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Session: Sequelae of Deployment TBI in Iraq and Afghanistan Veterans

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Whitney: And we are just at the top of the hour, we’ll go ahead and get things started. I would like to turn things over to Dr. DePalma. Dr. DePalma, may I turn things over to you?

Dr. DePalma: Yes, thank you very much, Whitney. It’s a pleasure today to have Dr. Sarah Martindale and Jared Rowland, research health scientists at the Hefner VAMC in Salisbury, North Carolina, speak about the sequelae of blast injury. They are members of the MIRECC and they are focused on post deployment mental health situations. Sarah is assistant professor of physiology and pharmacology, and Dr. Rowland is assistant professor of neurobiology and anatomy at Wake Forest Medical School. They’ve worked for about a decade in VA TBI research, and some of their important work really includes the Salisbury Blast Interview format, which does look at very specific aspects of blasts, as well as the MIRECC assessment of blast. And with that, we turn it over to them. Thank you very much, Whitney.

Dr. Sarah Martindale: All right, hello everyone, this is Sarah Martindale. And good afternoon, or morning, depending on where you are currently located. We do appreciate everyone who has joined in for our talk today. So, today we are going to be talking about research we have conducted on behavioral, cognitive, and neuroimaging outcomes associated with TBI that occurs in a deployment environment. And we have no conflicts of interest to report.

So, I want to jump right in and get everyone oriented to what we are talking about. And that is specifically mild TBI. So TBI is classified as mild in severity when alteration of consciousness and/or posttraumatic amnesia lasts less than 24 hours, and if there is no or any loss of consciousness less than 30 minutes. Mild TBI is also typically accompanied by transient vestibular, sensory, cognitive, or emotional symptoms, but these don’t define the criteria for the diagnosis, excuse me, and they’re typically expected to resolve quickly. And if not, they resolve in a matter of months, usually. And though Veterans experience moderate and severe traumatic brain injury, the vast majority are classified as mild. And really these can get tricky to identify clinically for a few reasons. First, most of our evaluations are retrospective, and when years have passed it’s somewhat difficult to determine whether an injury occurred. It’s very, very rare to see a Veteran who was evaluated for a TBI right after the fact. Really, by the time someone’s in my office for an evaluation as part of a research study, typically unless there was a clear loss of consciousness, we spend some time evaluating whether that blast exposure resulted in a TBI or whether the event was just really emotionally disorienting with no true injury occurring. So, in a deployment setting, especially in combat, there are so many factors to consider that are not typically present in a nondeployment environment, which makes identification of mild TBI acquired during deployment particularly difficult.

So, aside from the time since the injury event, there are three specific factors that further complicate diagnosis when TBI occurs during deployment. First, the environment is very different. And that can also vary considerably during a deployment. There are physical and practical challenges. These include exposure to toxins, delayed supplies, sleep deprivation, nutritional changes, being in a hospital environment. There are also emotional and mental challenges. And these can include moral injury, boredom, fear, uncertainty. And there’s so also social challenges that include lack of support, limited privacy, separation from family, and of course those are just a few examples of the multitude of stressors that service members experience when they deploy. And it’s possible that these environmental conditions could compromise the physiological reaction to an injury, or exacerbate injury outcomes. Such as the inflammatory response we typically see after a TBI.

Mechanisms of injury also differ in the deployment environment. Especially when you consider the prevalence of blast injury when compared to nondeployment TBI. And I do have to include the caveat here, that there are professions that expose workers to regular blast. However, those aren’t super common. Whereas the prevalence of blast is much more common in service members. And those service members also experience blasts in nondeployment environments, such as breacher training. These tend to be relatively well controlled. During deployment, especially in the wars in Iraq and Afghanistan, IEDs, mortars, RPGs, and weapons that can create a pressure wave, like a CIWS, are frequently present. Even explosive ordinance disposal can be difficult to control completely. And in addition, multiple mechanisms TBI is somewhat common in deployment TBI as well. So for example, if the service member is in a vehicle when it’s struck by an IED, it’s possible that they would hit their head on something in the vehicle in addition to experiencing a concussion wave. And of course, that’s a scenario that would be a lot more likely for a gunner than a driver, but regardless of all of those examples, the mechanisms of injury differ from what we see in a nondeployment environment. However, it is important to note that injuries due to factors such as falls and motor vehicle accidents still do happen in this environment.

