Mar 1-2, 2022 – BBQ Workshop – Day 2 – Transcript

Holly Moore: Hello. It's one o'clock, so I'll get started. Welcome everyone to Day 2 of brain behavioral quantification and synchronization workshop. For those of you who participated and attended Day 1, we hope Day 1 challenged you to think about behavior as more than just the output of the brain, more than a set of phenotypes to be compared. But to think of brain behavior as a complex system by which organisms individually and collectively respond to, and learn from and act on their environment. Our goal for today is to take this new thinking that we actually hope was generated yesterday, and take this new thinking to see how it can advance behavioral neuroscience. So today, we'll be integrating and synthesizing, those are the goals, and thinking about these questions as we go along. How do we integrate the whole organism and the environment into neuroscience research? More specifically for human neuroscience studies, how do we model neural regulation of human behavior while putting that human in a complex environment? Along the way, every step of the way, how do we integrate the science and the practice of ethics in the new behavioral science that we're talking about? We'll start off today with three talks by Molly Marti, [inaudible 00:46:50] . Each of their talks will be followed by a brief Q&A, and those three talks will then be followed by breakout sessions, moderated breakout sessions in which our participants will break into two breakouts. One that's focused more on human subjects, clinical neuroscience research, and the other focused more on organismal comparative research. Both of those breakouts focusing on how we can rethink behavior, new questions we can ask about behavior. The tools we need and the tools we have to approach these new questions and the challenges and barriers that we need to address. The human clinical research breakout session will be co-led by, Ayse Gunduz, and Catherine Skegos, whereas the comparative organismal breakout will be co-led by Kim Hope, and Donald Pereira. We'll end the day with some remarks and synthesis by the director of the brain initiative, John Nine. Sorry, that's my bad. Now I'll turn it over to our speakers. Our first speaker, Molly Marti to give her talk, and I think that she's going to basically run her slides. Damon will help her share. Thank you.

Molly Marti: Thank you, Holly. Yes. Let me go ahead and share my screen. Good, can you see that okay? Great. Good. Well, thank you so much to the organizers for asking me to give this talk into participate in the workshop I loved yesterday. I'm really excited about the discussions we're having, and I look forward to more today.

MALE_2: [inaudible 00:48:40] sign a treaty like the Paris [inaudible 00:48:43].

Molly Marti: Yeah, the organizers asked me to focus my talk on work my lab has done in the space of behavioral quantification and linking mechanistically neural activity to behavior, and so I hope that this helps in framing the discussion later today. So just to start off, there are a few points I'll try to make in my talk. Some of these came up yesterday. But foremost, I'll highlight the important model systems for developing and testing behavioral quantification tools and for developing methods for connecting neural activity and behavior. Second, I'll highlight the utility of studying natural behaviors to tap into computational problems that brains have evolved to solve. Third, I'll emphasize the importance of focusing studies at the level of neural computations. These are likely to be conserved across disparate systems. So for example, flies and humans actually solve some of the same problems during acoustic communication as I'll explain, and linking behavior to neural mechanisms in the fly provides a roadmap for how to do so as we move up in system complexity. Fourth, I'll discuss the behavioral variability rather than noise is actually an important lens through which to view the nervous system. High resolution measurements that capture variation can be useful in figuring out why the nervous system generates variability. Related to that point, I'll mention that behavior is often very continuously and trying to find discrete boundaries between behavioral elements can be challenging and may or may not be helpful. The primary focus of research in my lab is on social communication, and all those social interactions occur in complex, real-world environments as depicted here. The behavior of each individual is, actually, highly responsive to cues it receives from the social interaction. This means that the most relevant sensory stimuli in this context can be really well estimated using tools for quantifying behavior. To put it another way, the behavioral output of one nervous system constitutes the most relevant sensory cue for the other animal. This is how we distilled the challenge of behavior in complex environments, and we've leveraged this to make headway on the neural mechanisms underlying sensory to motor transformations during communication in Drosophila. During courtship, which is the behavior we study, male flies generate songs be a wing vibration, as you can see in this video. These songs carry sexual and social information. They're directed at the female, and females in turn respond to males by changing their locomotion and arbitrating during mating decisions. Drosophila song consists of two primary modes, called sine and pulse. Sign is a sinusoidal hum. Pulse is a train of impulses and I'll play you just a short clip if you haven't heard fly song before, so you can appreciate this patterning. So I'm going to take you quickly through some experiments from my lab, and I'm going to focus mostly on the male side of this behavior. So to quantify this behavior, we first developed software to automate the segmentation of song into these two major features without the need for proofreading. By tiling behavioral chambers with microphones, as you can see here in this video, we record song as the male performs his natural chasing behavior. I just want to mention that these methods for songs segmentation have now been extended by [inaudible 00:52:31] , a former postdoc in my lab, who now has his own lab in Germany to leverage deep learning, and I'll come back to deep learning at the end of the talk to improve not only the speed and accuracy of song segmentation, but to also make these methods flexible for segmenting songs from a number of other species. Okay, so here's an example of 30 minutes of Drosophila courtship. As you can see, males produce many songs doubts during this period. Starting from large behavioral data sets, we first ask, what determines which mode, pulse or sine that the male sings at each moment in time during his song doubts? This was important to address because as you can see from these doubts, I've aligned at the right, each song doubt is unique in structure, so it's highly variable from one doubt to the next. To do this, we use generalized linear models or GLMs, and initially, we were simply tracking the movements of flies. We could simplify those movements into these nine parameters which served as the inputs to the model. They constituted the stimulus histories. The outputs of the model were predictions about which song mode the male was singing. For example, at the start of a song doubt does he sing the pulse mode or the sine mode? Song doubts can be characterized by the state diagram. We found that every transition within the diagram was influenced by fly movements and interactions from whether or not to sing, which mode to start in, how long to sing that mode, when to transition, went to end a song. The two most predictive features from the model were the male zone motion, his forward velocity, and his distance to the female. So one important features of models like this is that we not only explain the variability in behavior, but we also uncover the specific timescales over which sensory information influences behavior. So for example, the distance between the male and female is predictive of decisions to sing a sine song with a lag of about 100 milliseconds, and the male's forward velocity is predictive of decisions to sing pulse song right up until the time of the pulse. Variability here proved to be the critical tool for discovering that song is patterned by female feedback. Our behavioral analysis also revealed that males not only modulates song pattern, but they also modulates song intensity, singing louder as they move further away from the female, much like humans do in conversation and some species of songbirds. We found that this modulation relies on a visual estimate of distance to the female. If we tether males and optogenetically activate neurons to induce them to sing, they will modulate their song amplitude with the size of a looming visual cue meant to mimic the motion of a female. We also found using unsupervised methods that individual song pulses shown here as red and orange dots could be clustered according to pulse shape. The pulse mode of song was actually composed of two distinct types of pulse or two modes. Fast pulse is shown in orange, which are louder, and slow pulse is shown in red, which are softer. This distinction was important to uncover because males can select which pulse type to sing, and the distance between the male and female is most predictive of singing slow versus fast pulse. So males bias towards slow pulses when they're close to females, and they increase the probability of singing fast pulses as they move further away. We now know that producing these two pulse types relies on different activity at the level of motor circuits. Uncovering this distinction in the behavior changed our interpretation of how the nervous system controls the modulation of song amplitude with distance. Okay, so prior to our behavioral work, we did not know that singing was a visual behavior. This knowledge led us to the visual system of the male, where we've since used genetic tools that allow us to target specific visual projection neurons at the bottleneck from the eye to the central brain. Here, we've uncovered a rich population code. Each of the cell types at this interface encodes many features of female motion as shown here and each drives many aspects of the male's courtship behavior. So while the GLM, the generalized linear model was critical for early work, we found it did not fully account for variation in the male song. We, therefore, developed a new modeling framework to determine whether there were hidden internal states in the male that shaped how he use sensory feedback to produce song patterns. So using the GLM alone on a moment-to-moment basis, we do better than a chance model, shown here at predicting song over time. You can see here the predictions from the GLM, this is the probability the model predicts of each song type relative to the actual song. Including three hidden states in the model produces a major boost in performance and this model can now accurately predict all three modes of songs sine and the two types of pulse, and it's actually excellent at predicting precisely when transitions from one mode of song to another occur. So we named the states in the model according to the male's average behavior in each state, and two of the states occur when males are singing close and chasing. Males spend less than a second in each state and they continually switch back and forth between states throughout courtship such that the probability of being in each of these three states is even over time. So here's a stretch of courtship song, below it is the prediction from the three-state GLM-HMM, you can see the model does a good job at accurately predicting the male's song, and above is the state the model predicts the male is in. You can see how these states fluctuate over time even during a song doubt. So the understand what is different about these states. Let's look outside the model. So here for two features, the male uses to shape his song male forward velocity and distance to the female. We've plotted the probability of singing pulse versus sine song. You can see that in the closed state as males move faster or get further from the female, the probability of them singing pulse song goes up. But the opposite is true in the chasing state. As males move faster or further from females, the likelihood of them singing pulse goes down, they switched to sine song. So in other words, for the similar or identical sensory cues, males produce different behaviors in these two states. Understanding that there were internal states governing the behavior led to us uncovering the neural mechanisms of the state switch. So in the chasing state, we now know that there's a direct pathway from the brain to the nerve cord of the fly, driven by female motion cues that tends to generate simple pulse only song doubts. But when males get a little closer and remember they're constantly switching back and forth between the states, stronger input to the same pathway drives a parallel arm of the pathway to dis-inhibit dynamics in the nerve cord and unlock the potential for complex song. Context dependence and motor patterning is common to virtually all nervous systems. Here, behavioral quantification and modeling led to experiments that uncovered in neural circuit mechanism for context-dependent songs sequencing. So what I've told you so far is that behavioral quantification coupled with collecting large datasets, leveraging computational models and using genetic and neurocircuit tools has allowed us to crack the mechanisms governing how the male sculpts his song relative to female motion. I hope I've illustrated that these transformations are not simple. They involve complex neural codes, fast fluctuations in brain state, highly variable behavioral outputs, even in what many may consider a simple model system. So more recently, we developed methods to track the poses of flies as they interact socially. You can see that here in this video, in just the last few minutes of my talk, I went to highlight the development of sleep for post tracking and some additional complexities to the behavior that we can now uncover. So Talmud Herrera, a former graduate student in my lab, who was also co-advised by Josh Shavits, he's here at the meeting and he's now running his own group at the SOC. Talmud pioneered the development of deep learning based methods for tracking animal posed during social interactions. This is a hard problem to solve because animals often overlap during these interactions and they're hard to distinguish because they're often interacting with conspecifics who look just like them. It makes it hard to keep track of their identities without labeling them with markers. Networks to track multiple animals can be large and bulky and slow and Talmud sped up this process by using custom-designed compact models that are fast to train and use on new data. So one feature of sleep I'll point out as is its flexibility to run in either top-down or bottom-up mode shown here. So using less than 100 frames of labeled data, sleep can either first draw a bounding box around animals, then find joints, and then put them together into skeletons. Or in bottom-up mode, first find the joints of an animal, connect them properly, and then track skeletons. The speed and accuracy of each of these approaches varies by dataset. So top-down is always faster but you can see that the accuracy depends on which dataset we apply it to. This highlights I think that there may not be a one-size-fits-all solution for these methods, so engineering and flexibility is likely going to be key. Sleep also implements two methods to address the problem of tracking individuals over time even if they appear visually similar and sleep is also fast enough for real-time closed loop experiments. Here we detect the pose of the male and female fly using sleep and when the male enters the zone indicated by the box, we trigger optogenetic activation in the virgin female to drive a behavior she doesn't normally produce in this context. The sleep tracking latency is low, it's only 10 milliseconds, so they added latency in this experiment actually comes from the hardware and the biology itself. Okay, so with this post tracking information, we now have access to additional aspects of the males behavior. For example, we've found that locomotor gate dynamics, the pattern of stepping during walking, increases in variability when males both walk and sing at the same time. This relates to theories and multitasking in larger systems that we can now study in Drosophila. We've also been able to examine how males continue to sing while switching from one wing to the other, so their song is seamless, they don't miss a beat during the switches. An important aspect of motor control across animals is the ability to direct behaviors to one side of the body or the other without disrupting patterning which is another aspect we can now study in this system. So what I'd like to end with in just the last minute of my talk are what I think are some of the challenges and opportunities ahead. So in terms of methods, I would very much like to see improvements in methods to bridge across temporal and spatial scales. This is something Ian Cousin brought up yesterday. There's certainly work to be done in capturing three-dimensional behaviors, particularly enlarged natural environments. I told you about pretty constrained environments and mostly 2D tracking today. I'd also like to see new methods for measuring different modalities of behavior. I talked about video and audio, but there are other signals, for example, olfactory that animals generate and we should incorporate. Coping with behavioral variation, I think is still a major challenge. There's a desire in the field to lump behaviors together into categories. We've done that with song, grooming, walking, etc. These are other examples. This can be useful, but I hope I've also illustrated how capturing variation with these methods is also quite useful. We definitely need work on computational models and theories linking large-scale neural activity connectomes and behavior. For those who know me, you know my lab has also been developing methods for brain wide functional imaging in Drosophila, as well as generating a whole brain connectome for the fly. But we still lack methods to bridge between these datasets. This is particularly true since we can collect large behavioral datasets with relative ease. But neural data likely comes from smaller numbers of animals and connectomic data wiring diagrams come from smaller numbers of animals, still usually just one animal. How do we bridge across these disparate datasets? Finally, I want to say that our work has greatly benefited from the large number of labs, many of whom are participating in this workshop working in the space of behavioral quantification. I think there's an opportunity here to form meaningful collaborations between groups who are working on similar technologies and scientific questions, but maybe across different systems. For example, pairing people like me who work primarily on flies, but who are clearly building tools that could be applied to more complex systems with folks who are working in humans. I would really like to see this happen through the brain initiative. With that, I would like to acknowledge my lab. They're wonderful group of people I have the privilege to work with. I want to give a particular thanks to the brain initiative and our brain initiative collaborations, I talked about some of the results from those collaborations today. Thank you.

