Thank you. Welcome to today's theme long terms effects of TBI Management and Support. Session T2002 Predictors of outcomes in military blast concussion. My name is Major Pamela DiPatrizio. It is my pleasure to introduce Dr. David Brody. Dr. Brody is the Associate Professor in the Department of Neurology, Hope Center for Neurologic disorders, Neuro-trauma Research Group, School of Medicine at the Washington University in St. Louis. Please join me in welcoming Dr. Brody.

(clapping)

All right should I go ahead and get started then?

Yes sir.

All right. Hello, everybody. My name is Dave Brody. I've addressed some of you before in previous webinars, but it's a pleasure to be back again. Thank you for inviting me again. I'm going to tell you a little bit about some of the work we've been doing with U. S. Military personnel evaluated in Landstuhl, Germany and also in several centers in Afghanistan. With then a clinical follow up 12 months later back here in St. Louis.

A couple things that you can see, this first slide about me little bit. I just want to point out, this concussion care manual has already been published. It's out and it's sold several thousand copies so far and it's been-- but I very welcome your feedback about the clinical care. I'm not going to talk to you about clinical care today. I'm going to talk about research, but this is something that I'm also very passionate about and I welcome your comments on this as well.

Okay. So getting started, the title of my talk today is 'Predictors of outcomes after blast related concussive traumatic brain injuries'.

These are my disclosures. I don't have any conflicts of interest. The learning objectives are to understand our standardized multi-disciplinary evaluations of outcomes in blast related concussive traumatic brain injury in U. S. Military personnel, and to recognize the major drivers of disability following blast related concussive traumatic brain injury in U. S. Military personnel.

I'm happy to address questions about neuro-imaging but for reasons of time I'm actually not going to be able to present any of our imaging work today. This would be two separate talks, but happy to address questions about the imaging separately.

So in outline, as I mentioned we have results to present today from two separate studies. One that was formed starting at Landstuhl Regional Medical Center from 2010 to 2013. And the other involving military servicemen enrolled at two sites in Afghanistan in 2012. We have performed clinical evaluation of service members from both of these cohorts six to twelve months after the initial enrollment back here in St. Louis.

We did not provide any treatment as part of the study. It's really a natural history study and none of the results of any of our evaluations became part of the participant's medical records or effected their disposition or their care. So they felt generally quite free to disclose how they were really doing without any fear of stigma or repercussions with regards to their medical careers or their military careers. And that was one interesting aspect of doing this as part of a military civilian partnership is that we could dissociate a little bit from the clinical care aspect a the military medical system.

So getting right into it. The first study was led by Christine MacDonald a talented post-doctoral fellow and junior faculty member in my laboratory. Started out at Landstuhl Regional Medical Center in Landstuhl, Germany. Enrolled 255 U. S. Military service members from 2010 to 2013. The times for enrollment-- from injury to enrollment were between one and 30 days with mean of eleven. And then we evaluated 183 of
them in person six to twelve months later at Washington University. There were five—were disqualified for incomplete performance or erratic performance, and data from 178 was analysed.

Now the diagnoses of traumatic brain injuries versus controls—other injury controls were mainly based on self report but confirmed by medical records when available.

So here’s a geographical orientation. The subjects in the study were either injured in Iraq or Afghanistan and then aero-medically evacuated to Landstuhl Germany where they were enrolled. And then followed up again in St. Louis. This is the ambulance on which they arrived and the aero-medical transport is another topic of great interest. These flying intensive care units were an area of great interest of ours.

I had the great pleasure of collaborating with four wonderful Landstuhl investigators: Colonel Flaherty, Colonel Fang, Lieutenant Colonel [Ohe] and Lieutenant Colonel [Doney] These were our site principal investigators at Landstuhl.

And this was truly a military civilian collaborative research project. There’s no way we could have done this without our collaborators.

So jumping right to the point, the overall outcomes. A remarkable finding. In two different groups, those with non-blast related traumatic brain injury versus blast impact traumatic brain injury—our overall outcome six to twelve months later were remarkably poorer in the blast related injury and the non-blast related traumatic brain injury than in the non-blast exposed controlled and in the blast exposed controlled.