And finally, frequency is a factor to consider. So, first, during deployment service members may experience several concussive events. It’s not abnormal at all for us to work with Veterans who report three or more head injuries over the course of a 12-to-18-month deployment. However, we also need to consider the delay between concussive events. So, in a deployment environment it may not be possible to evaluate or recover from an injury prior to the next one. For example, during an extended patrol a service member may experience a couple of concussive events within a couple of days. And it may not be possible for the patrol to end early. In some cases, resting might be life threatening. However, it is possible too that the service member may not recognize symptoms or may overlook symptoms of a TBI and not get adequate rest in between. And that’s probably especially if functional impairment isn’t obvious or severe. And alternatively, symptoms may be ignored in favor of faster return to service. And regardless, the frequency of TBI is potentially complicating to diagnosis, as well as long-term outcomes of deployment related TBI, because many TBIs aren’t diagnosed at the time of the injury event.

So in short, circumstances surrounding TBI a quired during a deployment can be very different from TBI acquired outside of a deployment environment. And anecdotally we’ve noticed when working with Veterans that outcomes related to deployment TBI seem to be worse than what we would expect from a mild TBI. Just generally. And because of this, one of the topics our team is interested in is determining both if and how TBI acquired during deployment differs from TBI acquired outside of the deployment environment. And we’re looking at this in a number of different ways. So first, behaviorally we’re looking at psychological distress and psychiatric diagnoses. Physically, health symptoms such as pain and sleep, as well as brain structure. And functionally, both cognitive and neurobiological brain function. And we’re especially interested in the long-term outcomes associated with deployment TBI to determine if there’s a special consideration that we should be evaluating or treating differently. If there’s something special about deployment TBI that we need to be paying attention to. And that’s critical to informing diagnosis and treatment that would ultimately lead to improvements in care for our Veterans.

So, the data we’re presenting today comes from a few studies our team has conducted at the Hefner VA healthcare system in Salisbury, North Carolina, and the Wake Forest School of Medicine in Winston-Salem. All of these studies have a pretty similar structure. All of them are cross sectional. They evaluated post deployment Veterans who deployed in support of the wars in Iraq and Afghanistan. So these are all post 9/11, 2001 Veterans. And this table shows the general demographic makeup across these samples. Our CENC study 34 was awarded from the chronic effects of neurotrauma consortiums that evaluated the effects of primary blast on the brain and behavior in Veterans who experience combat. The post deployment mental health study, or PDMH, is a multisite project that’s been ongoing since 2006 across the VISN 6 MIRECC. And the pilot study listed is what led to our CENC-34 study. All of the sample size numbers here refer to the largest sample that we pulled from for analyses, but our different outcomes for various manuscripts do have different exclusion criteria for analytic samples. So if anyone notes that, that’s where that comes from. So for example, though CENC-34 enrolled 341 Veterans, only 200 of them completed neuroimaging. So all of our neuroimaging studies only include some combination of those 200 who we have data for. And across the analyses we’ll be discussing today we did use our recently published Mid-Atlantic MIRECC assessment of traumatic brain injury, which we validated against the Ohio, the battle, the VCU rCDI, as well as clinician report and expert diagnosis. And we used our Salisbury Blast Interview to characterize blast exposure.

And I’m not going to go into too, too much detail about our blast exposure interview, because well, A of all, this is a presentation on deployment TBI, and B, this could be a presentation in and of itself. However, this is relevant for one of the analyses I’ll be discussing in just a minute. So as I mentioned earlier, blast exposure tends to be uniquely common to service members. Though there are some specific occupational and recreational caveats to that. And because blast exposure is a common mechanism in deployment TBI, it is important to be able to characterize it alongside TBI. A related challenge is that we know service members experience significant blasts that don’t necessarily result in a TBI. But we don’t really know what, if there are any, consequences we should be concerned about outside of TBI. So, our recently published Salisbury Blast Interview gives us the opportunity to fill this gap. To measure blast exposure. It collects comprehensive information about all lifetime blast events reported, and that’s regardless of the distance from the blast or severity of the experience. This interview collects information about the environment, circumstances, characteristics, effects, and distance for each blast event. And the characteristics are rated using behaviorally anchored Likert scales. And these include wind, sound, debris, pressure, temperature, and ground shaking. And we designed it to work with our Mid-Atlantic MIRECC assessment of TBI. So it truly allows us to evaluate blast independent from TBI.

So, when we evaluated our interview, it performed in the way we expected it to, and everything was in the direction we expected they would be. Which is awesome news. We were very excited about that. Our characteristic ratings were negatively corelated with distance from blast, and the graphs on the top right show the median distances in feet for blast pressure and wind ratings. You can see that ratings increased as distance from the explosion decreased. And these ratings were also unrelated, excuse me, two times since the blast event, or the number of reported blast events. Which suggests these variables don’t bias the reporting of individual event characteristics. And bringing your attention to the table on the bottom right, characteristic ratings changed as we would expect in relation to environmental and protective variables, such as being behind cover or being in a vehicle when an explosion occurs. So, something important to note is that higher ratings for pressure and temperature, and shorter distance from a blast were the most strongly associated with a resulting TBI. So, what that tells us is that these are the best indicators of a severity of a blast exposure based on our tool.