FEMALE_2: Thanks very much, Molly. We have a few minutes for questions and comments. I see Malcolm has his hand up. I'll remind everyone, participants feel free to use the chat or raise your hand. When you raise your hand, turn on your camera, so I can see you. Attendees, feel free to use the Q&A function in Zoom for questions. But we'll start with Malcolm. Go ahead.

Malcolm: Thanks for the super interesting talk. I'm looking at your state diagram. I'm just curious, have you been able to glean what the features are that make success contingent upon performance in terms of this state model or the aspects of the policy and the sign output which makes females more receptive or less receptive, what are they judging can you tell?

Molly Marti: Yeah, thanks for that question, Malcolm? So half my lab work's on this male side of song pattern in which I talked about, but the other half actually works on the female side of communication perception. Yes, indeed females are highly attuned to song information. They integrate song over time, they care about both the modes, and the feature of song they prefer are actually the length of these bouts. So those complex song bouts that had mixes between pulse and sign actually slow them down the most and are most predictive at mating success. We think of song like a language that females have to decode. What they're trying to do is estimate whether males are doing a good job of matching their locomotor speed. If a male is good at chasing her and understanding how she moves, he'll produce a song that's a good match to her movements. She can not only see him, but she can hear the song and can decode that song to understand that match. That's our current thinking about what's happening in the female brain. I didn't get to talk about all the work we've done on the auditory pathway and the neural circuits there. But I do want to make one bigger point related to behavior, which is that it's really useful to have this dual perspective and we can do these experiments in flies with relative ease, but I'll say that from the male's perspective, certainly he wants the female to be receptive and he's responsive to her feedback, but he may also be optimizing for energy constraints. For example, it's probably more costly to sing the pulse song than the sign song, since pulse song is louder. So thinking about what the male is optimizing for is not always clear in communication, part of it may be to perform for the partner, but part of it may be just to optimize behavior for yourself or within the constraints of your brain and body.

Malcolm: Great. So you're saying if you disorder foot falls then you'll make the male less attractive to the female?

Molly Marti: Disorder his walking behavior.

Malcolm: Yeah, so it gets desynchronize from the females?

Molly Marti: Yes, exactly.

Malcolm: Cool. That's super interesting. Thanks.

Holly Moore: Do we have other questions or comments? I was just wondering, while you were talking Molly, if I could walk and sing at the same time, not sure so, I can do as well as male flies, but why don't we move on to non-theistic talk. Thank you so much Molly for that wonderful talk. If Damon will put up Nadia's first slide.

Nadia: Can I share it with other guests?

Holly Moore: Yeah, she's going to share. Introduce Nadia to Susanna and take it away Nadia.

Nadia: Yes. Thanks for having me. This has been really fascinating. I really enjoyed yesterday's talks and discussions, looking forward to today. So shifting gears a little bit here to humans, I'm very excited about Molly's comment about collaborating across species and doing some of those interesting studies, so hopefully this workshop can help facilitate some of those. Can you see the slides okay?

Holly Moore: Yes we can.

Damon Kane: Yes.

Nadia: All right. So, let's talk about some studies that we're doing in humans, and my lab studies spatial navigation, episodic memory. Of course these behaviors are complex within the real-world occur within environments where there are others and there are lots of other things going on in complex environments. Whereas how we study in the laboratory is far from that. So, moving into the future, my hope is, of course, that we can get to more ecologically valid paradigms in humans. We study an area that is critical for navigation and forming memories within special contexts, and that's the medial temporal lobe. Medic consists of the hippocampus and terminal cortex, among other regions that are early on affected in diseases such as Alzheimer's disease and others that have severe episodic memory impairments. Traditionally, the neuroimaging of the medial temporal lobe in humans can only be done in stationary, immobile subjects because of the motion artifacts that are harmful to the signals that are being recorded. In studies such as fMRI, PET, you can record from these regions but participants can't navigate, they can't move around and then the techniques that can record from these areas such as intracranial EG also suffer from motion artifacts because of the wires that are tethered to large recording equipment nearby, so these individuals who are in the hospital being monitored for epilepsy have to also be stationary. Other techniques that allow for some mobility, scalp EG and other techniques that are coming out are presenting some exciting opportunities to record from deeper structures with more advanced analytical tools. However, we still struggle with these techniques to record clean signals, especially from deep brain areas. So because of the history in human neuroimaging, the tasks that are used in participants are often screen-based, argue based task where the stimuli are presented and not necessarily ecologically valid compared to real-world navigation in memory. In 2013, a device was approved by the FDA to treat epilepsy, these are implanted to record and stimulate at the onset of seizures to try to prevent generalized seizure activity. These patients are permanently implanted with these electrodes, so you wouldn't know by looking at them that they have contexts that can record intracranial EG, for example, in the hippocampus. In one patient here, you can see four contexts in one electrode. Here's a patient that came into our lab and volunteered for these studies and because the electrode is fully implanted and shielded, we can have them wear a scalp EG system as well as on body motion tracking devices that we can track with wall mounted cameras and we can ask them to do immersive VR or ART tasks and start to try to tie together the neural mechanisms underlying movement and also cognitive tasks in controlled virtual environments. Since we started doing these studies for wearable sensors that are out in the market currently for research settings, for example, eye-tracking devices that can look at people's size changes, gaze positions, the [inaudible 01:14:19]. In addition, of course, to these motion capture systems that can look at full body position with similar accuracy, speed, head orientation, walking orientation, etc. We can also look at physiological measurements such as heart rate, respiration, skin conductance, blood pressure, all of these things we have the ability to do so but it's not necessarily needed in each study that we're doing, so in some cases, we might just look at position, head direction, and eye movements, for instance. But depending on what your specific question is, this capability is there. The challenge here was synchronizing all of these wearable sensors with the intracranial EEG and scalp EEG which we are able to do with this perhaps clunky-looking backpack that has a metal frame in order to hold up this device that enables real-time wireless communication with the implanted system in the brain. Of course, VR and AR headsets, new ones are coming out every year and so these can be upgraded and integrated, and delivering complex behavior as well, recording deep brain activity. Here's an example of one patient, participant who's being recorded four channels of intracranial EEG in the medial temporal lobe, while the position is being tracked in the room as shown here, as well as their eye position or gaze position and people changes. They're doing a task but they're walking around looking for cues that they have to walk to that are on the outer boundaries of the wall. But of course, with VR and AR, you can start to simulate stimuli in the environment as well. One of the earlier studies we did with this system is just to track position during slow and fast movement speeds and record medial temporal activity. We found that there were theta oscillations, which had been discovered and animal studies through the moving rodents that play a part in spatial navigation and memory. Rather than continuous data oscillations, as you would see in a freely moving rodent, we saw these eight-hertz oscillations that would come and go and bounce and it's been similarly characterized with non-human primates. However, these bouts were more prevalent during fast compared to slow movement speeds. We also did a study where participants learn hidden targets in the room, so spatial memory task and alternate between walking to cues on the wall that you can see here and we found that this similar low-frequency activity in the medial temporal lobe increased whenever the individual was closer to the environmental walls, independent of whether they were moving or not, what direction they were looking in, or other variables that we tested. We also looked at whether this activity was present when the person was observing another person walking around, and we found that similarly when an individual was not moving and just observing someone else, their low frequency activity in the medial temporal lobe was elevated whenever the other person was walking or was near the environmental walls. Suggesting that in this system, there is a special encoding mechanism, not just for oneself, but for other people's locations as well. This just shows a video of what that looks like as the participants walking closer to the wall, you see an elevated data power. Here's the raw activity, here's their gapes position and here's their location in the room. Now, they're sitting in the corner watching someone else walk around, they're asked to press a button on a keyboard every time the experimenter crosses one of these locations that they had previously learned in this condition. As the experimenter walks closer to the wall, you see elevated data power as well. So this is just one example trial but consistently across trials and across subjects, we saw these effects. Next, what we saw was that this low-frequency Theta activity in the medial temporal lobe was also modulated by eye movements. The participant was wearing an eye-tracking device during this experiment and when they were making saccades, we saw elevated Theta power and that this effect was only present when they were actively searching for hidden target locations and during essentially the spatial memory task, rather than the condition where they were not searching for these targets and were simply just walking to these wall cues. This occurred both during self-navigation and observation, suggesting that saccade-related data which has been found in non-human primates stationary studies for example, that this saccade-related data in the medial temporal lobe is modulated by cognitive task goal or cognitive state. Perhaps even further that we have to look into this by this spatial encoding process that's occurring during this target search. The next study I just wanted to illustrate, is that we've been looking at these brain activity patterns during virtual reality. That's supposed to be video. While participants are navigating a room and virtual objects are presented, they have to learn those objects, locations and later retrieve them from memory. We can also do these studies and stationary subjects as well who have microelectrode recordings. These headsets, these neuro headsets are really nice and that they can also record eye movements, gaze position and people changes. So looking just at behavior over the course of these participants during these studies, we can measure it for instance, their air or distance to the target locations over time, which that seems to on average improve over repeated blocks and just looking at over across the whole task, you can see the nice sampling of positions all across the room as well as these target halo positions that they have to learn. Some initial preliminary results on this, we find that Theta activity in the medial temporal lobe increases prior to the retrieval of these target locations. That this effect only occurs when they correctly remember these target locations, so if you put essentially a threshold around the halo correct position, when they are getting close to that correct position, you see that activity's increasing, and this is not the case for incorrect retrieval points. No visual targets are seen during this retrieval condition, so these two conditions are literally the participant pressing a button every time they arrived at a remembered target location. Just for control, we don't see this effect to the actual target locations during the test. Here's just showing you an example channel top-down view of the environment where you see hotspots Theta power near these halo positions and average across the entire group of participants around eight hertz. You see this elevated power change during correct retrieval target locations compared to incorrect. So just to summarize some of these effects which I've gone through very fast just to give you a little bit of a snapshot. But we've seen that theta oscillations and in some cases Gamma as well in these regions, predominantly hippocampus and renal cortex are modulated by walking speed, such that the power or the activity is more prevalent during high speeds compared to low, the power increases during a closed positions to environmental walls compared to inner areas. These activity patterns are also modulated by memory retrieval and task goal including eye movements that are further modulated perhaps by task goal, and that these patterns can also be elicited by the position of other individuals. The presence of others presents an interesting opportunity for future studies, perhaps social encoding of location as well as social interaction. What I didn't show you is that we also found that these theta patterns are modulated by walking direction in a grid-like manner similar, consistent at least with grid cells and are freely moving rodents. Then a few more slides if I have time, cut me off, please, if I'm going over showing you what we're doing now. We're doing some of these spatial navigation tasks outdoors in the real-world using on-body wearable motion tracking sensors, and video, audio, and a lot of other GoPro and all things, synchronizing, integrated together. We've collected data from four subjects so far walking around UCLA Campus which if any of you know, South side of UCLA Campus is very confusing and we're measuring their navigation patterns over repeated walks and their memory for these routes that are a little bit circuitous in going indoors and outdoors. We're using computer vision techniques to isolate particular events in these complex experiences such as doors opening, other individuals, and of course, things like speed and position. We've also enabled the recording of this deep brain activity in two or more individuals who are navigating together in tasks where they alternate between observation and navigation. What you can look at here is things like inter-brain synchrony of these medial temporal activity patterns. I'll start to ask questions about how individuals are encoding locations and trajectories in the presence of others. Then lastly, I just wanted to mention that we've recently developed, well, not recently, it's taken about 10 years or so, a system that can enable single neuron recordings during walking behavior. The devices that we used in the previous studies can only record intracranial EG and so we can't look at single neuron activity, of course. However, through DARPA funding here and collaborators in engineering, we've developed a system that is miniaturized such that it can be wearable and carried on body to enable recordings of single neurons and local field potentials in patients who have micro-wire electrodes implanted for epilepsy. So walking around their hospital room and potentially in the hallways. The system also can stimulate, as can the system that I presented to you before with a variable levels of parameters that can be programmed by the user. We recorded in a handful of subjects in the EMU while they're walking just around their hospital rooms. So literally back and forth within a small square footage space and we've isolated single unit waveforms. Here are two example units and some firing patterns as they're walking through. The device is currently submitted for funding to try to expand and use a miniaturized version of this device, which is shown here, which is the size of a pill and eventually it could be implantable and record not only single neuron local field potential activity from high neural density channel counts and also stimulate with close-loop capabilities. With collaborations beyond my own lab, we're working with others to look at various other behaviors such as during sleep, social interaction, anxiety, fear, eating disorders, and others. There's a lot of opportunity here to translate these techniques and to ask other types of questions in the cognitive neuroscience domain. Last slide here, just to summarize we can record deep brain activity during ambulatory behaviors in humans. When you combine this with wearable technologies, you have an opportunity to characterize complex real-world behaviors. I didn't mention that all of these devices can stimulate and so we are also looking into using stimulation to develop new therapies for patients, for instance, with PTSD in our case. But there are other labs and you heard of yesterday several other great talks about this. As we have an opportunity here to develop these therapies, but also determine the neural consequences of this and the effects of these treatments during naturalistic human behaviors in complex environments. Then last but not least for our discussion later, perhaps ongoing challenges and opportunities in this space, there's still a need to hopefully spread these tools across a larger number of labs. Now that we have tools that are a little closer to bridging the gap between animal studies, I'm hopeful that we can start to ask questions across species and work together to see what are the commonalities and differences across species, and also, take advantage of each species' potentially unique capability to do certain behaviors quickly, such as in humans, in terms of certain tasks that are a lot easier at least for training purposes. You heard yesterday some talks that we also have challenges in terms of doing at home behavioral characterization. All the studies I showed you here today are in the lab with complex wearable sensors that are not user-friendly by the patients or participants. So being able to have those type of devices at home will be a game changer in this phase. When working with patients who have neurologic psychiatric disorders, of course, we want to be able to assess their disease states. In studies, for instance, in our lab with PTSD, we would like, of course, better ways beyond self-report to assess these disease states. Then last but not least, the data that we're getting, especially in the real-world, outdoor study is enormous. So parsing that data using deep learning and computer vision methods is something we're very interested in and hopefully others will also be interested in doing these things. These are the lab members who are doing all the work and lots of collaborators, commissions, industry collaborators and funding that make it all happen. Thank you all for listening and for having me, and looking forward to discussing all of this further.

