTSD, read them the 20 criteria for PTSD from DSM-5 and they're going to go, "Ah, that's all my life problems. If you could fix those 20 things, I will be good to go." Well, of course not. There's always others, depression, anxiety, substance abuse, you know, whatever, whatever.

So the other thing is, some of the things I'm going to share with you I have been using for training education in the military, particularly the Marine Corps, over the last ten years, since I joined the 1st Marine Division in 2004. And I can tell you that no warrior rolls their eyes when you try to explain to them the role of their brain in producing the symptoms that they have, the loss of function, the changes in function. They know something is different. And, you know, we in the mental health community are used to using metaphors and allegories and thinking in abstractions. Well, these things don't necessarily make as much sense to somebody who wants to know mechanistically "Why can't I control my anger anymore. I used to be able to, now I can't. Why can't I?" But neuroscientific explanations do make sense, and they also reduce stigma. Next slide, please.

So, if you want to know how much stigma still exists in the military around mental health problems, I urge you to read the eight MHAT reports that have been done since 2004, whenever

they started. There are little variations year to year. Marine Corps seemed to be doing good up until this most recent one, gaining some ground, but still, the responses to a standard set of stigma questions are unacceptably high. There are way too many people who think that having stress symptoms, having PTSD is a sign of personal weakness rather than some injury or some other problem, with part of just like their body, something that they didn't choose. They can do something about it, but they didn't choose it, it's not their fault.

So there isn't a lot of other research about stigma, unfortunately. I wish we -- I wish more people took it on. You know, what are the contributors of stigma? What are the elements of it? What do different groups in our community contribute to it? The one thing I want to focus on here is to what extent mental health professionals and health care professionals in general, in general, have a role in stigma, either promoting it or in reducing it.

These two charts, these two graphs are from a study by -- it's a survey done by Stephen Stahl, who is a psychopharmacologist from San Diego who was hired by the Army to go to Fort Hood and train some of their health-care professionals on the use of psychotropic medications. This was 2008, and he was there right around the time of one of the shootings. And he noticed when he was doing these trainings that there was a lot of stigma. There was a lot of assumptions, preconceptions, both among the cadre, the NCOs who actually worked on the warrior transition unit and responsible for the welfare of the soldiers there, but also the health-care professionals, predominantly nurses.

So he did this survey, and these are the responses to one of the questions. What percent of the soldiers claiming to have symptoms of PTSD do you think are faking or exaggerating? And you can see, if you look at the first chart is responses of the non-commissioned officer cadre, 310 of them, about 70% were in the rightmost two bars. About 70% thought half or more were faking or exaggerating. So that means they're thinking if somebody walks into the door and says "I have PTSD," chances are they're lying, that's what they believed. But then look at the nurses, who are the experts, who are the ones the NCOs look to to help them understand, well, what is this thing that's happened with these guys. And it's only about 25%, the rightmost two bars, who said half or more than half are faking, but still, that's one out of four. One out of four. And if I was an NCO who believed in my heart that these guys are faking and one out of four professionals says you're right, I'm never going to change my mind. Next slide.

So this is the only other question from Stephen Stahl's study I want to share with you. And this is how confident are you that PTSD is a real illness and that it's caused by military service? And they use the Likert Scale, one to ten, where one is little or no confidence, and ten is extremely confident. And you can see that if you look at the leftmost three, between one and six, sort of, you know, not exactly confident that this is a real disorder, about 42%, you know, adding up the first bars of the NCOs, about 42% don't even think -- are not confident, would not put money on PTSD being a real illness, a real disorder. All right, so that's NCOs. But about 30% of the nurses said the same thing.

Imagine what the dialogue in this country would be, how it would be different in terms of climate change and global warming if, instead of 3% of the scientists and professionals saying global warming isn't real and it's not caused by CO2 and human emissions, instead of 3% it was 30%, it would be hopeless. There would be no chance of ever enacting policy. So my point here is I believe that if more of these NCOs and health-care professionals understood a little bit more about the neurobiology they'd be less likely to say this is a crock. Next slide.

Of course, the brain is the organ of coping. I took a quote here from Lazarus and Folkman's very influential, important work in 1984 about stress and coping. And you see coping is something that's done. It takes effort. It's a decision, whether it's a conscious decision or an unconscious decision, it's not something that you just -- you know, stuff happens, it's something you do and it takes effort. To do something that takes effort requires intact cortical functioning. You have to have the ability to appraise, to think, to foresee, to reason, to make sense, to choose between alternative courses of action, and you have to have the ability to focus your energy and to actually do something. And it's the brain and the functioning of the nervous system that defines the limits of one's ability to cope adaptably. Next slide.

I was a flight sergeant in the Navy for a couple years, and so I got to learn a little bit about aviation communities. And one of the things pilots talk about is the performance envelope of their aircraft. This is a slide that shows the altitude on the vertical axis, speed on the horizontal. And there's only a certain envelope in which a plane can fly. You can't go infinitely slowly. You can't go infinitely fast. You can't go infinitely high. You can't go, you know, below zero altitude. So this envelope defines the performance limits of an aircraft. Every pilot, every helicopter pilot, every pilot knows the performance envelope for their aircraft. They have to know it so that they don't go too slow or too high or too fast.