Just a quick word about how we categorized our subjects that we enrolled into these groups. We asked them very specific questions about their history of traumatic brain injury to find if a loss of consciousness, amnesia for an event, alterations of consciousness following an acute physical injury to the brain. And then we also asked them about their blast exposure. And so some of them had blast exposures without meeting the definition of traumatic brain injury. And some of them had blast exposures and traumatic brain injuries as a result. But, many of them had other mechanisms of injury that did not involve blasts; motor-vehicle injuries, maintenance injuries, falls, some even sports concussions and theater. And then non-blast exposed, non-brain injured controls who were evacuated to Landstuhl for other unrelated injuries, injuries that were not part of the brain. Medical illnesses not related to the brain and not exposed to blasts.

So the first point is that a substantial number of them six to twelve months later were still impaired by the Glasgow outcome scored which rates their overall impairment. Importantly the Glasgow outcome score is not strictly working related to return to work or return to duty. Social impairment, interpersonal impairment and substantial symptoms that impair quality of life also count as a low Glasgow outcome scale into the marked disability category. Very few were severely disabled meaning that they needed help with activities of daily living. Only two subjects fell in that category.

So much of the interest after traumatic brain injury has been in cognitive performance. We performed a battery of cognitive testing at six to twelve months afterwards and interesting for the most part, most of our subjects performed very well on the cognitive testing. However, a small subset of patients or subjects in each of the groups performed worse than would be expected on the cognitive batteries.

So the first point, was as I said, most of the subjects did not have any abnormalities on neuro-cognitive testing which you could see, or had only perhaps the number that might be expected by chance. Maybe one test their performance was low but perhaps the rest of the tests their performance was quite normal. But more subjects than would be expected by chance, a substantial subset had two or more neuro-psychological test abnormalities. And the patients in the non-blast traumatic brain injury here in the orange and the blast plus impact traumatic brain injury in the tan—There were more of these subjects
with two, three, four, five all the way up to ten neuro-psychological testing abnormalities than would have been expected by chance.

So it's important to note here that these were all normed based on people whose age and education were similar to the subjects that were being tested. And all of these were performed, all the testing was performed completely blinded with regard to the diagnosis. So the take home message from this slide is that most--there was a mismatch between cognitive performance and overall disability. A larger number of people had overall disability than had cognitive performance abnormalities. There were a subset that had cognitive performance abnormalities but it was not most of them.

Many of our patients complained of headaches. We quantified the severity of their headache impairment using a test called the MIDAS. It's a self-report measure. It's a structured interview scale in which higher numbers represent more substantial disability related to headache. And again that was substantially higher in both of the traumatic brain injury both non-blast and blast plus impact groups compared with our two controlled.

Interestingly the blast and exposed controlled who did not have a clinical diagnoses of traumatic brain injury did have a higher burden of headache related ability than the non-blast exposed controlled. So there was something of a grade effect, with relatively modest burden of headache, higher burden of headache and even higher more substantial burden of headache in the injury groups.

In case it wasn't clear from what I've said before, all the subjects in the blast plus impact traumatic brain injury group had just that. Injuries related to blast impact. We did not enroll any subjects that pure blast related injury. It wasn't that we were excluding them. We would have loved to enrolled them if we could have but there just weren't any. That seems to be an extraordinarily rare event where the injury is related exclusively to blast and there's no impact component at all. So all of these should be thought of as blast plus impact versus just non-blast where just impact event.

There's been a lot of discussion of post-traumatic stress and depression after concussive traumatic brain injury. And we did gold-standard structured interview assessments of post-traumatic stress using the clinician administered post-traumatic stress or using trained raters. And also the severity of depressing using the Montgomery-Ashburg Depression Rating Scale, another standard measure in the field. And again we found that graded effect where there was moderate levels of post-traumatic stress and depression in the non-blast exposed controlled. Higher levels in the blast exposed controlled without traumatic brain injury and still higher levels in the non-blast and blast plus impact exposed individuals but no difference between the two subjects evacuated to Landstuhl Germany.

Substantial levels of post-traumatic stress and depression in both of these traumatic brain injury groups.

We evaluated combat exposure intensity. This is again with a measure called the Combat Exposure Severity Score. And here is where an interesting divergence occurred. Both the non-blast exposed controlled and the non-blast traumatic brain injury subjects had relatively modest levels of combat exposure. But both the blast exposed controlled and the blast plus impact traumatic brain injury subjects had higher levels of combat exposure and these were both statistically significant from their respective control groups.