Holly Moore: Thanks so much, Nadia. We do have time for just a couple of questions and I'll give you a couple that have appeared in the question answer field. One question is, besides seeing associations between data activity and visual saccades, do you see associations with other channels in the system such as skin conductance other psychophysiological channels?

Nadia: That's something we're looking at, especially in the context of these studies in PTSD patients and those with anxiety disorder. In the navigation studies, we didn't collect that data, because it just wasn't part of the question we were asking. But in the other studies, in PTSD patients and epilepsy patients who don't have PTSD we started to collect some of that data. We don't really have answers quite yet, but perhaps maybe some preliminary evidence in terms of increased skin conductance during trauma reminders that correspond to some increases in data activity in the amygdala so we see some of that is promising.

Holly Moore: Thanks. The next question is, can you comment on the similarity of your findings using active motion with the findings from virtual motion and using traditional methods like EEG or FMRI. Is there good convergence between active and virtual motion in using these methods?

Nadia: That's a great question that I cannot answer but we are working on that. We have a study that we created a virtual version of the real-world environments and so you can look at that. To some extent, when you have individuals alternate between real-world and virtual environments. They're some studies in animals that suggests that perhaps are differences, for instance, less special coding in these areas, in these brain areas, but it's just not something we have data yet on. But it's definitely an important question, what are the differences between the virtual environments and the real-world environments in terms of the brain patterns something we would like to look into.

Holly Moore: We'll take one more. Malcolm, you have your hand up?

Malcom: Yeah, thanks. Really interesting. I'm super fascinated by the target saccades stuff you showed. I'm just curious whether you think this can start to address this idea that saccades can be a form of primate VTE. So you're doing spatial memory recall, are there any tasks you're doing where there's a planning component or a difficult choice at issue or is there a structure within the saccades that precede walking toward the retrieved location. Can you say anything about that? Because that's super interesting.

Nadia: No, but that is super interesting. I do have a new post-doc who's interested in decision-making so we're planning to study to look at that. I think that will be potentially a question we can look in that context, but in our previous data, no, we haven't looked at that or had the proper tasks to be able to answer some of those questions. But it's very interesting. Thank you.

Holly Moore: Thank you. Now, that's really why we're here to identify questions that are super interesting, but we're not doing yet and talk further about it so thank you so much. We're going to move on to the next talk by Anita Farahani and that is framing the ethical context of brain behavioral quantification. Anita?