If they didn't know it, though, imagine what they would think if suddenly their plane fell out of the sky. It stalled. They would think that somehow it's their fault and, you know, they somehow didn't do something right. Maybe they didn't, but, clearly, they would understand the mechanism of that better if they understood that stalling is not maladaptive flying, it's the absence of flying. And that's why by analogy I think a lot of the symptoms that people present with after extreme stress is not maladaptive coping, it's the absence of coping. Next slide.

So that's what I just said. I think CNS -- and that's true not just for PTSD but major depressive disorder. You know, as a psychiatrist I was trained to diagnose major depressive disorder as being different from just sort of normal everyday depression in that it has progressed for long enough and has gotten severe enough that even if the person took a vacation, won the lottery, everyone suddenly loved them, all their stress went away, the depression wouldn't necessarily go away because something has changed in their neurobiology. They can no longer summon that enthusiastic happy response, and that's what medications for depression are for. So, just understanding that little piece, that that is a neurobiological change in the brain that is not -- that puts it outside of someone's conscious control. Not knowing that is to blame our patients for their own suffering. Next slide.

So here, case in point. Obviously, PTSD interests all of us, DCoE and my own work. So let's look at four main clusters of symptoms for PTSD and try to figure out what sort of higher cortical functions might be reflected in these symptoms or losses of these functions. So the first cluster is the intrusion symptom, involuntary distressing memories, dissociative reactions.

Any time you see "involuntary" -- and I didn't make this up, I took this right out of DSM-5 -- any time you see the word "involuntary", that's not a choice, okay. That's something that happens to you. So involuntary distressing memories is a loss over the authority to choose to remember something. When those of us who don't have problems with those parts of our brain, if a memory pops into our consciousness while we're doing something else, we can suppress it. We can say, "No, I'm not going to think about that now. That's distracting." But an intrusion symptom means you don't have that authority anymore, that it pops into your consciousness and you cannot suppress it.

So the dissociative flashbacks is the loss of the ability to tell memory to discriminate a memory from current experience. And a lot of studies have been done on the cortical areas that are important in different perceptions and how they're integrated together from memories. And actually, in terms of brain scans and functions, the occipital cortex, for example, which is for visual experience and visual memory, it looks the same on a brain scan whether someone is seeing something in real time or remembering it from the past. It's the same circuit, the same neurons. So somehow there's another part of the brain that has to be able to tell us this is not real, this is not happening now, this is not a hallucination, this is a memory. Next slide.

C cluster, trauma-related avoidance. Avoiding is a choice. You know, if I choose to not go out of a home, to not go in public places, not talk to anybody, you know, whatever, not watch the news because any of that will remind me of something horrible that I will provoke all these symptoms, that's a choice, but it's required, it's necessary to the extent I have lost my ability to say "No, I'm not going to think about that. I'm not going to remember that. I'm not going to have the cognitions that go along with the memory, the would of, should of, could of, all that stuff, the emotions, the shame, the guilt, the anger, the fear." That's why avoiding is necessary, because those individuals have, to some extent, lost that normal capacity to still those things. Next slide.

D cluster is alterations in cognitions and mood. Once again, you see inability to feel positive emotions, persistent negative emotions, dissociative amnesia. I'll give a thousand dollars to anyone who can intentionally choose to forget something, unless it's forgetting that I offered you a thousand dollars. Is that something we have control over, not conscious control? And I think there's -- you know, there's a challenge here. I want to throw down the gauntlet for people who work from a positive psychology framework. If having PTSD and D cluster symptoms means that parts of the brain that you need to be able to have control and authority over your own emotions, to choose to feel positive emotions, to choose to think positive thoughts, if that is damaged in somebody with PTSD, what are the limits of a positive psychology approach based on teaching that? So that means that there's -- you know, there's got to be a line there where potentially telling someone to think happy thoughts isn't going to do any good because they can't. Obviously, I'm way simplifying that. Next slide.

Okay, final, E cluster, alterations in arousal reactivity. These are the symptoms that I think people with significant PTSD and other mood anxiety disorders feel most every day, because you can't avoid them. You know, you can't just, no matter how much you lock yourself up and draw the window shades and avoid things, you can't slow down your sympathetic nervous system, the exaggerated responses of your physiology, the difficulty of slowing down, relaxing, sleeping, other than through alcohol, drugs, or, you know, distractive behaviors. So this is a loss of authority over those things. Physiologic arousal, which is hard to remember sometimes, we actually, in the pristine state, have a lot of control over. Okay, next slide.

All right, so now I want to just single out a few brain systems that are involved in these -- that are essential for having these kinds of controls, authority, over one's own memory, thinking, emotions, and behavior. And one of them is several regions of the prefrontal cortex. These are two views of the brain, the medial and lateral view. And prefrontal means ahead of the primary motor cortex, which is the strip of brain matter just ahead of the middle line of the brain that you see on the lateral view, so prefrontal, and there's many different subsections to it.