All right, so, back to deployment TBI. One of our first published manuscripts on this topic specifically looks at the differential effects of nondeployment TBI deployment TBI, and PTSD on self-reported symptom outcomes.

And with our large PDMH cohort we weren’t able to demonstrate that Veterans with a history of deployment TBI tended to report more symptoms and more problems than Veterans with no history of deployment TBI. These included depression symptoms, posttraumatic stress symptoms, poor sleep quality, greater substance use problems and pain, these are all highlighted in blue on the righthand side of the slide. And it is important to note that history of nondeployment TBI did not have an effect on these outcomes.

And we recently replicated this in our CENC study 34 sample. The manuscript is currently in revision. In fact, we just resubmitted it yesterday. And we found an effect of deployment TBI on the self-reported symptoms I just mentioned. But also found an effect on neurobehavioral symptoms, which was not measured in the PDMH study. And we also found a weaker but still significant effect of nondeployment TBI on sleep quality as well. And that might suggest that the sleep problems Veterans are reporting may be a more robust characteristic of TBI regardless of whether that was acquired during deployment or outside of a deployment environment. And none of these effects were altered when we looked at the number of TBI in either of these samples. So, a history of multiple TBIs doesn’t seem to be driving these outcomes. And that’s at least what we’re seeing in our data. And before I go further into research we’ve done comparing effects of deployment and nondeployment TBI, I’m sure a question on everybody’s mind is well, what about posttraumatic stress disorder? And that’s really a confound that’s unavoidable when we’re talking about injury events that occur in a high stress, high out tempo environment. Both of these analyses I just went over adjust for effects of PTSD. And those are present across all symptom measures. Though effects of PTSD did tend to be stronger than what we saw for deployment TBI. Deployment TBI still had an effect independent of a current diagnosis of PTSD. And this was true for both of these samples. So what does that mean? Well, that means that PTSD is important, but it doesn’t account for what we are seeing with deployment TBI.

And in addition to self-reported symptom measures, the PDMH study included the structured clinical interview for DSM-IV disorders, and using these diagnoses we were able to further demonstrate that deployment TBI was associated with a greater likelihood of lifetime diagnosis of major depressive disorder, alcohol use disorder, and posttraumatic stress disorder. Compared to those who did not have a history of deployment TBI. And these outcomes are largely reflected in the self-reported symptoms I went over on the previous slide. So, none of this in unexpected. And also, as I mentioned on the previous slide, PTSD is something that is still important to consider. The high rate of Veterans with deployment TBI in the sample with a diagnosis of PTSD highlights that quite well.

So, circling back to differences in effects of deployment and nondeployment TBI we’ve also identified effects of deployment TBI on cognitive functioning. Specifically on measures of simple attentions, processing speed, and executive function. So, specifically, performance was poor on these measures if the Veteran had a history of deployment TBI. The cognitive scores we used were demographically corrected T-scores, which means that this accounts for age, sex, education, and race. And we also excluded anyone who did not pass performance validity. After all of that, we were surprised to see no effect of nondeployment TBI or PTSD on these outcomes. Particularly PTSD. However, what is also critical to note here is that the sample had overwhelmingly normal cognitive function. And the rates of impairment were low. Which is what we typically expect years following a mild TBI. We really don’t expect to see any lasting cognitive impairment. We also didn’t see any interaction effects. So, these effects of deployment TBI on cognitive functioning weren’t depended on or exacerbated by either PTSD or a history of nondeployment TBI. So, this suggests that the experience of a mild TBI during deployment rather than a psychologically traumatic event may be a factor driving long-term subtle neuropsychological differences, at least in attention. However, it’s really important to interpret these results in the context of the sample. Again, all group level cognitive scores were within the average range. So, though performance was slightly lower in general for the Veterans with deployment TBI history, it was impaired only for a very small number of these individuals. So, clinically we might see that service members with deployment TBI may not perform as well as those with no deployment TBI history, and they may have higher rates of impairment on these tests as a group, but that isn’t something that we should be expecting to see on an individual level.

And because deployment TBI was the only factor associated, that was significantly related to cognitive outcomes in that sample. We looked further into how blast exposure may be influencing cognitive outcomes to see if that might be an explanatory factor. The analysis on the slide used blast pressure severity, which was found to be one of the best indicators of blast exposure severity, but based on the Salisbury Blast Interview. And this is also the same sample as the previous slide. So, the outcomes are the same, but we did not adjust for nondeployment TBI history. Again, we had significant effects of deployment TBI on trails A, which is a simple test of attention, and trails B, which is an executive functioning task. And as you’ll see, blast pressure did not have an effect on its own, beyond PTSD and deployment TBI. And this was true across all of our cognitive tests. So, simply put, blast pressure did not explain cognitive function beyond PTSD and deployment TBI.