Anita Farahani: Thanks everybody and thanks very much for having me here today and for also making ethics of focal points of the conversation. Let me apologize in advance. I am recovering from COVID, so my voice may give out a little bit as I go through this. Just when I thought I had missed the final big wave of the current iteration, I came down with it. But that being said, I hope that everybody can hear me well. I hope you can see my slides well and I'm excited to be able to have this conversation with you today. What I wanted to do was to just talk about how we might frame some of the ethical issues rather than necessarily address all the ethical issues that this exciting but also potentially risky area of research is opening up. To do so, it's really not that different than how we might frame any ethical issue so I just wanted to walk us through that so that we can think about it and hopefully give some context to the breakout discussions that will follow. A starting place for any ethical issue is to begin an ethical deliberation and about an emerging practice for the use of new technologies is to locate to the extent possible the specific ethical issues that are at hand. It's important to realize that sometimes what appears to be an ethical dispute is oftentimes really just to dispute about facts or concepts, which is why it's so important to really establish what it is that we're talking about. So, the most prevalent ethical construct that's often put into place in a context of public health or in the context of biomedical research or neurological research is a utilitarian framework which looks at risk and benefits. Some utilitarians might say that brain behavior quantification or deep phenotyping is essential, because existing methods of understanding mental health and disease creates significant inaccuracies in self-reporting and poorly described phenotypes. This deep phenotyping approach will produce the greatest good for mental health with the least amount of harm to society. Other utilitarians might argue that preexisting modalities of studying mental health are adequate and so new and potentially more invasive modalities of studying mental health and disease are already adequate. So, these new and potentially more invasive ways of doing so won't improve outcomes and will produce more harm than good. What we can see is that the argument between these two perspectives is an argument over facts rather than a moral framework or an ethical issue at hand and that the agreement is that we ought to be producing the best outcomes for addressing mental health and disease. I think it's really important that we start by saying, what are the ethical issues and to really clearly articulate what they are. Particularly, in this context, it's to say, what are the ethical issues and what are the facts and relevant information that can inform those issues? So we can start with, is there an ethical mandate to proceed with green behavior quantification. I would argue that there is, mental disorders remain among the top 10 leading causes of burden worldwide with no evidence of global reduction in the burden. It's only increasing and particularly within the past couple of years, we can see a market increase in it. The mere existence of the problem doesn't create the mandate, but there's also inherent limitations to date and our ability to well-characterized, address appropriately phenotype and intervene early enough in the course of mental disease and disability. There's also this question of what additional burdens and duties we have to the common good when additional tools and technologies like the ability to more precisely track and characterize behavior in natural environments of everyday life become available. When our computing power and tools from artificial intelligence allow us to find associations that we never before thought possible. We have the ability to aggregate data across multiple data streams, from health records to quantification of daily biometrics and activities, to self-reporting genetic data. There's now more than ever before possible to be able to gather new insights. In other words, new technologies can not only create novel ethical risks, but they can also create novel ethical duties to make use of those technologies to address the most pressing problems in society and this is one of those areas. But just because there's an ethical mandate to proceed doesn't mean that there's an ethical mandate to acquire and use every piece of information about an individual, particularly if doing so in certain contexts may be more intrusive than valuable. What that requires of researchers is to stop and reflect. There's a tendency to believe that just because some novel pieces of information can be quantified that we ought to do so. But I believe that we should adopt a more parsimonious view on data acquisition. With each new piece of information that we can collect about individuals, even if the initial purpose of collecting that data point is for the common good, we have to ask whether that piece of information is one that's necessary to improve decision-making or to understand health and disease. Which requires us to recognize the collecting certain kinds of information, incredibly sensitive or private information such as, for example, how often a person is engaging in sexual intercourse or self-stimulation in a home environment, or some private thoughts or correspondence or intimate conversations with others that they're engaged in may be more intrusive into the privacy of the individual than the value that data collection might yield toward our understanding and knowledge about mental health and disease. Finally, we have to realize that there are some knowledge that may create new duties and burdens such as questions about what points and whether one's pretty sensitive information about an individual. We have a duty to do something about it, such as early information that would suggest a person might self-harm or harm another or commit a crime, does learning this information in the course of research create novel burdens and duties on researchers that they may not have previously had. Which means at the end of the day we have to ask questions about how much do you need to know? Are there are some information gathering that while valuable are more intrusive than the value they provide? At what point do you intervene based on what you know? The second step of any ethical framing of an emerging area like this one is to look at the existing factual, legal, and ethical context in which the researcher arises. From a regulatory perspective, there are inconsistencies across institutional review boards and how they approach brain behavior quantification techniques, there are differences in viewpoints about whether this research should proceed at all, and if so, under what set of protections or guidelines? There's no consensus guidelines in this area, although there's a call for exactly that. There are efforts to bridge these gaps. Yesterday, we heard about the incredibly valuable new paper that was recently published by Francis Shen et al entitled, An Ethics Checklist for digital health research in psychiatry. This paper focused on what the researchers called the deep phenotyping and convened experts, stakeholders in a workshop in May 2020, they developed an ethics checklist. That workshop and their analysis also revealed that there is a significant ethical, regulatory, and normative gap that exist on how we ought to proceed with this area of research. And researchers are faced with very little ethical guidance in a complex and challenging set of ethical issues that will face them, some of which are new, and some of which touch on issues that are being faced by different actors across the spectrum. It's important that we anticipate what those ethical challenges are in the context of privacy, informed consent, duties and novel duties to act as well as novel risks that the knowledge or the research itself poses. Let's dive into those a little bit more deeply. Let's start with the privacy perspective. From a privacy perspective, obviously, one thing that is novel about this context is the unprecedented collection of data. Now, it's true and certainly the case that in the digital era, nearly every move that we make is being tracked. But one thing that has really been beyond the capability of existing technologies is to track the neural correlates of other behaviors, which may give more direct access to thoughts, emotions, and physical processing in the brain that wouldn't have been before possible. That not potentially increases certain risks and certain data collection transcending an area that we hadn't been able to do before, creating novel rest of cognitive liberty to freedom of spots, to development of self. It really, depending on the population and the targeted population, whether that's children or whether that's individuals in an employment setting, in their home setting, it really intrudes into a private realm of mental privacy that has not yet before been breached. It raises complex questions about norms of transparency and data-sharing increasingly, datasets have to be published, made widely available versus individual privacy. The richness of this data, the completeness of this data makes it incredibly easy to re-identify but also poses novel intrusions into the private lives of individuals that before wouldn't have been possible coming into tension with this growing norm for transparency. There are evolving norms and laws around data collection and privacy and this is a rapidly evolving and changing area. It's very difficult to keep up even for people who are deeply steeped in privacy literature and privacy norms, the researchers to be able to keep up with the changing requirements with respect to the collection, processing, and storage of data is a challenge. The private-public partnerships that this raises are unique and challenging. Many of the different sensors that are being used are ones that are operated by private companies who have different requirements with respect to data management and who have incentives around data commodification that may violate the norms that we would expect with respect to the investigators' visa-vis the participants. The second category is informed consent. This is always a challenging area. It's a particular challenge in this area where the risk to individuals from the aggregation of the data and what we may learn from that data is constantly evolving. How it is that you adequately provide informed consent to individuals when many of the risks are simply unknown today is challenging whether or not there requires an ongoing process of consent and ongoing process of transparency in order to maintain an established trust between individuals, but also to ensure that people fully understand the implications of participating in the research. Of course, a well-characterized area is thinking about the particular patient population if we're addressing people who already have mental disease and diminished capacity and how it is that we gain fully informed consent in those contexts. The third is duties to act. So one of the challenges of knowledge and information, of course, is the duties that this may impose upon the researchers. Those are duties from the simple, which are adopting best practices with respect to cybersecurity frameworks and plans for accountability if there are breaches of data. Duties to act and intervene that may arise. For example, as you learn that a person may pose a harm to themselves or others, how soon, how early, and to whom notification is required. Really complex questions about return of research results, particularly as machine learning algorithms are used to analyze what are right now a lot of unknown associations? How good does the fidelity of the insights need to be? How good does the insight need to be before you act and before you have a duty to return research results, how robust do the results needs to be before we think that it's something that needs to be returned to the individuals? In addition, if with the multimodal sensors that are being employed, there's a lot of additional incidental findings that one could find easily, is there a duty to search for, identify, and notify the participants about those particular risks? The last is this category of novel risks, only a few of which I enumerate here. These are, for example, potential risks of stigmatization and discrimination through the characterization of the different deep phenotypes that might be identified. Scientific categorization that individuals can reinforce bias, create justifications for discrimination against particular groups and be particularly harmful to the groups most likely already to be targeted by the research that also can be helped by characterizing mental disease and defects informed by the deep phenotyping that may be undertaken. One additional piece is just the normalization of technology and surveillance that this research entails, a force that's happening throughout society. But as we start to normalize, for example, the tracking of neural data and neural processes, brainwave activity, EMG activity that can lead to a normalization and an acceptance of an area that we have not yet quite seeded with respect to privacy. Once we've characterized and that's an ongoing process, of course, of recognizing what those ethical issues are and making sure that we're articulating those which are ethical issues rather than simple factual divides, you have to consider and make sure that you're engaging stakeholders throughout the process. To do so, you have to ask who is impacted by research? Are the full set of stakeholders engaged in advance and throughout the process? Of course, this means making sure that patient advocacy groups are also at the table, but also the families of individuals who will be part of a broader surveillance research activity because their privacy is also implicated. So two, is the social network of the participants, which means that a much broader set of individuals should be at the table discussing what the right privacy protections are to ensure that there isn't incidental violations of privacy for people who aren't part of the research study, who haven't consented to being part of what is a much broader surveillance study. This includes researchers and it should include the technologists who are developing sensors. The scientists and other experts a much broader setting just the people who are the primary investigators who are undertaking the studies. Regulatory bodies from the institutional review boards to broader ones who are thinking about data privacy and data management ought to be engaged. Public and private partners need to be at the table, ensuring that the manufacturers and corporate sponsors of the different technologies that are being used have a voice and an understanding of how their technology is being deployed in a context like this, and making sure we really have a full and iterative set who were engaged. It also means that we have to recognize that this is occurring in a much broader ethical and regulatory context. These issues about data aggregation and data sensitivity are far from unique to this context. What's unique about this context is layering in both the additional context of neural data, but also putting it into the context of mental disease, mental disorders, and characterizing the brains of individuals. That's a more sensitive area because people much more identify themselves with their brains than they do with any other dataset that's being collected in society. So what do we do from here and how do we proceed? There already steps in the community to try to characterize what the next steps ought to be. I call out again this paper that was discussed yesterday an ethics checklist for digital health research in psychiatry, it provides a very useful starting place, which is an ethics checklists by asking researchers to think about the set of questions, or at least a starting set of questions to think about these issues. I would argue that there is a broader set of questions, some of which I touched upon here that should be asked and a broader set of stakeholders need to be at the table to really make sure that we're able to proceed with this research in a thoughtful way and to really try to implement data per [inaudible 01:49:11] and to take a much more parsimonious approach to what kind of data is being collected. Recognizing there are certain data that, while potentially interesting, might be more sensitive than we think valuable at this juncture in the research. The second is making sure that we have stakeholder engagement and really understanding that to be a broad set of stakeholders to understand, and to use an iterative process of refining approaches and maybe that there are new technological solutions that enable us to do things like minimize data storage or to minimize data breaches. That iterative process is a really important one for us to be able to continue to refine what the ethical landscape should look like for this area of research. Developing best practices for data management and data privacy should occur within the broader context. The old OECD principles at this point for how to think about data management and storage, which are much more general than the contexts that we're talking about here, give us a good starting point and show us that neural data or the quantified data that's being collected and aggregated and analyzed in this context is part of a much broader conversation. There are best practices that we can already draw from. We don't have to reinvent the wheel. I just say, again, anticipate and iterate, anticipate and iterate it requires constant vigilance in such a rapidly evolving area, both of technology, but also our understanding what it is that we learn through the processing of the data that requires that we continue to do things like refine informed consent, refine what the processes are for both aggregation, analysis, dissemination, duties to warn, etc. We have to act in the face of uncertainty. One of the things that I have said here, is that there's a lot of uncertainty with respect to the risk and that's true. But I would say, taking a precautionary principle to this research, is ill-advised in light of the global burden that we're facing with respect to mental disease. In delight of how little we really know, based on a naturalistic understanding of human behavior, and a naturalistic study of human behavior in the brain. In the face of the uncertainty, we have to act. But we have to act in this careful as a way possible, which means not going for the large data grabs. It's getting any data in any context, but trying to be thoughtful about what it is that we're gathering, and being more targeted in the earlier stages of the research. Then finally, follow through with prudent vigilance. This is probably the most important aspect of continuing to have an ethical approach to this research. We will learn more at every step of the process, which means that we need to continue to anticipate, iterate, keep our eyes out for what it is that we're seeing, what it is that we're learning where we can refine, and improve the process, which means a continual process of engaging the stakeholders, a continual process of understanding what we're learning, seeing what the implications and the impacts are, and trying to address any misuse that may arise. Thank you for your attention. I look forward to any questions that you may have and further engagement on the conversation.

Holly Moore: Thank you so much, Anita. We have really interesting comments and questions in the chat. I'm going to challenge us to take them up into breakout sessions because they're probably going to have long answers. But I'll highlight a couple of them. In the Q&A, we have a question on, is there a gap between engineering and the biomedical ethics that these neuro technologies would require, or appear to generate? I think that that was much of what you talked about, and the answer to that is yes. There are ways to go forward with that. Justin Baker in the chat, offered or asked about determining what is acceptably intrusive in an ethical framework. How do we deal with the fact that many behaviors have that become disrupted in humans are socially and culturally normed as private? So many of these behaviors that become disrupted are socially and culturally normed as private. Even if they are biologically normal, doesn't dispose a risk for exploring actual human behavioral norms around concern behaviors that are in principle easier to capture and characterize across species. Who gets to decide what's acceptably intrusive?