We know a little bit about how the medial prefrontal works different from the orbital frontal, which is just above the eyes, different from dorsolateral, which is on the side. Together, I think some of the differences are clear, but a lot of them are not yet simply because, you know, research hasn't been done yet to sort through all them. We know medial prefrontal cortex, particularly the

anterior cingulate, which is right in front of the cingulum, is crucial for fear extinction. So to get over a fear condition response to a life threat, you need that to be working. It's also important for all kinds of other volitional control over emotions.

Orbital frontal cortex is also involved in emotional control, decision-making. I remember reading, when I was a resident some years ago, even back then people were doing studies looking at the development of gray matter, of neurons, growth of neurons, and connections between neurons in the orbital frontal cortex that directly paralleled good enough mothering, parenting. I say "mothering" in the old sense of primary caretaker. So holding, nurturing, loving, you know, responding to the baby is absolutely essential to grow orbital frontal cortex. And to the extent those things maybe didn't happen there's less of that available. So it's very important for social decision-making.

Dorsolateral is definitely more attention, cognition, control of thoughts, I'm going to think about this, I'm not going to think about that." Insula, which you can't see because it's inside one of those sulci between the frontal and temporal lobe, is a system through which we normally have control over our arousal, be able to calm down our body, slow down our heart rate, slow down our -- you know, to the extent we can do it.

Prefrontal cortex is like the cockpit. The whole rest of the brain does the work. The cortex perceives, makes associations, stores memories, retrieves memories. The deeper parts of the brain, you know, control the body and action systems. The prefrontal cortex is the interface between our sentient self and our body. So, as you're sitting there listening to my voice and reading these words on the screen, it's your prefrontal cortex that's telling your eyes, that's telling the rest of you that this is what you want to do right now. It's not you, it's your brain. Next slide.

Here's our first polling question. What structure -- those of you who saw "50 First Dates" with Drew Barrymore and Adam Sandler, what structure was damaged on both of the sides of the brain of Drew Barrymore's character in "50 First Dates" making it impossible for her to record new, long-term memories, so that every day she relived the same day over and over and over again? So, the four choices are A, hippocampus; B, amygdala; C, nucleus accumbens; and D, orbitofrontal prefrontal cortex.

All right, let's close the voting on there so you see the results. A lot of smart people out there. Yes, the right answer is A, hippocampus. Those of you who want to cheat, go ahead and click that in now. Yes, next slide. Next slide.

So hippocampus is a long curved gray matter structure in the temporal lobe of the brain. There's one on each side. And it has many functions that are very only just beginning to be studied, but the one that we know the most about is it's crucial role in laying down and consolidating new declarative memories, which are memories which can be recalled, as opposed to more process memories like how to play the piano. And we know that because of the serendipity like people Drew Barrymore's character, we've seen that people who lose both hippocampi don't have that capacity. They have very short-term memory, so they have working memory that allows them to remember what happened a few seconds ago, but what happens more than -- longer than that, yesterday, the day before, they can't store those memories.

Hippocampus is so important in so many diseases. In my work in geropsychiatry it is where Alzheimer's disease attacks first, which is why memory problems are so prominent in Alzheimer's. And it's very fragile for a lot of reasons we're going to get into. It's where temporal

lobe epilepsy, the most common form of epilepsy, most of the injuries in the brain that fail to heal and that create seizure foci are often in and around the hippocampus. Some of the things we know that it does besides declarative memory, we know that it's crucial for fear extinction, along with the prefrontal cortex; inhibition; spatial mapping.

Neuroscientists have done studies with rats and put them in, like, water tank where they learn that in a certain place in the tank there's something they can stand on so they can rest and stop swimming. They can find their way from anywhere in this round tank to that spot, they know where they are in that round space if they have a functioning hippocampus. But if something happens to the hippocampus they can no longer do that.

There's some really interesting, I think, new studies, new research being done, and obviously all of these topics I'm going to talk about, just going to skim the surface. I urge you to just don't take my word for any of us and look it up, learn about it. There's new studies being done on what role the hippocampus may have not only in storing and consolidating memories in all of their facets so that when they're recalled they seem like a unit, which is an illusion because they're actually stored in so many different places in the brain. But also important in constructing a coherent mental image when you recall the memory, which is crucial for meaning-making, it's crucial for not only knowing your space in a water tank like a rat but knowing your position in moral space, in social space. You know, at every moment we kind of know what our relationships are with other people, what we're here for, what's appropriate, what's not appropriate, and there's a lot of reason to think it takes a very plastic part of the brain to do those things. And the hippocampus is one of the most plastic, where it can, you know, learn very quickly and it's very sensitive. Next slide.

Okay, so the amygdala is another brain center I want to talk about. It's also in the temporal lobe. It's physically attached to, connected to, next to the hippocampus, but it's very much opposite the hippocampus in its role. Whereas the hippocampus is more recallable memories and volitional control, the amygdala is more about emotions and responses. It's a threat detector. It's probably the most studied part of the brain because of the dominance of the fear conditioning model of PTSD and anxiety disorders.