So there is a mismatch between combat exposure and post-traumatic stress, depression and outcomes. If you flip back here for example, you see the mismatch between the combat exposure and post-traumatic stress and depression. It's clearly not just combat exposure that is causing or driving these-- the disabilities that we're seeing, the post-traumatic stress, depression and disability.
And in fact, when we looked at correlations, the quantity of correlations, between combat exposure score and either post-traumatic stress or depression. The correlations were modest in the control groups and completely absent in the injured groups.

We put it all together to see if we could predict overall disability as a way of determining what the most important drivers of disability might be. Raising from hypotheses. So in a multi-varied analysis where all of the variables that you saw previously presented and demographic variables were combined into a multi-variate logistic regression model. What we found was that the overall severity of depression, the number of neuro-psychological abnormalities, the headache burden, the MIDAS system measure of headache burden and whether they were in the traumatic brain injury versus the control group were the strongest drivers, or the strongest predictors of overall disability and it had a moderately good area under the curve of close to point eight in its receiver operator curve. So this is good but not perfect.

But importantly some of the other factors were not substantial correlates, like blast versus non-blast was not a substantial correlate and the severity of post-traumatic stress disorder did not come out of this. Age, branch, officer versus enlisted, gender, none of those were significant predictors in the demographic domain and that's in contrast to some of the data that I'm going to show you next.

So in conclusion we did a prospective study of blast related versus non-blast related concussive traumatic brain injury U. S. Military personnel and we found substantial overall disability six to twelve months after injury. Primarily related to depression severity, number of neuro-psychological abnormalities, even those were relatively rare and headache burden. However, the mechanism of injury was not associated with any detectable difference in outcome in these cohorts. This has been a topic, blast versus non-blast, traumatic brain injury and this cohort, using these measures, we did not find differences between those two groups.

Once the outcomes were substantially worse than previously reported in civilian concussive TBI and then even for poly-trauma cohorts in which 22-47% had 6-12 months moderate to severe disability. In contrast, for example, with sports-related concussion, where only a very small number of people have [inaudible] disability 6-12 months injured [inaudible] after injury.

But we recognize that increasing combat exposure tends to be correlated with PTSD severity in the controls but did not correlate in military personnel with TBI. Based on these observations, one of the hypotheses we formulated was that there may be separate mechanisms underlying PTSD symptoms such as structural impairments in brain circuitry responsible for emotional regulation in TBI subjects but not in the controls. In work that's currently ongoing, we're using advanced brain injury methods that are sensitive to injury in orbital frontal and limbic system region to test this hypothesis. That will be something that will be coming up in future directions to be able to determine the extent to which there are structural abnormalities that underlie some of these depths that's in emotional regulation after traumatic brain injury.

Taking a pause for a second. Now I'm going to tell you about the second study that we performed, enrolling subjects directly in Afghanistan. One of the questions that arose as we were performing studies in [inaudible] is whether we were truly getting a representative cohort in [inaudible]. It's possible that some of the subjects that had more typical symptoms or more typical injuries were remaining in theater and not being evacuated to [inaudible]. The logical next step was then to perform studies in Afghanistan itself.

I traveled to Afghanistan as a civilian consultant in 2011 to help with the logistics of the study and oversee some of the aspects of the concussion restoration centers and concussion care centers, so it was really gratifying to see how successful those were and then to be able to do some research together, gather some research data based on those concussion clinics.

Here's one of them, the Warrior Recovery Center at Kandahar Airfield, which was one of the most successful sites. This study was led by Lieutenant Commander Octavian Adam, a neurologist who was station in Kandahar during that time in 2012 and was a close collaborator of ours during that period. For
this study we enrolled 196 US military service members from 2012 at two sites in Afghanistan and
Kandahar and also Camp Leatherneck. Times from injury to enrollment were 1-8 days, median at 3. We
were able to evaluate 72 of them in person 6-12 after injury at Washington University. As you can
imagine, it was much more difficult getting these patients back in St. Louis, because many of them were
returned to duty after their injury in Afghanistan. Here in Afghanistan, diagnoses were based on clinical
provider evaluations. The clinical diagnoses were what was used.