Anita Farahani: Yeah, these are great questions. Let me start by the question of whether or not there's a gap. Interestingly, a lot of engineering ethics draws from biomedical ethics. If you look at a lot of the principles that had been adopted by many of the different Engineering Ethics Organizations, or AI Ethics Organizations, they draw on the same principles. But they don't necessarily draw on the same principles recognizing what the originating text or context was. You see a tradition, I think, in biomedical ethics that draws from bioethics in some well-known text and approaches to principles of ethics and frameworks for ethics. Whereas I think, a lot of times what I'm seeing is a feeling of reinventing the wheel in engineering. I think that speaks to the complex interdisciplinary nature of biomedical ethics to begin with and is it drawing from philosophy? Is it drawing from the interdisciplinary field of bioethics? Is it drawing from Greek philosophers much more historically? Etc. So there is some divergence, but I think there's a lot of commonality there. The difference in some ways, though, is, biomedical ethics is used to dealing with incredibly sensitive information because we've always treated health as deeply personal and deeply sensitive. Engineering, in many ways, is more infrastructural, or broader based, and so it may not be approaching it in the same way of sensitivity. Is thinking about a more general population, all of this is huge generalities. Which is to say, there may be applications of technologies from engineering that were unanticipated in the health contexts like this one, that are more sensitive and that haven't been built-in by design into the technologies itself and that an iterative conversation can help us better contextualize. With respect to who gets to decide what's intrusive and what's private, whether, or not a lot of ordinary behaviors such as grooming and other ones have become defined as private. What you see, is those have become defined as private because they're often ones that are within the home, or they're hidden, or that people tried to shield others from. There's a cultural norm for trying to shield, or avert the eyes of others and to keep it to a smaller enclaves. That's culturally true across most of history in most contexts. All that being said, that's part of why its stakeholders who have to be engaged, and that includes, and I emphasize not just the research participants themselves, but the others about whom the data is also being collected. The families in which they arise, the social context in which those types of behaviors are also being collected, because it matters that those people have not opted into being part of the study, and yet a lot of data about them is also being collected. But stakeholders, ultimately gets to decide. Because they're the ones who are part of the process, they're the ones who help to define it. That's what the process of deliberative democracy is meant to do, is to help us arrive at a shared set of norms for guiding research forward, so that we can ensure that it is responsible progress of science that garners the trust, and the goodwill of the people who were part of it. So, I don't get to decide, although, I hope that I'm a stakeholder at the table. I think it's a much broader set of stakeholders who have to decide.

Holly Moore: Thanks. Malcom?

Malcom: Yeah. I have a question regarding this framework, privacy informed consent duty stack novel risks. I wonder whether you think you might add a category, although, this might be sensitive novel research obligations. I guess what I'm thinking of is, if you think about the history of the categorization or diagnosis of autism, in the Bettelheim phase, it was refrigerator moms, it's evolved a lot, it's a lot more scientific now. But arguably, some would say that parts of the DSM are causing harm, and would argue for a science or database revision of the DSM. So, I wonder whether you think this framework might actually have moral imperatives suggestive in the domain of what research had to be done?

Anita Farahani: I think so. I think I put that within duties to act as well, which is their ethical mandates to act. There are ethical mandates to update and correct, and then there's a risk that that updating and correct increased new stigmatization categories. The new stigmatization categories that begin a lot of biases that we may be even less aware of. When you start using machine learning particularly, if it's not explainable AI, for example, that you're using to make a lot of inferences, and those inferences start to draw on diet, or socioeconomic differences to create categorizations because it's picking up on things that are consistent, that may be red herrings. There are risks of new crimes of categories that can be created that track along with all of our existing biases and stereotypes. I think there's absolutely a duty to correct and a duty to act. One of the things that I started with was really saying, new technologies can impose upon us new duties, to make use of those to correct preexisting biases, to correct pre-existing lack of knowledge and gaps in knowledge and to address and to use that technology to the benefit of society. That's supposed to correct and to recognize the novel risk that creates especially when it exists within a black box.

Holly Moore: Thank you very much. I think we'll move on. We are just a few minutes behind. We'll move on to the moderated breakout sessions, and Damon if you could just load up the slides that give us the orientation. I'm not seeing them, so I'm going to move on because I'm not sure we need visuals. Oh, there we go. Great, and I'll need to have control. Thanks. Now, we move on to our moderated breakout sessions. We have two breakout sessions. One that's focused more on how to advance human clinical research. Another more focused on basic research questions about behavior. In both of these, we're going to concentrate on how to advance behavioral signs along the lines of what you heard about in the talks today. The breakout sessions will be led by Isagundus and Catherine Scandalous, that's the human clinical and will be moderated by Holly Lizby from NIMH. And our organism on comparative breakout will be co-lead by Kim Huck and Tom Pereira and moderated by Patrick Abert of NSF. The charge we're giving our breakout groups is to generate new ideas and organize a report out along three themes or three topic areas, and that is rethinking behavior. What are the next big research questions we need to be asking about behavior in a perfect world. If you could ask a question about behavior that you're not asking now, what would those questions be? What are the theoretical frameworks that we need to start integrating, and in cognitive neuroscience, should that be informed by other theoretical frameworks like evolutionary biology? How does bioengineering come into it? What do we need to integrate to ask these big questions? The second major category or topic area for our breakouts is tools. What are the tools that we have now that we can adapt to our new questions, and what tools do we need? Similarly, or in addition to that, what modeling approaches do we see that we're going to need? Where does model we need to go to answer these questions. Finally, what are other challenges and barriers that we need to address along the way? Those would include a way of doing new teams science that actually involves multidisciplinary teams that integrate disciplines that we don't normally see at the table together. Maybe we had to start thinking about a new research ecosystem, the way people interact across the private and public sectors would be another idea there. Of course, as Nita and Karen yesterday and others have highlighted along the way into intimacy round, what are the ethical questions and principles we need to really weave into this process? So, we'll move now to those breakout sessions, the two breakout sessions. Each of the participants in the breakout sessions needs to leave this webinar now and go and find the link that is linked to the Zoom meeting, that is where the breakout sessions will be. I'm asking people to leave the webinar now, link over to the breakout sessions. Thank you.

Holly Moore: Thanks to everyone. We're just waiting a few minutes as people are transported back here to the webinar. If the breakout leaders would turn on your cameras so we can see that you're all here as well as the moderators. I see Kim and Tomo. If the other leaders could turn on their cameras so they come to the top that would be great. Looks like we might be waiting a bit for Katherine. What I'll suggest is that we'll start off with the organismal comparative group. So at this point or at this stage, we're going to get some report outs. We've asked each breakout group to prepare a report out that highlights some of the ideas and questions that came up that were generated as part of the breakout groups. Each report out we have budgeted about 15 minutes for each report out. They can go a little longer than that if they need to, and that will leave us some additional time for general discussion. While the breakout leaders are giving their reports, feel free to put your comments and questions in the chat or the Q&A and we'll see if we can integrate those into discussion after the breakout reports. So why don't we start with Tomo and Kim Hook for the report out on the organismal comparative breakout group.

Tomo: We agree. Definitely, just did this the last few seconds, so bear with us. So the format that we did this in was we just had a big doc here. We see it ended with a few questions. We're just going to repaired back a bit as part of our synthesis so he's going to walk through some of the big points in each area. Forgive me participants if I cut out your thing in the three minutes of synthesis time we have.

Holly Moore: Tomo, is it possible to zoom in or enlarge it just a bit?

Tomo: Absolutely is.

Holly Moore: For those of us above a certain age.

Tomo: Perhaps we need better tooling as we might soon find out. In our organismal comparative research section, we wanted to tackle three big points. The research to pursue. What are the high priority research areas and behavioral quantification? I think this breaks down into roughly four different general areas, recover many other things, so think of these as just like a sampling of the examples. Definitely, I think the biggest thing that came up was how can we move towards more stimulating or modeling more ethological or natural settings? Now that we're able to quantify behavior better, we want to do better behavior. He had a great example about the mesoscale and we've seen plenty of examples of going from the microscale to the behavioral ecology collective scale. How can we practically approach realistic population sizes supposing our experimental setups, but also the types of questions that we asked? But does it make sense to do post tracking with 1,000 individuals in an environment for their entire life? Are there better ways to do this in the lab in ways that we can validate that where we're creating the lab is similar to what we do in the field? That might involve things like bringing lab assays to the fields and then bringing them back, making sure we're getting the same results and ensuring that we're actually getting to more truly natural settings and not curtailing our behaviors of the areas that we're measuring. Another big point was, how can we bridge different species and body plans? I was working on very different animals, many nonstandard model organisms. At the end of the day, we're not going to figure out the brain by just looking at the behaviors that mice exhibit in their home cage. So, as we branch out, how do we compare across those and is going to be especially relevant to our ultimate goal of translating this to humans? Variability, I think is a huge concern, especially as we develop more of these technologies and especially it has become easier and easier to use and automate. There are may different ways to define behavior, both theoretically depending on the field that you're in. But also just very practically, we can't all agree on what about a rooming is. We can't all agree what an instance of associates ratcheted. That is difficult and requires plenty of extra study. Some of the tool developers have already been trying to tackle this in Chetty, in particular, as well as other people. It would be good to fully flesh out what the entire lab variability is. In some of this has been tackled in the past as more classical behavioral assays and looking at reproducibility. But I think we all agree that we'll take take a more holistic view, especially as we again begin to rely more on these supervised machine learning systems. Then finally is bridging these different formulations of behavior going from the psychophysics classical behaviorism, cognitive neuroscience side of task-based, more cognitive type behavioral testing to the neuro or pureology to the behavioral ecology and even developmental changes in behavior levels of analysis. I think, one of the poor things that we'll need to do that is to not only consider the environment very explicitly by not just modeling it, but I understand it's measuring it, but also modeling it. But also considering behavior at the organismal level. We can study motor control and reaching of a single fall but at the end of the day that [inaudible 03:24:10] make it to the entire animal. That will be necessary in order to bridge across these different levels, more whole organism behavior. Could deep learning play a role then, and in unifying the different approaches? Deep learning can service as a certainly I think a glue that's very tractable, just numerically. Integrate different types of modalities of data that would otherwise be difficult to integrate to different models. There is the challenge of how you interpret a deep learning system, and it was brought up that they're very much are emerging approaches to create more explainable by its very design interpretable AI. It may even serve as a key feature in the way that we bridge. For example, things like connectomics, genomics, and behavior, because it affords that flexibility and still track the ability that we didn't have another kinds of bottling frameworks. But ultimately, I think it was very, very clear that we need more theory. A lot of this obviously hinges on the fact that we don't have unifying theories of behavior. Part of it is a notion of behavior comes from these different fields. But as we get better and better computational tools to measure it regardless of the setting, we now need a way to glue all the data together. They didn't build a whole Large Hadron Collider before coming up with the standard model. We need something that we can test as we scale up and develop as a field. Tools. So those were the high priority research areas. What's the stuff that we want to figure out, and there's absolutely necessary, but that is a technology development. That's definitely been I think as distributor field forward very quickly over the last few years. This is like a sampling of the very large landscape of behavioral quantification tools, and it's enabled all sorts of things from motion tracking to data analysis of different kinds of modality streams, and even some that enables more specific types of external paradigms I didn't have before, but we're still missing a lot. When we brainstormed then forget the bunch of texts here, so it just focus on the bolt, is on falls within three different categories. First is hardware. We have not had as much funding for behavioral hardware, as we have had, for example, neural activity monitoring hardware. We don't have a neural pixel for behavior. All we have is webcams at the worst, or Baslers and FLIR cameras at best, which as we all know, rather overpriced and don't necessarily fit all of the needs that we have, and be able quantification when we monitor animals or humans. For example, making sure that we can reach large fields of view while still capturing small features, able to monitor them quickly, scale them up and have it here. But yes, waterproof. Absolutely crucial to be able to do naturalistic, be able monitoring to have cameras and machine vision cameras that they achieve the qualities that we need to quantify behavior, but still can work inside the water and more natural environments. Synchronization is a huge one as we increase the resolution of our behavioral capture. It's very difficult to even just string up multiple cameras together. Synchronization is absolutely nontrivial. The field of human neuroimaging, for example, has broach this topic I think quite extensively and try to synchronize with different instruments with EEG caps and perhaps tell us the other section. But there has often too many unified efforts to do so for behavior. Synchronizing our stuff without using a very explicit [inaudible 03:27:54] is a highly non-trivial issue and requires excessive electronics expertise, but it's something that we have a set of needs that are shared across all of the [inaudible 03:28:06] compared to behavioral folks. In particular, the data taken these behavioral types of hardware and then integrating that with your activity modern technology. For example, by being able to record from [inaudible 03:28:21] or single cells. Not only simultaneously with behavior, but also at the timescale of behavior. A lot of behaviors constrained by the fact that we have to stick them under two proton that they can't move around with. We need wireless technologies that integrate well with what we're able to do with their camera based and other types of systems. These kinds of technologies were able [inaudible 03:28:44], so we can really address them with developmental questions and questions that come from the other funny related fields. But again, that requires more specialized hardware. Wearable systems, like we set out to develop our markerless motion capture technologies like sleep in the blanket., it was largely motivated by the fact that we can't ask our flies and for the most part are mice to wear a motion capture suits like we can for Hollywood actors. That still extends to many sites or rather egocentric sensors like head-mounted cameras or things for measuring physiological signals. Closed-loop technologies again, relates to the specific hardware needs on synchronization and timing, and reaching out to the mesoscale of mammal to measure behavior in larger arenas, more complex ones, and ones that require more and more space or complexity. On the software side, acquisition is a total wild west. Many of the tool developers, I think, expresses a bit of a frustration with the fact that we get videos from practitioners from our end users that simply are not encoded correctly because their camera software spits out some proprietary EDI format that maybe makes sense for security applications or for YouTube streaming, but not for behavioral quantification. We have very specific needs in our types of video data, then perhaps what we need is better software that is aware of the types of outputs that we're asking it to generate. Apache interfaces and utilities for analysis for things like FA/localization or integrating across these different types of measurements. Finally infrastructure, I think this is going to be one of the major bottlenecks in our behavioral quantification as we move forward. Because not only is data storage difficult, as anybody who has tried to purchase data storage systems and had their institutions as surely experienced, but compute is one that's even more tricky, because there's certainly, as we use more deep-learning based solutions, we need GPUs. Conventional [inaudible 03:30:56] GPUs are built for gaming and apparently crypto mining, but not for behavioral quantification. So we asked, is there a middle ground between the free tier group [inaudible 03:31:06] in your institution's high-performance compute cluster. I think one of the solutions that might fit the bill for our field might be a Cloud, AWS Cloud Platform, and part of what we need for that though is Cloud native tooling and incentives to build them. They have flexibility of allowing us to scale. They give us the advantages of containerization. But these things, Cloud software engineering, containerization, and moving stuff. Is moving a file from your computer to the