Joseph LeDoux at NYU, and Elizabeth Phelps, who I worked with on the Institute of Medicine PTSD Committee, have done a lot of the work on this. LeDoux has written two great books for popular consumption, you can get off Amazon, about the amygdala and its role in fear and anxiety. But it does a heck of a lot more than that. We don’t know all these other functions so well because the studies have not yet been done. But we're learning that it's also important for appetitive conditioning, not just fear conditioning, not just aversion, not just the things you want to get away from, the things that are good that we want. A mother cannot care for a baby without a functioning amygdala, without the ability to have that emotional investment, and that's what the amygdala does is, it helps us get emotionally invested in things. Mine are firing right now, I tell you. Next slide.

Next polling question. Which neurotransmitter in the brain is most directly involved with experiences of pleasure, including the rush of engaging in risky behavior? The choices are adrenaline, A; epinephrine, B; serotonin, C; and dopamine, D. Go.

Okay. I tricked you a little bit there, but I -- and that's because most people associate the word "adrenaline" with "rush" as in an "adrenaline rush," but most people got the right answer which is dopamine. Dopamine is the pleasure neurotransmitter, it's the addiction neurotransmitter. Adrenaline and epinephrine are actually the same thing. Okay, so it's dopamine. Next slide. So

when somebody adrenaline rush you have to tell them, "No, you really mean dopamine rush, don't you?"

So this is a slide of the mesocortical system. "Meso" from the mesencephalon, which is the brain stem. You can see sort of almost in the center of that slide, the blue dot that says "ventral tegmental area," that's where the bodies of these dopamine neurons are and they send axons, you know, fibers out to connect with all the whole prefrontal cortex, with nucleus accumbens, which hopefully is there somewhere. And these dopamine circuits, there's another set of dopamine circuits in the brain that are particularly more for movement, for coordinating physical movement, and those are the ones that are -- those dopamine are depleted or damaged in Parkinson's disease, so people have tremors and they can't initiate movement, they can't stop movement.

So this is a parallel set of dopamine neurons and circuits that are more for attention, because it's for switching, for focus, for being able to change your focus from one thing to another. And, of course, kids with ADHD, people with a great number of mental disorders have problems with that, and it's because their dopamine circuitry in the prefrontal cortex is not doing its job. But it's also in nucleus accumbens, which is sort of a -- I can't think of the word -- like a clearinghouse or a coordination center for these dopamine fibers is essential for motivation, for goal-directed behavior, but also for addictions and craving.

Every addictive drug, every addictive behavior that's ever been studied in the brains of humans and animals is mediated through dopamine fibers in the nucleus accumbens. To have motivation, to be motivated, to feel good, to have wellbeing, to experience pleasure you have to have functioning dopamine neurons in this part of your brain. So you can see right away that if someone loses their ability to feel good, as in anhedonia, as in depression and other psychiatric disorders, it must be related to some loss of the functional capacity of this part of the brain. And many, many, many studies have confirmed that. And the problems with addictions is that while someone is using the addictive substance, those dopamine neurons are firing like crazy, they light up, there's huge pleasure, euphoria, but then there's a withdrawal, there's depletion. And in between those addictive behaviors they're anhedonic. They do not have a normal ability or as much ability to motivate themselves to do anything other than seek the addictive thing. Okay, next slide.

This is a cartoon that I actually paid an artist -- a comic book artist to draw for me ten years ago, when I was deployed to Iraq -- just before the Battle of Fallujah. And I asked them to do this as an analogy or metaphor for the way these brain systems that I just described to you, prefrontal cortex, hippocampus, amygdala, dopamine, and sympathetic nervous system, how they work together under normal stress. And I've shown this chariot slide and a couple others to many groups of warriors, including Marines after the Battle of Fallujah. And when I have shown it to service members, one of the first things -- or health care professionals, one of the things I ask is look at this slide and tell me what's wrong with the way this chariot is being driven. What would make this impossible if it was real life? And, you know, somebody will say, "Well, there's no left wheel on the chariot and the horse's hooves don't touch the ground. But sooner or later somebody comes up with, "Oh, yeah, one guy has the reigns and the other guy is cracking the whip." I mean, how [ridiculous] is that? That would be like two people driving a car, driving the same car, where one person had the gas pedal and the other person had the brake and the steering wheel, right? That would take a lot of coordination.

Well, you know, it's kind of a flier to, for me, to put this together ten years ago, but I just -- I breathe a sigh of relief, now ten years later the research that's been done there is only

increasing my conviction that one of the central challenges for the brain in stress is that coordination between those two important controllers. Next slide.

And they are the guy with the cape who's the uber-dude here, whatever, is the prefrontal cortex and the hippocampus working together, these gray matter, cockpit, you know, the brain systems through which we can be sentient and make choices. The amygdala is the threat processor, the emotional responder, and he's cracking the whip. And I, increasingly, in my reading of the neuroscience literature, I'm seeing discussions about a struggle for control, a struggle for control of your organism between the prefrontal cortex and hippocampus on the one side and the amygdala on the other. So when you think about that struggle for control. Next slide.

All right. So let's just take a little side trip here and talk about this issue of normal stress versus extreme stress, because ultimately we want to get to the point of being not only recognizing which brain systems are involved in stress but how are they affected by extreme stress. So what the heck is extreme stress? In every scientific discipline that looks at this, whether it's from a psychological, social, biological, neuroscience perspective, they have their own definitions. But these definitions up here, normal versus extreme, kind of parallel what you're going to see almost in any science, I think.