This was our flow chart of the patients, the subjects, that we enrolled. You can see our exclusions. Most
of them were from Kandahar. Some were also from Leatherneck. Most of the subjects that we invited to
participate in the follow-up were, in fact, able to follow up, with a few excluded for things like test of
memory, malingering less than criterion score, suggesting that they were not actively participating in our
tests. Most of them did show adequate effort where our results were considered valid.

This is an outline of the characteristics of the subjects that we enrolled in Afghanistan. Due to the nature
of the enrollment, we did not have a perfect match between the concussive brain injury patients or mild
traumatic brain injury patients and the controls. In particular, there was mismatch in officers versus
enlisted men. You'll see later on, we did some group analyses where we just compared enlisted with
enlisted men and women so that we could more adequately make these comparisons. But, for the most
part, all the conclusions that I'm going to show held in some group analyses, where we performed the test
comparisons based on match demographic symptoms.

As expected, from the nature of the cohort, these early concussive traumatic brain injury subjects had a
very high level of symptoms. This is the Rivermead post-concussive symptom questionnaire, a standard
measure of the severity of post-concussive symptoms, much higher than the control. Many of the
symptoms in Rivermead are things that other people that have not had concussion experience, and there
were symptoms that could be considered post-concussive symptoms in the things like irritability and
depression [inaudible] and difficulty concentrating, but the levels were much lower in the control group
than in the concussive traumatic brain injury group. It's often been said that these symptoms are non-
specific. It is true that individually they're non-specific, but as a quantitative burden, they are substantially
higher in concussion individuals than they are in controlled, even in the same environment. Furthermore,
balance was impaired on the balance error scoring system in the concussed individuals compared to the
controlled. You can see, though, there's quite a range in balance performance on the balance error
scoring system performed in theater.

There was, interestingly and unexpectedly, there was a very high degree of depressive and post-
traumatic stress symptoms acutely after the concussive injury. On the Beck Depression Inventory and
post-traumatic checklist, the military versions. This was surprising because most of the time when we
focus on depression and post-traumatic stress-related symptoms, we're looking maybe months to years
after the injury. We're not thinking about those sorts of symptoms immediately after the injury itself. The
result, however, was highly -- There was some burden of these symptoms in the control group, but
substantially higher in the concussed individuals. We don't know how many of these symptoms were pre-
existing and we don't know how much of them were due to injury to the brain itself. It's quite plausible that
injury to the brain's emotional regulation circuitry could cause symptoms that mimic aspects of depression
and post-traumatic stress. That's a hypothesis. That's not known for sure. This is a hypothesis-generating
data set here.

There were highly significant acute symptoms and deficits, as you might expect, just from these groups.
This is from the [Anan] testing. Reaction times were impaired. The processing speed was impaired. The
learning was impaired. Memory was impaired, as expected from these -- In other cohorts from the [Anan]
study. There was sleep deficits as in the concussed injury patients that were more than in the controls as
well. Interestingly, the acute symptoms predicted time to return to duty. So, as I said, most of these
subjects, 90-plus% of the subjects returned to duty after their injury. Their return to duty times ranged
from 1 to about 29 days after their initial injury.
Loss of consciousness, whether they had loss of consciousness or not, was only a modest predictor of how quickly they returned to duty. But the Rivermead, severity of Rivermead symptoms, people with more severe initial symptoms, on average, took longer to return to duty. People who had more severe change in their reaction time on the [Anan] took longer to return to duty. People who had a higher post-traumatic stress symptom burden took longer to return to duty. And people who had more depressive symptoms took longer to return to duty. None of these predictors were strong enough to stand on their own, so a multi-variant model was used, and the multi-variant model was stronger than any of the individual symptoms. So, we could say that with a moderate degree of accuracy we can predict, based on initial symptoms, how long individual service members would take to return to duty. That was an important outcome from this study.

The traditional injury characteristics that were used to quantify the severity of a concussive injury were not accurate. The length of alternation of consciousness was not a predictor at all. Although we get very interested in whether they were unconscious, whether they had alteration of consciousness, or whether it was a short duration or a longer duration, that had no predictive effect on the time to return to duty. Likewise, the significance of anterograde amnesia or retrograde amnesia was zero. There was no prediction of the stint of return to duty based on anterograde or retrograde amnesia.