Cloud is highly non-trivial? We need better software infrastructure that needs at least of behavioral qualification. Scientists, is simply is not something that you like and pick up and just start using. We need to encourage new behavioral tools, to not just be able to output stuff on a single workstation, but be able to also work transparence scale up to the Cloud. Finally, the third area where about the barriers we need to address. In particular, as we scale up to broader initiatives that would enable more transformative advances in motivating here is in cousin's slide from yesterday of the gap between the microscopic and the macroscopic scale of behavioral analysis. We had, I think three major categories here. One is, how can we enable team science? We asked, what would the Allen Institute for Behavior Quantification look like? The big consensus is that, we don't really know precisely what it is that we're measuring. In comparing this high energy physics again, when they built a large hedge glider, they had a unifying theory. They sat down and worked out precisely what it was that they were going to be able to go out with the measurements before they set out to scale up their instrumentation. In our case, if you analogize it to say that the Human Genome Project, well, it doesn't necessarily make sense to create the Mouse Ethel Project just yet because we don't have consistent definitions for that. We haven't defined the scope. So perhaps, what a team size issue would look like is something more like a consortium or more of a consulting or matchmaking type service that allows us to put together the disparate expertise necessary to create these definitions, both from the scientific biological side and from the engineering side. Finally, if however this takes form, we absolutely need to address the problems credit assignment in author's contribution. In high energy physics, they've all come to terms with the fact that we're going to have 3,000 authored papers. But if you were to have one in nature neuroscience, it still feels like your contribution is going to be diluted to the point where it's not necessarily worthwhile use of your time or resources to contribute to that large-scale team initiatives. So if our funding agencies are willing to commit to recognizing individual contribution in large-scale efforts, they might indeed be a very crucial and enabling action to create such consortia. Standards, we talked a little bit about this. I think that as we talk about more about tooling and infrastructure for behavioral quantification tools. One thing that's perhaps slightly missing the landscape, although addressed in other fields, like the medical field and up to date or even in our field, noble behavior which is still in its nascent stages, a consistent way of reporting new tools and as well as the standards for describing them in an ecosystem repository. The brain initiative is, I think, exceptionally well position to orchestrating coordinate as centralized repository for this type of thing. Because they already found many of the tools that are being developed in this field. Adding a requirement that tool builders must submit, a particular very structured type of metadata to a common tool repository will make it much easier to stay on top of the constant growing innovations in our natural landscape. Then finally is expanding our circles, which is motivated by the fact that we benefited a lot in the recent years from bridging over to computer vision and deep learning and certainly this is still going to have to extend another for disparate fields in order to meet the need, engineering and technological needs that we've identified in the high priority research areas and others. In particular fields like computer graphics and robotics as well as it will go back to the more theoretical computational modeling side. Fields like economists science and more proper neuroethology, cross-species comparison and bringing it back to how can we use these types of innovation and engineering of these fields like in video game development, environment designing order to create for realistic simulations that are more minimal to lab studies. Finally, how can we reach out to non-academic partners such that if they do have the skill and the infrastructure to build better hardware that we all need. Maybe the best way to do it instead of coming up with it ourselves and having to find academic collaborators that have electronics expertise to instead reach out to Basler. Can you make a behavior camera that works for us rather than for purely industrial manufacturing machine vision type needs? Okay, with that, that's very shortlist of ideas, I think that roughly covers our synthesis of what we came up with our session. There are plenty more ideas and maybe we can share those at a later time.

Holly Moore: Thank you so much to Tomo and Kim and to Patrick for moderating that session. We'll move over now to the breakout report from the Human Clinical Neuroscience group Aisha and Catherine. Take it away.

Catherine: Sure, I will just share my slide. I'll start out and then Aisha can jump in on the second section. So this is some of our ideas, let me make it a little bigger as well, that we discussed in our human group. So how do we rethink behavior? What are our big research questions? So, one of the things we discussed is what is the best theoretical framework to study behavior. It was discussed that there's not really enough information out there yet to be able to answer that question. Once we decide on that, how can we then match the technological improvements of our devices and sensors to that model? So for example, we ended up using a dynamic network model that we heard about during this workshop. We may need to have multiple sensors then multiple biomarkers. We may need to develop our biomarkers based on different types of features. We also discussed what the best temporal and spatial resolution for these sensors and for exploration into different behaviors, which in this temporal and spatial resolution for each of those behaviors or internal processes may be different and how do we come to terms with those differences? A second thing we discussed is how can we close the gap between human and animal research? And this has been terms of the Valley of Death. One of the problems is that the questions are quite different so we may be stimulating the entire hippocampus in a human, but you can never do that same study in animals because you need to stimulate specific cell type. So that gap is problematic and prevents us from doing some of the forward and backward translation that could be helpful in understanding the effects of stimulation and continuous digital measurement that we're obtaining in relation to specific behaviors. If we were able to do that, we discussed that we could take common features across disorders or across species, and we'd be able to examine them in much more precise ways. We also discussed what the best approach for personalized medicine or precision medicine as a strategy to understand internal states. The idea behind adaptive or closed loop stimulation, or do we need to be looking at functional and structural connectivity, and what other strategies are there to make advancements in this area. We talked about a continued focus on how to integrate and synchronize signals. We discussed that the clinical scales that we have now are very problematic, and they have look-back times of weeks. So new skills may need to be developed that help us correlate these types of clinical skills with these new continuous measures that we are collecting or we may need to develop intermediate outcome measures that help us cross that gap. We also discussed that we need increased study of the measurements themselves. What do they mean? Are they reliable? Are they actually measuring what we think that they are measuring? We talked about how do you capture full brain complexity and the complexity of the environment. So we discussed, what is the full brain system doing rather than just taking out one area of the brain or studying one's particular brain behavior. How can we understand those behaviors, and brain regions, and context of the full system? What does the context or the state, how does the state a system is in play a role in the outcome in both the behavior and in the internal states? We discussed that there is a gap in the internal states and what we can measure behaviorally, we can't always access the different internal states, and can we come up with new strategies to do that. We discussed ways to capture, or is there a way to capture a patient's life in society? In the context of their life and the people they meet, and the different activities they perform. These are some of the big research questions. Before I pass it on, I'll briefly address the barriers and then pass it on. [inaudible 03:41:54] shall discuss the tools in greater detail.

Dr. Aysegul: Before you do that Catherine, can you also introduce yourself to the general audience because some of the people in the other workshops didn't get to hear from you.

Catherine Genghis: Sure. My name is Catherine Genghis. I am a medical director at [inaudible 03:42:11] , and I'm an Assistant Professor at UCSF, and I was working on a clinical trial, I was leading clinical trials closed loop deep brain stimulation at UCSF. Back to the barriers that we are addressing. We discussed a couple of different areas. One is that we need greater access to algorithms and devices. We need to be able to give these tools to more people. Not only the algorithms, but the devices and their current barriers that make this challenging. We discussed the need for greater private sector involvement and end-user participant, and more collaborators across the dot space, in order to make improvements. We discussed strategies, as I mentioned, to unite human and animal research, or that these strategies are needed. There have been a number of different consortia or working groups to try to do that, there needs to be more improvement in how we can do that. We discussed development of ethical considerations and frameworks. Understanding how data is used to ensure that it will specifically improve brain health, and won't be used for other purposes and the lack of understanding potentially of people, patients, or participants in the studies and the researchers themselves. We also discussed that using multimodal data and synchronized data, could influence the ethical consideration. You may be more likely to match data to a particular person, if you are synchronizing data across multiple sources. We discussed the need for team science and the barriers to that. The common language is often different. There are different incentive structures. There isn't necessarily a strong incentive structure for large teams. Some of the consortia that are being developed may not be comprehensive, providing access to algorithms, but not the devices themselves, and a need to achieve larger sample sizes by building these collaborations across the different institutions. I'll pass it along, at this point.