Extreme stress is of either high intensity or long duration, so it's not moderate and it's not short in duration. Normal stress is cyclical, right. You work for eight hours, you go home, you chill, you eat, you go to sleep, you go again tomorrow. So it would not be normal stress if you didn’t sleep and you didn't stop working and you just kept going on and on and on. So stress that lasts too long is extreme, or stress that's of too great an intensity, even if it's short duration, is extreme. So, in a lot of neuroscience research, whether it's with animals or humans, they talk about controllable versus uncontrollable, like one of the paradigms for inducing uncontrollable stress in a rat is to hang it by its tail, you know. It doesn’t kill them but it freaks them out. They can't control it.

And so the point that we made with this Stress Continuum Model grew out of the 2007 tri-MEF working group that the Marine Corps convened, actually chartered by the commanding generals of the three Marine expeditionary forces. They said, "We want to build our own COSC program, Combat and Operational Stress Control. We want to have our -- we want to be able to teach our own people how to monitor stress and manage it." So they came up with this stress continuum of these four stress zones, green, yellow, orange, red. And yellow is the normal reacting stress, and orange is extreme stress. And in the Stress Continuum Model they, even back then in 2007, they recognized that there were four potential causes of extreme stress in humans, and one is fear, life threat; another is loss; another is moral injury or inner conflict, as it's called in the doctrine; and the last is cumulative stress.

Okay, so next slide, this is just very briefly I want to show you some unpublished results from the Marine Resiliency study. This is currently being reviewed, Journal of Abnormal Psychology. We did a with Brett Litz at Boston and his staff, with data collected by the UCSD Marine Resiliency Group Team. Over the course of several years we enrolled 2,600 Marines and evaluated them at four time points, before deployment, either after Afghanistan, and then, like, one month, three months, eight months later, biologically, psychologically, socially.

And this slide shows you the results of the most highly combat-exposed group of Marines in our studies, basically one infantry battalion that went to Afghanistan in 2010, very highly combat-exposed, and looking at what were the natural subgroups of patterns of change in PTSD symptoms over time, trajectories. And we found that most Marines fit into one of these three

patterns. And the dotted line is the nuance set group, the ones who had low symptoms before they went, and then had enduring PTSD symptoms at a high level afterward. And I can't see the percentages here on my slide. Regardless, there's a solid, dark line is the group that had preexisting symptoms, and then lightest line, lowermost line is those who had relatively low symptoms across the board.

So I'm showing you these trajectories because one of the things we did in the study, one of the questions we wanted to ask for the Marine Corps, for DoD, for science, is, "Okay, so what are the predictors of membership in these trajectories?" What are the things that predict who's going to have enduring PTSD and who's not? Who's going to have low symptoms? And I just showed you three of the predictors there on this slide. Prior lifespan trauma, fairly significant. We used the childhood trauma questionnaire, not a significant predictor. Combat experiences, not significant, I mean, not when allowed to compete, at least with these other predictors; looked at it by itself, of course, people who had higher levels of combat exposure were more likely to have PTSD symptoms. They were correlated.

But if you let all these predictors compete against each other, the two that emerged as the strongest predictors of who had nuance set of PTSD and who didn't or who had preexisting PTSD was peritraumatic dissociation or avoiding coping across all time points. And peritraumatic dissociation is blowing a fuse, it's losing control, it's going blank, it's having a panic attack, it's freaking out. You know, we still don’t know exactly what happens in the brain during a peritraumatic dissociation, but I think the point here I'm trying to make is there -- you know, I think there's -- and there are other sources of evidence that suggests that this line – there is a line between yellow zone, normal stress, and extreme stress in the real world, and that peritraumatic dissociation and other changes in behavior may be markers of that. Next slide.

Okay, I need to hustle here a little bit because I'm a little behind in my timeline. But I just want to go briefly over, okay, so what goes on in the brain that marks extreme stress as different from normal stress, and there are a few modulators of this process that I just want to single out. There's a ton more. Corticotropin-releasing factor and cortisol, most people know them by cortisol, corticotropin-releasing factor; brain-derived neurotrophic factor, which is like Miracle-Gro, it's a peptide that's released in various parts of the brain to stimulate new neurons to grow, to arborize, to connect; and then glutamate acting at a particular kind of receptor called NMDA. Next slide.

Okay, third polling question. What type of chemical messenger is corticotropin-releasing factor? Is it a hormone that's released into the bloodstream as part of the endocrine system? Or is it B, a neurotransmitter released into synapses in specialized neurons in the brain? Or is it both A and B? Go.

Okay. You guys are very smart. Maybe I telegraphed it too much. But, you know, when I was in medical school we thought that it was just part of the endocrine system, that it's released into the portal circulation between the hypothalamus and the pituitary and it starts to cascade of endocrine changes that lead to cortisol being secreted into the blood by the adrenal glands. But it's also a neurotransmitter in the brain, and it is the most important modulator of stress. It's the on-switch for stress. And if you remember my chariot slide, it is the whip. The more stressed you are, the more CRF pours into the body, into the brain. The more CRF there is in the brain, up to a certain point it motivates improved performance, learning and wellbeing, beyond that point though, it has the opposite effect. It degrades performance, degrades wellbeing, and actually causes the loss of neurons. Next slide.