However, we did look at interaction effects to determine if blast pressure exacerbated or acted as a proxy for what deployment TBI was doing. And what we found is really kind of cool. There was a significant interaction effect between deployment TBI and blast pressure on trails A, which is our task of simple attention. And we ran a Johnson-Neyman analysis to probe that effect, which is the graph you see on this slide. And I realize that this looks a little bit bizarre, but give me just a second to walk you through it.

So, on the left, the y-axis, is the strength of the effect of deployment TBI on simple attention. And zero, the horizontal line at the top, refers to no effect. So, as you get farther away from zero in either direction the effect becomes stronger. And on the bottom, the x-axis, we have blast pressure reported, starting at a pressure of zero and going up to a maximum pressure of five. So, starting at about a blast pressure of one, we see significant effects of deployment TBI on attention, and the size of these effects increase significantly as experienced blast pressure increases. So, what this tells us is that blast exposure alone may not be sufficient to affect cognitive function. However, for Veterans with a history of deployment TBI, if they are also exposed to blast pressure they may experience amplified effects. At least on simple attention tasks.

All right, so at this point we have demonstrated that history of deployment TBI and nondeployment TBI are associated with different long-term outcomes, including cognitive function, self-reported psychological and health symptoms, and psychiatric diagnoses. And we have also demonstrated how exposure to blast might influence cognitive outcomes for Veterans with deployment TBI. So, there does seem to be something about deployment TBI that is contributing to these outcomes that we are seeing.

And now I am going to turn my presenter duties over to Jared Rowland, who will talk about what we are seeing on structural and functional neuroimaging related to deployment TBI that might explain some of these findings.

Dr. Jared Rowland: Thank you, Sarah. Hello everybody. So our CENC study 34 collected several types of structural MRI. Including flare, susceptibility weighted, diffusion tensor, diffusion kurtosis, and even magnetization transfer. As well as functional neuroimaging, including functional MRI and magneto encephalography, or MEG. And first I’d like to discuss some very interesting findings related to brain volumes. So the overarching aim of this analysis was to extend the literature that it was examining the relationships among PTSD, deployment TBI, and brain volumes. Now there are well established relationships between PTSD and several brain regions, including the hippocampus and the amygdala. However, the directionality of those relationships isn’t always clear. And the relationship between the deployment TBI and specific brain regions is even less well understood than that of PTSD, particularly when you’re considering the effects of PTSD in that relationship. So, to help clarify some of this we employed a standard FreeSurfer volumetric pipeline to extract the volume of different brain regions. We then used a regression analysis to examine the relationship of deployment TBI and PTSD to these brain volumes. Beyond covariates such as age, time since injury, and medications. We selected brain regions for this analysis that were previously demonstrated to have a relationship with PTSD, including the hippocampus, the amygdala, anterior cingulate cortex, the insula, and prefrontal regions. So interestingly, we found a strong relationship between deployment TBI and three different brain regions after FDR correction for multiple comparisons.

So here you can see the model a little bit better. So after entering covariates main effects of PTSD and deployment TBI were entered we included main effects of current and lifetime PTSD as mutually exclusive variables. And that was really to address questions regarding altered brain volumes representing risk factors for the development of PTSD or consequences of having the disorder. And here you see the results for the left hippocampus. And you’ll note that deployment TBI but not current or lifetime PTSD was associated with a reduction in volume in that area. Here we see the same pattern of results for the right hippocampus. And then again, the same pattern for the right medial orbitofrontal cortex.