Dr. Aysegul: Thank you Catherine. Hello everyone. I'm Dr. Aysegul Gunduz. I'm an Associate Professor of Biomedical Engineering at the University of Florida. I'm also [inaudible 03:44:51] with the new [inaudible 03:44:54] Institute for neurological disorders. We have a very collaborative campus. I guess the last point that we had really fruitful discussion on is basically, what tools do we need to achieve these goals that were summarized by Catherine? Obviously this program, the brain behavior quantification program is under the branch, which also has a private, public, partnership in place. Again, we basically need all the stakeholders to join these conversations. Hopefully, the program could define all the stakeholders for us and that basically whatever outcome that comes out of this workshop is basically communicated to all of the stakeholders. Again, we shouldn't forget the 'S', in the [inaudible 03:45:52] , the brain behavior quantification and synchronization program. We didn't touch base too much on synchronization yesterday, so [inaudible 03:46:05] synchronized neural activity with natural behavior in complex environments. Again, we also need to remember the social context. Our state tendons, that also needs to be synchronized or integrated with neural data and behavior. We basically have touched base on an example of the experience of deep brain stimulation patient that had received this therapy for depression, their mood was elevated. But then, they actually had to attend the funeral in which they just couldn't then experience sorrow and they felt really embarrassed because of this. Again, we touched based for those in the private sector. That is developing these devices, especially implantable devices that's reporting the neural data. We really need to have a conversation of whether we're receiving the temporal on spatial scales that we need, especially to do network neuroscience. If we want to develop personalized psychiatric therapeutic tools, we might need to basically sample trouble. Wider network, again from [inaudible 03:47:24] talk earlier, basically, that we also may need to know the importance of microscale as well as the microscale that we're receiving right now. Again, when we talk about network science, we need to do, again on the modeling side, we are really interested in causal relationships as well as structural and functional connectivity. We need basically to be able to do network neuroscience. We need electric coverage that is widely distributed across networks. When talking about the wearable technology, so the technologies that are going to give us labels of the biometrics data, we need these wearable technologies to be portable, we can't have faulty equipment. Because then, we will basically affect this natural behavior. People can't act naturally if they are basically having to wear these bulky equipments, no matter how cool we think they are as engineers. In the modeling domain, we also would like to have transparency of the algorithms but that is really crucial. We really need to be able to then map back whatever the input-output relationship model is creating us. We may need to be able to and translate that back into neuroscience. If the network model is too complex, if we can't basically map it back to a neuroscientific understanding, that might not be as valuable. Again, then necrotizing these modern technologies, as well as actually the simulation on the technology itself we just mentioned, that's based on that as well. So again, brands that provide technology simulation, modeling simulation, an understanding of the models of how they work will be quite important. Then, as we publish our scientific findings, we need to make sure that the pirate partners are actually reading them so that they can also tune their hardware designs to the needs that we now have. For instance, I think it was obesity, OCB, even freezing of gait that we've found actually the neural biomarkers are low-frequency signals, and these companies have been actually banking on making rhythms that are a little faster than those. So again, we really appreciate this effort of bringing this workshop together, but we also would like to basically have all the stakeholders at table next time around so that we all can give each other feedback.

Holly Moore: Thanks so much to both of you, Aysegul and Catherine, [inaudible 03:50:44] from monitoring that session. Howe put in the chat for everyone to see information about a new DARPA initiative that is quite relevant to the workshops, so take a look at that. We have some time for discussion about basically your reactions to the report out, so those of you who are warned in the human clinical may want to ask some questions of Aysegul or Catherine and vice versa. Those who were in that breakout session might have some questions for Tomo and Kim. So you can put your questions in the chat or raise your hand, turn your camera on. But let's open it up for discussion.

Dana: We do have a hand, Karen?

Karen: Hi. Thanks for those very extensive summaries of how to capture all that. Then I felt like I was in that first breakout group even though I was in the other. So thank you for that. I just wanted to move back in some of the ethics considerations and some of those. I'm curious how the group might think more deeply about how some of these scientific questions are also ethical ones. For example, it's a hard task, but in our attempt to try to objectify everything, have we turned also humans into objects? A lot of what I heard about the scientific design it had very, especially in thinking our group about humans, was a lot about the type of question one might ask, but not a lot about consideration of the human in the place he was going to be quantified and the possible opportunity for them to be actually research partners, even collaborators, and giving us greater insight into the ways this technology might be designed. The types of questions we might be able to reasonably ask in the wild. The types of considerations and concerns they might have about the ways that they are being categorized, and the types of ways they might eat their information and inferences from their data might be interpreted. So I wonder if there are any offerings, this group think so deeply about behavior. How we might explore some of those relationships with the partners who might be humans. I guess there's a lot of certain comparative researchers here too. But how we might avoid the trappings of this over quantified self movement that really started, many of us know of, started in Silicon Valley as a kind of a marketing scheme anyway. How do we move beyond that into something that was really meaningful, and inclusive. I see John on here, I know he's someone who deeply cares about this as well.

Holly Moore: John, did you want to react or do we have other hands up?

John: Well, I'd love to hear other people's thoughts.

Holly Moore: Thanks. I wasn't, so we leave some space.

John: I have another question for the group, but I'd love to hear other people's thoughts on those.

Holly Moore: If your hand is up and I can't see you turn your camera on. Thanks. Allison?

Allison: Right. Just paraphrasing a conversation that we had yesterday to see if that stimulates some conversation, but what opportunities come to mind that we might miss out on when we really consider the agency of our patient partners. So for example, maybe our self-report measures are inadequate or the timescale of them as inadequate. Maybe we'll never be able to find a behavioral readout of a particular internal brain state, but the individualist capable of modulating that brain state. So then, we skip the issue of trying to measure it, and instead our proxy is the person's ability to move in and out of that given brain state, in some training and constraint. Just giving an example to stimulate some brainstorming.

Holly Moore: Malcom has put a comment in the chat. Malcom, if you're still here, you want to speak up.

Malcom: Oh, sure

Karen: Thank you.

Malcom: I appreciate the point about objectification of humans. I'm not sure how to avoid that in the context of the need to quantify behavior, but I do think that subjective state is not adequately measured, and I, myself, I'm not doing research on psychedelics, but I've heard people who are doing research on psychedelics are thinking about this, and whether anybody is doing that research or know some of the techniques that might be brought to bear on a better science of subjectivity.

Karen: Nadia?

Nadia: Thanks, Karen. That's a really good point and I think it becomes even more relevant as we start to go in the home recordings, and quantified climate behavior is to have really these patients be collaborators because otherwise it just doesn't work. We don't have the same that technical tools available at home. The other thing in the lab too, and I wanted to mention is that, as basic scientists working with humans, we're often motivated by the animal studies and the objectivity and the rigor that we have there. But at the same time, we sometimes may forget or ignore the fact that as humans they can shift very easily between cognitive states based on a simple verbal instruction. I think we need to not shy away from potentially exploring those shifts and those differences across species. I think a lot of times, that's met with a lot of hesitancy to be open to the fact that there are perhaps cross-species differences and the whole picture will provide insight into these behaviors. So thanks for bringing that up. I think it's really important also for us to design objective studies that are controlled and rigorous. But at the same time, remember that these are human beings, yes.

FEMALE_5: Raising isn't working. But I also wanted to say that, I really agree with that as well, and in fact, when our patients in our trial come in, that's what we tell them that this is partnership. There's much responsible for contributing to the research as we are, that we want it to be a partnership that because everything is so exploratory at this time, it's really necessary, and we don't have good measures of internal state right now, so we need the patients themselves to say, this isn't really a capturing what I'm feeling, or it is capturing what I'm feeling or how can we change this scale to better capture that? Or what states can do feel are representative of a natural environment at home that we can try to recreate, and let's come up with a list of those together with the patient. I think we haven't captured them in those questions, but I'm glad that came up because I think it's really critically important.

Dr. Aysegul: Paul Suzak, I saw your hand first.

Paul Suzak: Yeah, I wanted to follow-up on the point that Allison raised that even if we can't understand the states, the humans themselves can change. Are you suggesting something like a high-tech biofeedback where they can try to control some estimate that we have of some mental state that they want to stay away from, and essentially learn through the feedback through the machine. Is that what you suggested? I'm wondering whether that becomes tricky because then they're learning to control what we read out and present to them as feedback. I guess the bottom line in the end is are they getting better. But do you see any?

Allison: Yes, and in this conversation, it's important to clarify when we're talking about harnessing an agentic force to advance our science. So what happens when we include that in our experimental design? Somehow, maybe to get around the issue of self-report being too ambiguous or on their own timescale, and then dissociate that or differentiate that from another question which is the role of the patient that has an agent in their care. I think sometimes those two very interesting topics get confused when we talk about issues in close loop brain stimulation. But actually there are two different things.

Dr. Aysegul: Right now, like the tools we have, like the patients can put markers as I'm feeling better and worse I've experienced term around so forth, but yeah, we're limited in that. The next hand.

Holly Moore: Aysegul, I'm going to read from the Q&A, if you don't mind, before we move on to a different topic. Sorry to interrupt. Along the lines of basically assessing internal states using a diverse set of behaviors, there's a suggestion in the Q&A that the psycholinguistics community focused on American Sign Language, and really brought in the deaf community into their research process. That's an example of how to bring in stakeholders. It's also an example of bringing in different communities where the behavioral output of internal states is quite diverse. Moving on, we can discuss that and I can also invite Tomo to chime in if that's on the same topic. If not, let's take that for a few seconds, and then Tomo chime in.

FEMALE_6: I think Tim Brown also had his hand up.

Holly Moore: Yeah. Sorry. Maybe, Tim, you have more to add there.

Tim Brown: No. You're calling me now.

Holly Moore: Yeah, sorry if you wish. Sorry. We're trying to organize around topics sometimes not just go in order, but yeah.

Tim Brown: Great, great. I just wanted to underscore the previous comments about objectifying through measurement. Thinking in terms of not only how we incorporate the human subjects and their agency and take into account their agency or their ability to be, as Alison mentioned earlier, an agent of their own care, but also a representative of broader social groups. The question from Chris or the comment from Chris really encapsulates the challenge and the opportunity here, where not only are people trying to advocate for themselves, but they're trying to advocate for people who are in situations like their own. In determining whether or not a measure is working for them, or a task is working for them, or a specific technology is working for them. So, I would like to invite everybody to think about the social agency here, and the social-cultural ties that every human subject brings into our studies. Use whatever opportunities possible to bring communities into the research process.

Holly Moore: Thanks. Tomo?

Tomo: Different topic but because in the other breakout session, I was curious if, from the human perspective, there was a discussion on technology development with respect to hardware and engineering efforts that pertain to behavioral quantification. Like one thing that was brought up often in our session was the difficulty of leveraging standard types of video cameras to enable better motion capture, as well as integration with other instruments. Particularly like being able to have wireless communication and synchronization across our tools. I feel like you guys probably have dealt with that to a fair extent. So, I was wondering if there are any ideas there that we could borrow for the [inaudible 04:03:56] one compared.

Dr. Aysegul: In terms of the patients being the stakeholder here, we obviously would like to have something that is not bulky for them to be able to basically act as naturally as they can.

Tomo: We will like that for our animals as well.

Dr. Aysegul: Okay, fantastic. Because sometimes as engineers, we don't like doing cool things, but we'd never asked the end-user whether they think it's cool, whether they like to use it, and whether that would actually affect their natural behavior. In that sense, we do have the opportunity to basically talk to the stakeholders being the patients right now. I really like the idea of bringing social-cultural ties. For instance, I teach neural engineering, and in the same class that I teach, we actually have American Sign Language being taught and there is a course called Deaf Culture. Deaf people definitely have a culture of their own. They're artists and they don't like being thought of people with disabilities because they actually can communicate. We need to widen our roles and learn American Sign Language. In that sense, I love that you brought that up.

Holly Moore: Thanks. John, your thoughts?

John: Great. Actually, I'd like to generalize Tomo's question to the group for everybody to consider. Let me frame this by saying that for a bunch of reasons, we had separated these two groups into human and what we call a comparative. My conceptual work, comparative is not as a euphemism for non-human, it really is working comparative models teach us, and of course, humans are animals too. So for logistical reasons and for reasons of convenience, we did separate the groups, but ultimately, I really see the power in having folks who are working on human behaviors, talking, and interacting with and learning from people that are working on non-human systems and vice versa, so it's the issue of translation, reverse translation. I was just wondering for everybody here, they're hearing that the report outs maturity groups. I mean, what do you see as possible opportunities or even barriers for that more direct and seamless interaction between people studying different organisms, including humans. Let's just put everybody together. Of course, working with humans poses very important other considerations. Not that working with animals doesn't as well, but I think not just to different degrees, but also different contexts altogether. But, what do some of you people see as areas that could enable your research by learning from these different research communities?