So this is summarizing a ton of different studies and trying to make sense out of them in one slide. And if there were, like, one take-home for this whole presentation I think it would be this one. And just briefly, these are the three brain systems, looking at the prefrontal cortex and hippocampus, looking at the amygdala, and looking at the nucleus accumbens, and the dopamine system, and look at how are they affected differently by CRF, cortisol, and brain-derived neurotrophic factor, and other things in low to moderate stress and extreme stress?

Low to moderate stress, prefrontal cortex and hippocampus are stimulated to increase the density of dendrites and synapses, to grow new synapses, to grow new neurons. That's all we want. That's what we send our kids to school for. That's what we train people for. Training in low to moderate controllable stress grows new brain. It grows new connections. It gives us new capacities and abilities. Low to moderate stress has the opposite effect on the amygdala, which is good, because it makes it easier to remember that struggle for control between the prefrontal cortex/hippocampus on one side, amygdala on the other. Low to moderate stress makes it easier for our sentient parts of us to have control over our organisms because it decreases the intensity, the number of neurons, dendrites, and synapses in the amygdala. Nucleus accumbens, low to moderate stress, increase in dopamine release, which means more motivation. It means more wellbeing. It means active coping, problem-solving, less depression.

Then extreme stress, everything is flipped upside down, and it's because of the actions of these modulators of stress. Under extreme stress there's a loss of new dendrites, a loss of synapses, and actual loss of gray matter in the hippocampus and prefrontal cortex, that's been demonstrated in so many different animals and so many different paradigms, including people with depression, PTSD, other mental disorders. And the opposite in the amygdala, extreme stress increases the number of neurons in the threat detector. So imagine the amygdala is like a smoke detector in your house, and extreme stress makes it louder, makes it more likely to fire, right. So it gets to the point -- and that's one way to conceive of some of the symptoms of PTSD is like one of those dang smoke detectors that you just can't turn off.

And nucleus accumbens -- and this is fascinating stuff, under extreme stress -- it changes the response of the dopamine neurons from problem-solving to helplessness to avoidance. So some of these things that we think of as avoidance coping actually are mediated by, seem to be in some of these studies, mediated by dopamine neurons going through the nucleus accumbens under extreme stress. Next slide.

Okay. Last polling question. In which of the following tissues can excessive glutamate signaling mediated by NMDA receptors result in the death of neurons? A, retina of the eye; B, hair cells of the inner ear; C, hippocampus; D, prefrontal cortex; or E, all of the above.

Oh, you guys are too smart, too smart. This blows me away to think about this. These are all tissues in which these important neurologic functions are mediated by, are possible only because of glutamate neurons, which is the primary excitatory neurotransmitter in the brain, but that use the specific type of receptor called an NMDA-receptor. These are the tissues that are the most sensitive to the environment, which our retina has to be, our inner ear has to be, our hippocampus and prefrontal cortex have to be, they have to be plastic. They learn quickly. But this is their Achilles' heel. It also makes them fragile and vulnerable to being damaged by excessive signaling. Next slide. Okay. So, next slide. There we go.

Now I'm not going to ask you to pour through this thing. This is from a paper by William Nash, not Robert Nash, but looking -- talking about the stress injury model and what is called excitotoxicity in glutamate neurons. And just starting at the top left you have increased signal

intensity. Increased transmission in these neurons. It causes more release of glutamate, which are the purple stars. They attach to NMDA receptors on the postsynaptic neurons. And after a certain amount of these things -- a certain intensity, density of attachment, magnesium ions are popped off of these pores in the NMDA receptors and calcium ions are allowed to pour into the cell, which can cause the actual death of the cell. Now, at least initially, they shrink and then they can actually die.

So what happens when a glutamate neuron dies? It releases glutamate, and glutamate is the excitatory neurotransmitter. So that has potentially a regional effect of increasing the intensity of glutamate signaling and other neurons around it, which can lead to actual loss of brain matter. Next slide.

So this is revisiting my chariot. And this is looking at extreme stress, where the prefrontal cortex and hippocampus together, because of the effects of corticotropin-releasing factor and cortisol and allostasis and everything else, that the struggle for control of our organism has greatly shifted and we're now acting -- this may be a paradigm for dissociation, for rage, for panic, for going berserk, where for some period of time our ability to volitionally control ourselves is lost.

Okay, the last slide. So, conclusions, whereas normal stress is good for us, necessary, if you just stay home and stay in bed all the time you're going to lose what capacities you have, whereas that's the case, extreme stress actually degrades our abilities and can lead to permanent changes in the CNS. They can regrow, and I apologize, I have not addressed what are some of the things that, given our current understanding, that it can actually reverse this process and promote regrowth, but they can't.