We then went on to examine potential moderating effects of deployment TBI on the relationship between PTSD and brain volumes. However, no result in that analysis survived FDR correction for multiple comparisons, and in fact, there was really only one region that was significant prior to correction. And that was the left amygdala, which demonstrated in increase in volume when PTSD but not deployment TBI was present. So these findings suggest that deployment TBI is a significant factor in altered brain volumes of combat exposed Veterans beyond the effects of PTSD and other covariates. And these brain regions are frequently associated with PTSD. So, the lack of a relationship in this sample was unexpected. And one potential explanation that we’re curious about is that this was a combat exposed sample, so it’s possible that due to the combat environment a larger percentage of individuals who experienced traumatic events went on to develop PTSD. And this explanation fits well if the brain volumes of these regions are actually risk factors for the development of PTSD, rather than consequences of the presence of the disorder. However, the specific mechanistic role of these brain regions in the development or maintenance of PTSD is really not well understood. And studies of the relationship between PTSD and hippocampal volumes in Veterans and service members haven’t typically considered deployment TBI as a covariate. The one study that we found that did actually observe the effects of both TBI and PTSD on brain volumes. So this suggests that studies of brain volumes in similar samples to combat exposed or post deployment samples really should be considering the effects of deployment TBI in their models. And I actually think this is a pretty important area for us to understand and follow-up on because, so we know deployment TBI is a risk factor, an independent risk factor for the development of PTSD. And if volumes of certain brain regions impart increased risk for the development of PTSD, and deployment TBI alters volumes in those brain regions, then this really could represent a mechanistic pathway where interventions could be developed. It’s also important to reiterate here that this sample is on average 9 years post deployment, and 11 years post injury. So these are not associations that are being observed during the acute phase of deployment TBI. But really represent chronic effects observed years later. And while these data are not longitudinal and we can’t make calls of inferences based on them, we are certainly curious about the effects of time. Given some of these hypotheses we have.

Now I’d like to look at some results of functional neuroimaging. And give you a sneak peek at some of the findings in our CENC-34 sample. So my particular area of study is in the application of MEG to study functional brain networks in post deployment individuals. And this figure lays out the different steps in that process. Including data acquisition, where you can see a picture of the MEG here, under number, under letter A. source reconstruction, which establishes the activity in specific areas of the brain. The calculation of functional connectivity among brain regions, which results in these adjacency matrices that you see under letter D. and you can really just think of those as all the all correlation tables. And then when you threshold those adjacency matrices we get what we refer to as connectomes. And we can calculate network metrics that tell us about the function and the topology of those connectomes.

So these are the results of a pilot study we conducted in 28 Veterans using the methods I just described. And the results demonstrated effects of PTSD and TBI on small world properties of the networks. With PTSD being associated with decreased small world properties, and TBI associated with increased small world properties. Now small worldness, you may be wondering, is kind of this ubiquitous biological network structure. And it is seen across a bunch of different environments and entities. And it’s a structure that takes advantage of the clustered and hierarchical nature of lattice like networks. And at the same time, addresses the shortcoming of those networks that have long path links by sneaking a few shortcuts in the network. And this drastically improves the efficiency. So it really kind of takes advantage, gets the best of both worlds here. So, we also observed effects on a frequency at which connections occur. But what I found most fascinating is depicted here in the figure on the right. So participants with PTSD in this figure are identified by the colored squares, the blue and the red, and are divided quite nicely by the presence or absence of TBI. And this is actually one of the results we leveraged to obtain our CENC funding, and I would like to share the results of a paper we recently submitted that conducts a similar analysis with that much larger CENC-34 sample.

So since we had a larger sample we were able to conduct a more robust analysis. And we included a number of covariates, including age, sex, race, time since injury, and number of deployments. Main effects of deployment TBI and PTSD, as well as their interactions were entered after covariates. And this table lists the network characteristics that were significantly predicted by this model. In the left-hand column here. Along with the non-standardized parameter estimates for deployment TBI, PTSD, and the interaction. And the bolded parameter estimates are significant after FDR correction for multiple comparisons. So, these results really seem to mirror those from the pilot study. Primarily demonstrating interactive effects between PTSD and deployment TBI.

Now I tried to create a similar figure to that scatter plot I showed you earlier, but this larger sample size really doesn’t lend itself to that kind of presentation. So, instead I plotted the means for these groups, adjusted for all of the variables in the models. So, this is an example of two of the interactions, and really all of the interactions followed a similar pattern to what you see here. So when PTSD was not present, so we look at the blue line, the effective TBI on network topology was really rather small. However, when PTSD was present the contrast between the presence and absence of TBI became much larger and mirrored what we saw in that pilot study. So, PTSD alone, the red dot on the left, you can see is associated with lower levels of metrics. And with these particular metrics represents a shift in topology towards that of a random graph. With lower levels in modularity and clustering. Now in contrast, the presence of both PTSD and deployment TBI, that red dot on the right, is associated with higher levels of metrics. This pushes the topology to be more lattice like, with increased numbers of subgroups and clustering within the network. These contrasting findings are significant because these metrics are related to the hierarchical nature of networks. And that nature is what allows for specialization. However, much like the inverse u curve that describes the effect of stress on performance, there’s really a delicate balance that has to be struck, and being pushed too far in either direction will disrupt the function and performance of the network. Which in this case is our brain function.

So quick summary of the neuroimaging findings. First, deployment TBI was associated with reductions in brain volume in the hippocampus and orbitofrontal cortex beyond PTSD and other covariates. And second deployment TBI was also demonstrated to have interactive effects on functional brain networks with PTSD. Pushing networks in the opposite manner than PTSD and the absence of TBI.