6-12 months later, when we evaluated the subset of individuals back in St. Louis for their overall outcomes, even though the grand majority of them had returned to duty actually in theater never required evacuation to [Launch Stool]. Still, 63% of the subjects had moderate to severe disability 6-12 months later, as compared to only 20% of the controls who had other injuries or other issues for which they sought medical attention in Kandahar or at Leatherneck. Again, this is substantially higher than what would be expected for a sports-related concussion, substantially than civilian poly-trauma and very similar to the subjects that were evacuated to [Launch Stool], suggesting that there was not a substantial difference in overall outcome, regardless of whether the subjects returned to duty or whether they were evacuated to [Launch Stool]. This is a surprising finding. We were expecting that these would be the less severely injured and they would have better outcomes if they had returned to duty, but that was not what our data showed.

The subset was similar to the initial cohort in the extent of their concussive symptoms, their balance, stability, their post-traumatic stress, depression symptoms. This is just analyzing the subsets of data from the individuals who returned for follow-up in St. Louis 6-12 months later using that same data that we gathered in Afghanistan. This is likewise the [Anan] performance, just displayed a little bit differently but fundamentally, all the same, there were impairments in all of the [Anan] domains in our subsets of cohorts. So, it was not that the subset that followed up in St. Louis was different somehow from the overall cohort. They were, to the best of our ability, very representative.

We parsed out a little bit the nature of the disability of these subjects when they returned to St. Louis by using something called the neurological recovery scale. What we found was that, again, there was overall high level of disability, but that executive and cognitive function were a big part of the overall disability, mood and affect were a big part of this overall disability. Those were the two most significant aspects, though disability in other domains was less substantial than in cognitive, executive domain and the mood affect domain.

There were very few focal neurological deficits, as expected for concussive traumatic brain injury. Few olfactory deficits, a few had partial hearing loss, a few partial gaze deficits, but the olfactory deficits were very similar in the controls in traumatic brain injury subjects. Only the hearing loss was at all different and that did actually not make disabilities significantly different. So it was not based on focal neurological deficit.

As in the previous cohort, there was a substantial burden of migraine headaches. As you can see, the traumatic brain injury subject had much higher migraine scale. The migraine grade - severe, moderate, mild -- Notice disability was higher in the traumatic brain injury subject. The headache frequency was
substantially higher. This is frequency per 90 days. Notice the many of these subjects had met a 90 out of 90 [inaudible] having headache every day for the last 90 days. The average was about 50, so about half [inaudible]. The controls had very few headaches. The pain intensity was also substantially higher. But, really, the chronic burden of headache was substantial in these individuals.

This is another measure of headache burden, which would, again, reveal very similar results [inaudible] suggesting concordance in the data.

We gave the same sort of cognitive performance testing in these subjects as we did in the previous cohort and found a very similar result, which was that a subset of the patients in the traumatic brain injury group, but not in the controls, had more cognitive performance abnormalities than would be expected by chance. Again, most of the subjects perform normally with no deficits or [mid-crafts] deficit, as maybe expected by chance. But, many more, 15 out of 38, than would be expected by chance, had two or more cognitive performance abnormality than in the control group. When we compared enlisted subjects only in the two groups, this remained statistically significant. Again, officers and enlisted service members have different levels of education and so it was a more fair comparison to perform this analysis. This and all the other analyses held in this subgroup.

As with the previous cohort there was a substantial burden of depression in the traumatic brain injury cohort and in the post-traumatic stress disorder symptoms in the traumatic brain injury cohort. When we [in-let] the sub-types of post-traumatic stress disorder, we found that there was high burden in all of the groups in their re-experiencing the [inaudible] numbing and in the [cap-D] hyper-arousal groups, so suggested it was across the board. All the types of symptoms were present.

Surprising to us there was no difference in self-reported alcohol abuse. We did not find a substantial alcohol abuse in the cohorts. We were able to find, again taking all the data into account, that early predictors of six to twelve month global outcome included high, early, post-traumatic stress symptoms, control vs. TBI, with TBI subjects having higher disability, and age, with older subjects having higher levels of disability, higher likelihood of moderate to severe disability than younger individuals.