And my second point is health promotion programs, whether it's prevention screening, treatment, rehabilitation, we've got to embrace these neurobiological concepts so that we can be relevant in all situations, not just normal stress. I think that the more we look at signs of crossing this threshold between normal and extreme stress, I think the smarter we'll be at applying indicated prevention, early interventions, things like peritraumatic dissociation. And I really think teaching, learning and teaching neurobiology can reduce stigma. So I'd like to turn it over to Tony for questions.

All right. Thank you, Dr. Nash, for your presentation. I know that we have already some questions that are rolling in, but if you do have questions right now for Dr. Nash, please submit them now via the question box located on the screen. Again, I know that we have a number of questions already, and we'll permit others to send their questions in. But maybe I can start, Dr. Nash, by asking you a little bit more about some of the damage to the brain, to the CNS, with regard to the exposure to extreme stress. Is there any further information about maybe the nature of the stressor, of maybe the duration of stress or the intensity that would, you know, signify some kind of threshold as what extreme stress might be?

Yes. Well one new area of research that's just beginning is looking at different event types and comparing fear-based trauma, which is life threat, to loss, you know, the absence of someone or something that's cherished, moral injury or inner conflict, which is betrayal of trust and moral values, and comparing that to just cumulative stress. And such a new thing, but I don’t want to steal their thunder but STRONG STAR's study, which is a collaboration in San Antonio between University of Texas, Boston VA, doing outcome studies for various kinds of treatment programs for PTSD in service members. And they actually have done imaging. And this is under review somewhere, it's still being written, but they're going to publish, I believe, data to compare how

different parts of the brain are hypoactive or hyperactive in these different event types. So that's one thing that could be helpful in the future.

Right, I think probably for a lot of clinicians out there, you know, participating in this webinar, they may be wondering, probably on both ends of that whole continuum that you showed in one of your slides, so on one hand I think back to your aviator analogy, and I wonder about is there a way that we can adjust that performance envelope with regard to models of resilience or ways that we can increase performance? I know that a number of people are encountering more and more ads for things that one can do for the brain to increase, you know, brain resilience and other brain functions. There's that aspect of it. On the other end of the spectrum with regard to the injury aspect, you know, what are the implications for clinicians? What can clinicians consider in their use of or approaches in their treatment of patients?

Right, those are two awesome questions. You know, resilience fitness, I think resilience promotion or universal prevention, health promotion at one end of the spectrum is crucial for expanding the performance envelope, for making it less likely that someone, at any given time, at any point in time when we've pushed over their own personal threshold. And understanding neurobiology, cycles of neurotransmitter use and recovery, depletion, replenishment, some real simple obvious things, sleep, you know, these neurons become less effective and more likely to be damaged if they're not given a chance to recover. Sleep and rest and distraction, not just distraction but fun, recreation, you know, doing something totally different, social things.

And obviously one of the key resilience capacities that causes -- that empowers the prefrontal cortex and hippocampus to tell the amygdala to chill is trust, trust in your values, trust in the people you're with, knowing someone has your back and they have your back, you know, being alone, isolated, or losing trust in others or in our beliefs and in the institutions, those things make people way more vulnerable. But one of my main arguments here, one of my main points is no matter -- it's just like sports. You know, training, fitness, all these things can make people perform better and make it a little less likely they'll get injured, but people still break. We have limits. And so that's the other part of this. If you want to have – if you want to build resilience, you want to have a fitness program, you need to pair that with, okay, so what happens when that is not enough, and because of what you've been asked to do, you're pushed beyond your limit? You need to be able to.

And, once again, increasing brain-derived neurotrophic factor, exercise, yoga, meditation, those are huge. Also, SSRI antidepressants; there's studies to show that long-term use of SSRIs actually promotes release of brain-derived neurotrophic factor in the prefrontal cortex and hippocampus, which promotes healing. So that's a huge – there's a lot more involved in that, but great question.

Okay, I know we've got a number of questions from our participants there on the webinar. And maybe I can start with this one: how do you talk with a PTSD patient who is taking a Benzodiazepine, which is presumably interfering with fear extinction? How would you explain to them how this is a problem?

Yeah. Well, it is a problem, and benzos are hazardous, at the very least, for the treatment of any of these sorts of problems. And so one of the first things I would want to explain to them is that it is so -- dependency and tolerance is built up so fast to benzos that the benefits are going to be very short and they're going to very quickly get to the point where they're going to have to keep taking the benzos just to prevent the withdrawal symptoms. So then they'll have to keep taking it just so they don't withdraw, but it's no longer going to do any good unless they increase the

dose. And the other thing I would do would be to compare it to drinking. I mean, clearly there are long-term hazards to using that kind of short-term fix, and it clearly doesn't fix anything, and it actually, as the questioner pointed out, it actually interferes with processing.

Okay. Thank you for that. There's several other questions I know that people are anxious to ask. Let me get to this one. The Levy-Gigi 2013 study, it's been interpreted to indicate that some CBT psychotherapies can actually reverse hippocampal volume loss. Is that correct?

Yeah, I am aware of some of that work. And, yeah, absolutely. The cool thing about the hippocampus and prefrontal cortex compared to the retina and the hair cells of the inner ear, which don't regenerate, don't regrow, these important control neurons in the brain, glutamate neurons, they can re-arborize, they can make connections, they can grow new gray matter. And therapy that works is reflected in increased connections, increased growth of neurons, just as the initial experiences of parenting and training and mastery of life are reflected in the growth of those things in the first place.