So, the overall conclusion, the overall takeaway message from this presentation is really that deployment TBI has effects on individuals that are unique from those of other conditions. Including PTSD and nondeployment TBI. And these effects can be observed a broad range of outcomes. So we demonstrated that deployment TBI is uniquely associated with increased levels of psychiatric and health outcomes. Including symptoms of depression, PTSD, pain, and sleep, as well as the actual diagnoses of major depressive disorder, PTSD, and substance use disorders. We also saw effects on cognition that were amplified by blast exposure. And finally, we demonstrated effects of deployment TBI on both brain structure and function. And I want to highlight that these effects are all beyond those of PTSD, and were not really associated with the number of TBI that were experienced.

So there’s several factors that might explain why deployment TBI is associated with poorer outcomes, whereas nondeployment TBI was not. And first, the most obvious one is the mechanisms of injury. And kind of like we talked about earlier, estimated 80% of injuries in the wars in Iraq and Afghanistan involve blasts or explosions. Then that can be contrasted with civilian and nondeployment calls is that are primarily falls, motor vehicle accidents, blunt force traumas. So while we’re beginning to understand the unique effects associated with blast exposure, this literature is really still in its infancy, and there’s a lot that we just don’t know yet.

So another potential factor is the physiological milieu at the time of injury. Which can really be easy to overlook and difficult to quantify. So, during deployment individuals are immersed in an environment of constant stress, altered sleep patterns, increased exposure to the elements, and even maybe poor nutrition if they’re really out on patrol. And these conditions likely compromise the physiological reaction to an injury. Or exacerbate the outcomes of an injury. Particularly the inflammatory response. And individuals with deployment TBI may also not receive immediate medical care, and may not be able to alter their duties, or take a break, and really just due to being in that battlefield environment.

So the second takeaway message is that the typical timeframe for expected recovery from the acute effects of mild TBI may be just that. Recovery from the acute effects. So these results suggest that deployment TBI in particular may be associated with long-term negative behavioral and health outcomes. And this is an area of ongoing research, and we could even say debate, there is some literature suggesting long-term associations with, between TBI and increased mortality, higher rates of hypertension, diabetes, coronary artery disease, even neurodegenerative disorders, but this is really when we look in the very long-term on the order of decades post injury. In the shorter-term deployment TBI has been associated with increased risk for the development of psychiatric conditions, particularly PTSD and suicide in the post deployment population. Now this literature has led to the suggestion that TBI be conceptualized as a disease process, rather than an event with a clear beginning and ending. And while this theory might be appealing, the mechanistic links between TBI and increased risk for these long-term outcomes are not well understood or well established. And the current findings really can’t provide direct calls of support for this conceptualization. However, the current findings can provide cross sectional or clinical observations that offer what we might call correlative support. That the sequelae of deployment TBI may be longer lasting and more complex than the way we typically think of complete resolution within 3 to 12 months.

And the final point I’d like to make is that negative outcomes following a deployment TBI are not a foregone conclusion. I’d like to draw a parallel with PTSD here where lots of people experience traumatic events, but only a minority of them go on to have psychiatric issues, or develop PTSD. And it seems likely that TBI, including deployment TBI, is actually more like that traumatic event. With only a minority of individuals going on to experience these negative outcomes. So the overarching aim of our lab is really to help understand the mechanisms, risk factors, even the individual characteristics that are associated with the development of those long-term negative outcomes following deployment TBI. And we think that it’s really only by understanding these relationships that we’ll be able to identify the opportunities for intervention or subsequent treatment of those outcomes.

Now this slide has relevant references for anyone that would like to read more about the work we’ve presented today. And the last slide, finally we’d like to thank our funding organizations and our collaborators who make all of this work possible. And we’d like to thank you, the audience, for your time and attention. And we would be happy to answer any questions or take any comments with the time remaining.

Whitney: Thank you, Sarah and Jared, for presenting. So we have quite a few questions lined up here. I’m just going to go down the list. Here we, any breakdowns by those pursuing service-connected disability rating or increase versus those not litigating or those service verse those who are not?

Dr. Jared Rowland: I can jump in and answer that one.

Whitney: Okay.

Dr. Jared Rowland: So, in our, we’ll talk about the CENC sample in particular, in that sample, so there’s a high percentage of individuals in our samples that do have service connection. The majority of our individuals in all of our studies are receiving care at the VA. However, we do often, we include tests, symptom validity tests, performance validity tests, in all of our analyses. And so we try to make sure that we’re getting valid presentations. Even in samples that may have service connection, or be applying for service connection.