So the other domain, even though they were substantially worse in the traumatic brain injury subjects compared with the control, were not the predictors of the overall disability six to twelve months later. So this is an important finding, because early after-injury post-traumatic stress symptoms are not currently typically being evaluated outside of a research context. And yet they are the strongest early predictor of overall disability, in addition to the things that are clearer, like traumatic brain injury and age.

So this has an important future direction, which is that these symptoms should be assessed early on as a way of assessing the subjects who are most likely to have difficulties six to twelve months after their initial injury.

We did also perform correlation analyses of the current levels of symptoms or their contemporary levels of symptoms. And we found again that post-traumatic stress, depression, combat exposure, and age were the strongest correlates at six to twelve months later. But correlates are less useful than predictors. Predictors, at early times, give you an opportunity to intervene. Whereas correlates tell you what's the problem now. So this we think is probably the single most important finding of our research, was that these early predictors were available shortly after the injury itself, but they strongly predicted six to twelve month disability.

In conclusion, we performed a prospective study of acutely enrolled US military personnel with blast-related concussive traumatic brain injury, and we found substantial disability at six to twelve months, despite high rates of return to duty within twenty one days. The strongest initial predictors of disability were the extent of early post-traumatic stress disorder-like symptoms as well as age. And both PTSD severity, depression severity, combat exposure intensity, and age were all associated with disability at later times.
So future direction? Further analysis would be desired to determine the extent to which the predictors of overall disability reflected military duty performance, other non-military work performance, and interpersonal relationship-related impairment. Anecdotally, we hear from our subjects that much of their disability is related to their interpersonal relationships. Many of them are returned to duty and are working full time, but they are not involved in much in their interpersonal lives. Their symptoms are quite disabling in that regard.

So optimal early recognition of post-traumatic stress disorder-like symptoms may be important for [inaudible] of injured military personnel who could most benefit from proactive continued [inaudible] intervention, even after they have returned to duty.

And this is our list of collaborators. It's been a wonderful team effort, including [inaudible], Tanhar, Camp Leatherneck, Washington University, my own lab -- And it's been really a wonderful presentation and opportunity to collaborate on this important topic, and looking forward to your questions.

Much of the work that we discussed has been published. A paper in Neurology, a paper in [inaudible] Neurology, and a paper in Brain, all out in the past year. Where all the results presented have been published, and there's a lot more. I presented only about half the data that was presented in these three papers. Thank you.

Thank you. It is now time to answer questions from the audience. Our speaker will respond to as many questions as time permits. Any questions from the live audience?

Hi, Dr. Brody. This is Scott Livingston. What would you summarize is the take-home message for our providers, both here on site at DTHQ and those participating virtually, concerning the potential for long-term disability among this sub-group of patients?

Excellent question, Scott. So what we've found is that much of the disability in the long term can be related to post-traumatic stress and depression, but that there is also a subset of people that do have cognitive performance abnormalities, and that headache burden is another substantial contributor. So there's a wide variety of issues that would be important for a provider to address regarding causes of disability. There's not one single cause of disability, not one single driver. There's multiple.

All of these are treatable to a certain extent. We did not provide any treatment as part of these research studies, but putting on my other hat, as the director of our concussion clinic here at Washington University, we treat all of these symptoms that are the drivers of disability.

The second thing is that return to work is probably not the only measure of disability. Substantial impairment in interpersonal domain is another major source of disability. This blackout outcome score extended, although it is a so-called gold standard measure for a clinical trial, is a crude measure, and overall levels of disability really need to be parsed out more finely into the different domains. Work-related, interpersonal-related, and quality of life-related. So that I think is an important direction for future investigations, getting more into outcomes research in terms of what the real nature of the disability is in these individuals.

Thank you, and I had just a quick follow-up to that. What do you think the implications are for educating service members and veterans about what to expect in terms of long-term disability, when for quite a substantial period of time the messaging has been getting out that the majority will recover, there are very few long-term problems, and yet this body of research seems to suggest that that's obviously not always the case.