So that is – one of the limitations seems to be, and I wish I had cited this one particular study that looked at regrowth and "re-arborization" of these glutamate neurons in the prefrontal cortex and the hippocampus is the short neurons grow back much more quickly, but some of the long ones, especially those in the mesocortical tract between the prefrontal cortex and the dopamine system, because they're much longer and the neurons can only grow so fast, in one study showed that even after a year-and-a-half a lot of the deficits and the connections had not yet been remade. But, absolutely, psychotherapy, I believe social support, peer mentoring, there's a whole host of other things that can do the same thing.

Okay. Related to that there's a question about where can we go to find out more about reversing the CNS damage?

I wish -- what you're asking -- the questioner is asking, so what are some good resources for translating this neuroscience into practice, and I'm here to tell you that's hard to do. So, there are, I mentioned, Joseph LeDoux's books. Doug Bremner wrote a book relevant to these things. But there really aren't many resources out there where people who are smarter about it than I am, who explain it in ways and draw inferences from these studies and say, "Okay, now how do we use that." I wish there were more. But I would urge anyone who has an interest in this to just regularly search the literature, just look and see what's coming out.

Okay. Clearly there's a lot of interest based on the questions that we're receiving, and one of the others, again, along similar lines is, "What mental health/therapeutic approaches would you suggest (those that give proper attention to the central nervous system)?"

I'm sorry, say that again.

What mental health/therapeutic approaches would you suggest that give proper attention to the topic that you presented today?

Well, I would think -- I think that begins with psychoeducation and our models of how we explain to our patients and clients and to ourselves and each other how what we do works. So that's number one. And then being aware of the more we learn about what promotes healing and regrowth, what doesn't, making sure those things are attended to. Some of these things we already know and are smart about, you know, people use things like SUDS, Subjective Units of

Distress, things like teaching in clinical settings, teaching self-soothing, self-calming. And in order to regrow these self-controlled neurons you have to practice self-control.

It's like anything else in the nervous system, you can't learn to play the piano unless you put your fingers on the keyboard, right, and you have to do it over and over and over again. So a lot of what we do is already kind of thinking about that, but I think the next step is teaching people what is the neurologic basis of this, explain, for one thing, why it takes so long, why there's no one-shot learning when it comes to these things, and why seven sessions or 12 sessions is not going to solve the problem, it's just teaching a skill that has to be practiced.

Okay, I have a very quick question. And another one here, "Would it be okay with you, for those of us on the talk, to use your slides in talking about the neurobiology of stress in our discussion with patients?"

Please do. I give them to you to use any way you want.

Okay. And then probably one that really deserves an answer as well before we wrap up, "Do you have a list of treatment recommendations for those whose CNS damage may be permanent?"

I think that's a challenge that's very similar to that which faces people with TBI or seizure disorders or other mental disorders. Number one, losing capacities doesn't mean you don't have the ability to develop new and parallel capacities. The brain is very plastic in workarounds. There are people who have had almost total damage to their speech centers who can learn through practice, through training, to speak again.

There's one case of somebody who had almost one whole side of the brain missing, which should mean that the opposite side of the body would never move again, but it is possible. It's wicked hard, so patience and working at it, you know, you can learn workarounds. And I think – and I do a lot of work with Wounded Warriors and Semper Fi Odyssey, and I think a crucial thing here is not seeing yourself as broken beyond repair, as this is an obstacle, how are you going to work around this so you can be the best person you can be?

Okay, Dr. Nash, thank you so much for your presentation with us this afternoon. You've given us certainly a lot to think about. And I really like the way that you've really focused on the neurobiology in these psychiatric conditions and really have given us really more thought to consider with regard to thinking about structure and function. And even with TBI, even though that wasn't specifically a focus today, but how some of those vulnerabilities associated with TBI might lead to certain vulnerabilities in the psychiatric conditions that we often see comorbid, given our service member and veteran population. But thanks again for your presentation.

I want to point out that today's presentation will be archived on our monthly webinar section of the DCoE website. And after the webinar please visit http://continuingeducation.dcri.duke.edu to complete the online CE post-test and evaluation, and download your CE certificate or certificate of attendance. And to help us improve future webinars we encourage you to complete the feedback tool that will open in a separate browser on your computer. To access the presentation and resource list for this webinar, again, visit our DCoE website, that's dcoe.mil/webinars. We'll post the downloadable audio podcast and an edited transcript of the closed caption text to that link.

The chat function will be open for an additional ten minutes at the conclusion of the webinar for attendees to network and chat. In the next DCoE Traumatic Brain Injury topic is "Do Helmets Prevent Concussions," and it's scheduled for July 10th, from 1300 to 1430, and that's Eastern Standard Time. The next DCoE Psychological Health webinar topic is "Hearing and Vision Impairment from Combat Trauma," and it's scheduled for July 24th from 1300 to 1430. Now, thank you again for attending and have a great day.

That concludes today's conference call. Thank you for your participation. You may disconnect at this time.