Whitney: Okay. All right, thank you. So our next question is, in regards to behavioral outcomes, like sleep, what other, were other cause of sleep disorder ruled out, factored in, [inaudible 43:34]

Dr. Sarah Martindale: So, as far as sleep disturbances for the PDMH study, Jared, can you hand me control so I can go back to the slide? So for the behavioral outcomes we did not covary for any sleep disorders, such as sleep apnea, insomnia. Sleep is actually my primary research interest. So we did not adjust for that in the, in our large PDMH sample. We were simply looking at sleep quality. So, we do not have that information as part of what we presented here. I will note though in the volumetric paper that Jared presented on, we did adjust for sleep apnea and, I believe it was sleep apnea and sleep medications in that analysis. So we do understand that sleep is an incredibly important covariate. As well as sleep diagnoses. And we do look at that, we just did not in these sleep quality outcomes analyses.

Whitney: Okay. Thank you. Our next question, with the increasing understanding of impact of suggestion on symptoms, outcomes, and even side effects, what do you tell patients?

Dr. Jared Rowland: So that’s a great question. And I think we, you know, we take it on a case by case basis. Yeah, I, you know, I agree with the person asking the question, we don’t want to set up an expectation that there are going to be negative outcomes. But the same time, if there are negative outcomes we don’t want to ignore them. So, I think as we continue this work and we can better understand what’s going on, and the timeframes in which it happens, I think we’ll be better able to say what would be expected and maybe what the base rates of those expectations would be. And I think, I mean given the state of everything right now, we do want to, I would set the expectation for recovery. And encourage people, you know, engage in treatment if you have symptoms, and don’t worry about it if you don’t have symptoms. That would be my personal response.

Whitney: Okay, thank you. Please discuss ramifications for clinical neuropsychological assessment and rehabilitation.

Dr. Sarah Martindale: So, as far as ramifications for clinical neuropsychological assessment, I think that we need to consider what we found, consider the sample, again, in that the overwhelming majority of participants in these samples were cognitively intact. And we don’t really expect there to be lasting cognitive effects and mild TBI. So, for clinical neuropsychological assessment, I think that you might tend to see Veterans with deployment TBI perform maybe more poorly on tests of simple attention, but I don’t think that should be the expectation. I think overwhelmingly we should expect performance to be within an expected range. And then I would also echo what Jared just said as well, that we should set the expectation for recovery.

Whitney: Thank you. Was there any evaluation of post blast medical treatment, such as opioids or NMDA antagonist amnesiacs medication with the structural difference in PTSD alone and PTSD with TBI?

Dr. Jared Rowland: So we did covary for some medications. We didn’t look at those, the particularly the NMDA in particular, those I don’t think are very common right now. So, I would say no to that one, in this sample. Just because there wasn’t a high frequency of it.

Whitney: Okay. Thank you. And this question is for you, Jared. Did you consider the age effect on amygdala volumes independently from the experimental effect? The amygdala volume typically regresses with age.

Dr. Jared Rowland: Yes, good question, we did include age as a regressor in that analysis when we did the regressions. We didn’t pull out age prior to doing the analysis, we’d included it as a covariate in those regression models.

Whitney: Great. Thank you. And this, I’m curious about the attribution process. Individuals who attribute symptoms to brain injury versus those who may view symptoms as due to trauma exposure and whether the few symptoms as, and whether they view symptoms as malleable?

Dr. Sarah Martindale: I think that’s really important as far as recovery is concerned. Certainly we have folks coming in here who are 15 years past a mild TBI with no loss of consciousness, and they’re pretty sure that all of the problems that they’re having are due to the TBI and not some traumatic event, even though the symptoms are largely nonspecific. And I think that that would certainly affect recovery. We haven’t, let’s see, so whether they view symptoms as malleable, that’s not something that we have really evaluated, but that’s a really interesting, that’s an interesting question. Jared, I don’t know how, if you have anything else to add to that?

Dr. Jared Rowland: Yeah, I would, you know, and this is speculation at this point, right? But I think there is a thought out there that if the symptoms are related to TBI they are not malleable, and if they’re related to PTSD they are malleable. And I don’t know if that distinction really holds true when we start getting into treatment. I think you could definitely see people that have post concussive symptoms that recover from those symptoms. You know, that’s the expectation. And so if people are having problems, whether they’re cognitive, emotional, you know, whatever they are, I think they’re probably going to be malleable. Regardless of whether it’s due to PTSD or TBI. So I think setting that expectation as well could be very helpful.

Whitney: Great. Thank you. Next question. If we are seeing someone with a TBI and multiple mental health concerns what would the best treatment approach be if we tried to treat the anxiety insomnia first will that be effective in any way given the brain mechanisms at play?