Right. So it's important question. So what I tell my patients in clinic is that we hope that you will do very well, and there are many people who do very well. However, not everyone does perfectly well, and there
are these issues that may arise, including headaches and depression and sleep disorders and post-traumatic stress type symptoms. But that we can treat many of those concerns, so if you bring them to our attention at relatively early time, and we can treat those things. And especially if treated aggressively and early, we can change the natural history. Now, I don't have the data to show that that's the case in traumatic brain injury patients from the US military, because we did not perform an interventional study, but what I tell my patients is a note of cautious optimism, but also realism. That they are not -- So that they don't feel like if they're still having symptoms, that they are making it up, or that they are weak in some way, or that they're alone, that they're the only ones that have these symptoms. But instead that they have symptoms that many other people have and that they are for the most part treatable in the right context.

So one of the things that I think is going to be really important going forward is evidence-based randomized controlled trials of specific interventions starting early after concussive brain injury, so that we can build up our evidence-based -- So that we can tell our patients with more accuracy what the nature of their disabilities are, and what the nature of the appropriate treatments are.

So one of the things that is important about our findings is that there is sometimes a mismatch between what our patients, our subject matter in our group, were telling us, versus what they were telling their military health providers. Because they told us what they thought was really the truth, because we told them that this is not about you, this is about future generations. This is about helping the guys and gals that are still out there and will be injured in the future. But oftentimes, just anecdotally now, what they told us was that they were not fully disclosing the nature of their symptoms and disabilities to their military health providers, because of fear of stigma and consequences, repercussions with regard to their military careers. So this sort of fully anonymous, fully protected outcomes research I think is really important to get at what the actual symptoms and the actual disabilities are occurring. And that's purely my opinion. I do not speak for my other coauthors and my views represent only my own views, not anyone else's.

Tom [inaudible] here. Really terrific set of information, and this is just such important data that you're getting out. One of the interesting things of course our service members' tell us is that neurocognitive testing and testing of their capabilities really doesn't represent their day-to-day activity. In that they can hold it together long enough to spend a half hour, and hour, on a test on a piece of paper in front of them, but when they try to do their activities and perform their duties at work for eight hours a day, nine, ten hours a day, that they really have to work twice as hard to get the same amount of work done. And then that affects their interpersonal life, which I'm very glad you brought out, as a feature of some of the disturbances that occur as a result of head injury. But it stems a lot, at least in their opinion, by the fact that they're wiped out at the end of the day, and who gets the brunt end of being wiped out is their family members once they get home. Of course, it's a huge problem. One of the things we help our service members and their spouses recognize, and one of the potential fallouts.

What I wanted to ask you is, since many times the service members don't believe that the neurocognitive testing reflects real-world disturbances when they have to put in day-to-day work, what do you see in the future as a way of being able to increase the stress of the test, as it were, to see if there's a way we can more accurately describe the day-to-day disturbances in their capabilities, as opposed to single-point testing.

Tom, you've raised a really important point, and I'm really glad you brought that up. One of my regrets about the design of this study was that we did not include measures of fatigue in any of our outcome measures. And we gave our subjects every opportunity to perform optimally in the neuropsychological testing. The tests were performed in a quiet, well-lit room, with no distractions, in the middle part of the day, after they've had a good meal and a good night's sleep in a hotel here in St. Louis, with the -- They even had a curfew. They had to be in bed by 11:00 the night before. So they were not even out drinking and carousing around in St. Louis the night before their testing. So really what they represented was their optimal capability, not necessarily their daily, real-world performance.
So it's a challenge for our neuropsychological colleagues to design optimal tests that capture that real-world performance. One of the things we're talking about is a standardized set of distractors, such as for example a telephone ringing, music and television on in the background, interruptions with having to get back on task. An interrupted task restart test, which is something that many of our subjects complain about, is inability to get back on task later after they've been interrupted. And performing the testing at the end of the day, to mimic what you've described. After a whole long day of work, how do they do at 7pm or 8pm, with substantial fatigue on board?

So this is I think a really important domain. The question of how gracefully their performance degrades under stress. So their performance could be very good under stress-free conditions or low-stress conditions, but degrade more quickly than someone who has not had injury under a stressful condition. So that's I think a really important future. I think the next five or ten years or so of neurological test development, will help standardize those things. Because the counterpoint from our neuropsychological colleagues is that such tests are very difficult to standardize, but critically important. I believe our patients. When they say these things, I believe them. I don't think they're malingering or telling something that's not the case. I think they're exactly right, and I think we, the clinicians, are just not evaluating it accurately.

Thanks, I think that's a terrific approach. I absolutely agree with you, and it highlights again the opportunity, with your forward thinking on that kind of approach, to bring out some of the underlying neurological disturbances as well as the psychological disturbances from the co-morbid state. Terrific.

Thanks so much.

And now we'll answer some questions from our virtual audience. The first one is, no one else has reported as high a level of disability one year after concussion. How do you explain this?

Yeah, that's a great question. Why is it that our levels of disability are so much higher than previously reported in the literature? One of the major differences between our study and previous studies was that first of all ours was a true cohort study, where we enrolled a full spectrum of people from the foci of injury, which for example was [inaudible] or at the two centers in Kandahar. Most of the previous studies of which I'm aware took instead a subgroup analysis of people at one particular site in the United States. And so I don't know if that explains the difference.

The other major differences is that we were not military researchers, and we made it very clear that everything that our subjects told us was strictly confidential and would not have anything to do with their overall performance. I mean, their overall military careers, and would not be disclosed to their commanding officers, superiors, at all. We also worked very hard to establish a rapport with these individuals with phone calls every month prior to the six to twelve month evaluations, and so I think we had a level of honesty and a level of trust in our research group that I can't say whether other studies had that same level of rapport and trust. So it is possible that we were getting the actual answer and that some of the other reports were under-reporting.

It's also possible that we were getting over-reporting. I don't know why that would be, but it is formally possible. And it's also possible that the subjects we're evaluating were just a different cohort of subjects. They were just injured more severely or had less appropriate treatment, had less appropriate rehabilitation compared with other groups in other studies. So it's hard to say for sure.

Okay. The next question, sir, is, is the GOSE the best outcome test?

Yeah, that's a great question, and the GOSE has fallen under a lot of fire recently for its lack of sensitivity and its lack of specificity. So no, it's definitely not the best test. However, we did use a neurobehavioral rating scale, which was largely concordant with the GOSE, and this is an area of really important future
investigation, is to design optimal outcome measures for traumatic brain injury, especially of the concussive type. As you know, the GOSE was designed originally for moderate to severe traumatic brain injury by the folks in Glasgow. It was never really intended for concussive injuries. But we don't have standardized really appropriate measures for outcomes following concussive injuries and so I know the track TBI groups led by Chuck Manley and the other Department of Defense administration and civilian research groups are working on designing such outcomes, and that will be important. But at the time when we started this study, designed this study, 2007, the GOSE was the best there was, and still actually isn't really clearly been replaced by anything that's substantially better quite yet.

Thank you, sir. Do more resources need to be diverted to the service members for the problems you identified?

So I'm not really qualified to say much about resource diversion. I do feel strongly, though, that early after-concussive injury, all service members should be assessed for post-traumatic stress type symptoms, at early times, not just at the late times, not just a wait and see approach, but an early assessment approach, and the logical hypothesis then would be that if they do have substantial burden of symptoms, that the treatment would be offered. In most domains, early treatment is more effective than later treatment. That's not a sure thing that would be the case in this domain, but if more resources would be required for assessing and treating those early post-traumatic stress-type symptoms after concussive injury, then that seems to me that would be a good thing. I can't say with any evidence base that that would be helpful or would improve disability, but it seems reasonable at this stage. And of course the best thing to do would be to do a randomized controlled trial to determine whether it helps. Whether it matters.

Thank you, sir. Another question from the virtual audience: Was a PLCM score of 50 used as your criteria for symptoms?

No, we did not use a specific dichotomous criteria cutoff. We used the PCLM as a continuous measure, not dichotomous.

Thank you. Another question, sir: Is anybody researching the helpful aspects of treating spinal sublocations to treat headaches?

That's a good question, and I don't know the answer.

Thank you, sir. Another question was, what was the average age of younger versus older soldiers?

Ah, yes, that's a good question. Let me go pull up that data. Even the older ones were quite young. But even the slightly older subjects, who were -- So let's see if I can blow this up on my screen. So the age of the subjects ranged from 19 to 41. And the average age was 26. So the younger were in the 19-to-26 range, and the older were in the 26-to-41 range. So certainly none of them would be called older, especially as I get older. That sounds like they're all young to me! But the very young versus the slightly less young is how I would describe it.

Thank you, sir. That's all we have. That's all the time we have. Thank you everybody for submitting questions. Please join me in thanking our speaker.