Dr. Sarah Martindale: I’m not sure there’s a good answer for that. I think that all of the presenting problems are important. Yeah, Jared, I’m going to let, I hear you laugh, and so I’m going to have you jump in, because you clearly have thoughts.

Dr. Jared Rowland: No, I think this is kind of in line with what we’ve been saying. It, most of the times we’re going to treat the presenting problems. Regardless of the cause. And especially when they symptoms are so overlapping between like depression and PTSD and post concussive symptoms. And I think that even the underlying brain structural changes are not immalleable. You know, when we see individuals take SSRIs sometimes we can see increases in brain volumes. And brain volumes aren’t static either, you know, they fluctuate with our water contents. You know, if we get dehydrated we see brain shrinkage. So I would hesitate to say that there are specific, and especially in mild TBI, there’s specific changes or PTSD that would prevent someone from improving in their symptoms. Now, when we’re talking about strokes and things like that, I think this is, that’s a very different area. And that’s a significant insult to the brain. So this is me speculating again, I just think that I would be careful about assigning these mechanistic this is never going to change attributes to some of these symptoms following TBI.

Whitney: Thank you. This one, one of the last questions. Are those Veterans with post concussive symptoms also those with more positive neuroimaging findings? Are these correlated on the individual level?

Dr. Jared Rowland: Good question. And that’s something we’re working on now, so I don’t have a specific answer for you. In the pilot study we, that we ran, we did not see correlations between symptoms levels and changes in the network topologies, but we did see differences between group differences in the diagnostic categories. That is a small sample size though for that kind of, for correlations. And so I think when we get into it with the larger CENC study 34 sample we’ll be able to have some firmer conclusions about is it the symptom level, the severity, or just the diagnostic category? And I think that’s true with everything here. So we’re looking at group differences, we’re looking at trends, and I think it’s very hard to go from this kind of data, when we’re looking at group differences, down to the individual level. You know, eventually we’d like to get there and be able to predict, you know, put in all these numbers for individual and predict exactly what we’re going to see. But I don’t think we’re quite there yet.

Whitney: All right, thank you. One last question. Is it fair to say from these findings that there is a different recovery trajectory such that long-term clinical follow-up for those with combat related mild TBI should be different than for those with other types of mild TBI? If so, in what way?

Dr. Sarah Martindale: I think it’s still a little to early to determine that. However, I do think that our evaluations for TBI are sufficient to be picking up on what we’re seeing. Yeah. Anything to add to that, Jared?

Dr. Jared Rowland: I think it’s a good question, and I think it’s an open question. We don’t really know that, you know, some of our findings here are suggesting that there would be long-term negative outcomes associated with deployment TBI. I would also expect those to be the individuals that are presenting for treatments, since they would be having those problems. So I don’t know that I would necessarily advocate for calling people out of the blue that aren’t having problems and having them come in for assessments, but I do think consideration of deployment TBI in that evaluation when people are coming in, even if it’s been 10 years or 15 years, I think that would be important.

Whitney: Great. Thank you. So that’s all the questions we have for today. Thank you so much for taking time to put this presentation together and present for us. Do you guys have any closing remarks?

Dr. Sarah Martindale: No, I don’t think so.

Dr. Jared Rowland: Nope, just thank you for all these excellent questions and your attention, and we really appreciate the opportunity to come talk about what we do.

Whitney: Thank you. Dr. DePalma?

Dr. DePalma: Well thank you very much, Whitney. And thank you very much Sarah and Jared. First, we were over 200 listeners for this, which is actually one of our world records. Second, I’d like to reply to the last questioner. We have one of our evidence synthesis reviews that shows that people subjected to combat TBI, and particularly blast, have a higher prevalence of dementia. So, I think that the two presenters have been very modest in answering their question, but there is clearly something very different about combat TBI, particularly blast, and ordinary head bonks. So I hope that isn’t too simplistic a clinical answer, but I, it looks like from many, many aspects they’re quite different. So I’d like to thank these reviewers and these presenters and the questions for such an elegant presentation with quantification, the blast effects, as well as their insights into the clinical aspects and possible treatment of combat TBI. Thank you very much.

Whitney: All right, thank you. And for any questions that we did not get to today, I apologize, the presenters’ emails are listed on your slides. And then for those who may be interested, please join us tomorrow for HERC’s economics of traumatic brain injury TBI biomarkers webinar at 2 PM tomorrow. And with that, when I close the meeting out momentarily you will be prompted with a feedback form, please take a few moments to complete the form. We really do appreciate and count on your feedback to continue to deliver high quality Cyberseminars, thank you everyone for joining us for today’s HSR&D Cyberseminar, and we look froward to seeing you at a future session. Have a great day everyone.

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