Dr. Aysegul: I think for human neuromodulation therapies, learning from animal, the causality aspect that all models could bring, especially with optogenetics would allow us to maybe select targets better. For instance, Parkinson's SDN and GPI work. Basically, we're at war with GPI group here at UF and we're one of the rarer ones. Because when it was first developed, people went to SDN because it was a smaller target, so if you were in the SDN and if your ETA rolling or tissue alteration was big enough your symptoms would be suppressed. But then, GPI is a larger nucleus. So if the neurosurgeons couldn't put it into the moderate part of the GPI, these symptoms weren't suppressed enough. Basically, this was back in the day when high-resolution imaging wasn't available. This is grandfathered in that people do STN rather than GPI. I think again, for instance, for [inaudible 04:07:53] we don't know whether the central reading [inaudible 04:07:55] thalamus is better than the anterior part of the GPI. I think, animal models could definitely guide the clinical practice in a better way than just doing what was grandfathered in.

John: Sure. That's a great point. Clearly, a lot of techniques and devices and approaches have been developed in animal models first. But beyond that, I mean it just in terms of fundamental understanding, basic biology. What can basic animal studies do to inform human behavior and neural circuit function and vice versa? I mean, it's automated to be flipping, but humans are a great model system for understanding biology. So they're intensely studied, they're being phenotyped every day in hospitals. We have a lot of amazing tools to bear. Sure. Translation is a big goal of what we're trying to do, but stepping back about 20 steps in terms of basic understanding, is what can we learn from each other, to make each of our fields move ahead faster, ultimately toward translation.

Holly Moore: I know Nancy has had her hand up for a while, so why don't you go ahead.

Nancy: Now, I have a bunch of different things in my head. But to answer Tomo's questions, we very much do struggle with this issue of synchronization, and especially the more sensors you have. We don't have the issue of Miniaturization as much, obviously, as you do. But one thing that we've been exploring lately that I am hopeful and optimistic about, is NTP protocols in order to synchronize without physical connection between data streams. That's something that I'm optimistic about. To your point, John. This is something I also think a lot about because I started in animal research and moved into humans and a lot of my lab members are former animal researchers, which to me provides a benefit to the insight in terms of applying some of these tools that are not necessarily crossing this bridge or this gap. I also think we need to, like I said earlier, reiterate my point that we need to be open to working together and not being hesitant or fearful that what we find in one species may be different than another. I include non-human primates in this discussion as well because that's an important bridge between the two. I probably forgot all of my other points, but those are just here.

Holly Moore: Thank you. Catherine?

Catherine: I was just going to add that I think some of the ways that studying these similar questions in humans can occur. For example, if we find a biomarker in humans while we're doing intracranial brain stimulation, we can see, is it there in the animals as well? That's for the basic question. But then, how can we modify it, which cells are involved in creating it, are there other pathways that it influences, and how does that happen? We can build models on anxiety or some behaviors that are common across and then test it in different scenarios. I think, part of the way we can do that is reason as we pass the numbers. We don't have as many humans that we can test this question, so we need larger numbers. Then the flexibility, where we can only study a couple of different parameters, stimulation parameters, for example. But we could do a lot more in animals. We can look with much more specificity in the animal than we can in human. Then ideally, we'd be able to take some of that information that we gained and then test it back in the humans. An example, I think UCSF is from some of the work that Eddie Cheng had done is trying to hippocampal amygdala biomarker. This is a data coherence variance that was published on awhile ago. Then take that into the animal's, find the same marker, explore it, and then take it back to the humans with much more information about how it arises, when it arises, and other aspects.

Holly Moore: Thanks. Timothy, right, and Kim put some interesting comments in the chat. Timothy and Kim, do you want to speak up and join orally, verbally?

Timothy: Guess this isn't directly to John's question, but this was more in terms of an ongoing conversation about sensor and sensor availability. I was just pointing out that, in order to accurately measure, it's great that human commercial devices are getting good enough for use on humans, but animals pose a lot of other different challenges and how they move through the environment and the environment they're in, and that their sensory abilities differ from those of humans. There may need to be some investment if we want to more accurately captured behavior, tools in evidence.

Holly Moore: I think the phrase, moving through the environment, is an operative there that if we think about the kinds of sensors that we need to really capture the animals experience including human animals, then that moving through the environment component is part of what we're thinking about. Kim?

Kim: Thanks. I was really trying to summarize the recurring theme in our breakout session. We all agreed that there really isn't an overall theoretical or conceptual framework of how the brain is working to control behavior and so, if we even want to know what the rate measurements are, we felt like having much more comparative work across many more animals performing diversity of behaviors and diversity of environmental context, is really our best hope to be identifying those fundamentals of what should we even be measuring in any animal to understand how its brain is regulating behavior.

Holly Moore: We have a couple of comments that are related, that are in the Q&A. One is that there are industry partners actively tackling the issues of modality and synchronization. Data joint is one. Another related is working in industry in animal and human research. Jessie, Michelle wants to basically second Tim's comment. There's so much diversity and animal research, it's hard to focus on just one to be a successful company. Funding goes to one developing model and specific tools. How do we actually prioritize, I think is one of the things I took from that comment, and if we value, and that gets back to Kim's comment, if we value comparative research, we can't study every species there is, we have to have a theoretical framework by which we actually can agree on the value of a particular comparison, for example, and then we need to develop the tools to do that. Do we have others who wanted to jump in besides my cat? Karen?

Karen: I wanted to just chime in. I think industry has been mentioned a lot. As a monolith that has one incentive structure only towards money and not towards scientific inquiry, which I think actually varies across the type of sector you're talking about, just like across scientists. I mean, I think it was even brought up how do you incentivize scientists to work together when authorship is tied to funding. I mean, this is just the reality of the practical infrastructure, like everybody has their demon that sways them. I think one of the things I've been doing in cross-sectoral work is understanding that a lot of industry partners are actually very interested in looking at new ways to solve problems and have also tested these things in the real-world and understand both technical and ethical issues in ways that I haven't encountered with academic scientists, and I've found that very exciting. So, I think we have an opportunity to not just think about collaborating and how can we get industry as a monolith to let us use their tools, but also think about what might we learn from each other and be able to exchange. Not to mention some of the cloud questions that were asked there. The whole decentralized science movement led by people who consider themselves social justice warriors and are come from a cryptocurrency background, which is interesting. But they are working on very creative solutions for like data wallets, for health, and having hackathons on how to strip down multiple different hardware devices to raw EEG and then be able to re-categorize that and see what meaningful information can be gotten, particularly around wearable neurotechnologies. So there's this whole other world that I've noticed that is operating separately. One is this decentralized science movement and the other is this monolithic industry identity that comes up a lot, and I'd be interested in seeing just as there are diversity of scientists here within their techniques and their universities. It would be interesting to consider a plurality of those identities too so it's not just one industry representative coming and trying to speak on behalf of everybody. That might be a lot for us to learn, and I think many of you already have industry collaborations that we might learn from as well.

Holly Moore: Thanks. It would be important to learn how people create precompetitive spaces where science can be decentralized and ideas can be shared while keeping intact the incentive structures that are necessary, for example, for some private people in the private sector. So that would certainly be a part of the conversation going forward. Molly added a comment in the chat that relates to John's previous question about what we can learn from animal models. Molly, would you like to elaborate?

Molly Marti: Sure. I was just getting the possibility. Hold on. That the brain is a plastic organ, and many humans are going to have impairments in different parts of the brain, and we need to find compensatory actions for the brain to handle those impairments. If we start asking or investigating other animals that use different pathways to solve particular problems, we can actually identify different targets for specific tasks. So that's why I think there's going to be great power in the comparative approach to find compensatory pathways for humans.

Holly Moore: Thanks. I see more in the chat. Lena, would you like to chime in?

Lena: Sure. I think we're going to have a lot of data, and I think finding those relationships between brain activity and behavior are going to be highly variable, how do we deal with that? I actually think that some of the scientific methods like [inaudible 04:20:11] grants, and we want to talk about personalized medicine or quantification of how people use their brains and movement defy the standard statistical models. The way that we think about means and standard deviation just doesn't even work, and especially with this machine learning if we're categorizing things or we're trying to look for regularities. We may be losing a lot of this variability and not being able to do that type of personalized medicine for each person's brain because it is plastic and totally reorganizing itself based on a particular disease and our experiences and maybe how they went about seeking medical help. All things are going to change the endpoint and then the way to restore the function that they might want.

Holly Moore: Thanks. I just want to highlight another comment you put it in the chat that I think is something for us to think about when we're thinking about data-driven approaches and models where we need to have a teaching set, for example, and that is who gets to decide what the teachings set is? Who gets to decide which people or which animals contribute to a teaching set for a machine-learning model of a particular behavior. There are cultural differences across different communities of people such that, that has to have deeper consideration. Maybe we should think about cultural context, when we're thinking about which behaviors are normal and that, in turn, influences the models that we generate with data-driven approaches, I think. I see one last comment besides lots of people agreeing with each other, which is really nice, by Raji with regard to the comment about the need for pre-competitive spaces. That the semiconductor industry has done some pre-competitive has a pre-competitive research agenda. Raji, do you want to speak more about that?

Raji: Just as the model to study it's very well-known. It's very multi-decade long, large consortiums. The idea is that if you have a road map, typically, then you can put timelines. Then you can come to what is pre-competitive, what is competitive. Full disclosure, I was 15 years at Intel, worked on lot of SRC projects during that role. Some model to study for understanding what works for that translational joint university model, as well as the next step. The caveat is one of the reasons I think among various industries that the semiconductor industry was highly successful, I don't know, it's the conceptualization of a road map, the Moore's Law. Whether or not that was actually based on science, in my perspective, most likely a business role not a science. The science was incidental. But having a road map helps then differentiate what is pre-competitive and what is competitive, and then build a model for research. Maybe something to think about for this community is to understand how to study some of those successful models.

Holly Moore: Thank you. With the idea of a important next step being to think about and developed that road map, maybe that would be a good time for us to move on from the discussion and have some closing thoughts. I'm going to hand it back to Dana [inaudible 04:24:13] to introduce John and wrap up the meeting.

Dana: Well, I'm going to go ahead and hand it over John Ngai. John Ngai is our Director of the Brain Initiative. I can't remember. Seems like he's been there forever, but I think that's only been a couple of years or so. But we've been excited to have him and I'm going to leave it off to him to give his closing remarks and then I'll just come back at the end and close the meeting.

John Ngai: Thanks, Dana. Can you see my slide? Yeah, we good?

Dana: Yeah.

John Ngai: It only seems like forever. It hasn't even been two years. Sorry.

Dana: I mean, that in the best way.

John Ngai: I know. Anyway, thanks everyone. This has been a great two days. I've learned so much and we covered so much ground from many, many different perspectives, which I think is really what the field needs to move these very difficult problems into a better light. So I just prepared a few closing remarks while you folks were in your breakout rooms. I was feverishly trying to figure out how to sum up. A lot of the things I'm going to mention have come up again this afternoon, so I'll try to be brief. I'm going to try to make this work. So, a few emerging themes, and this is not at all exhaustive. It's a few things that got my attention. One thing is the importance of studying animal behaviors, not only in humans, humans are animals, not only in lab conditions where we think we're controlling the environment very well, but also in more naturalistic conditions. I think these approaches together will have a greater potential to reveal the full repertoire and complexity of behaviors, as well as I hope eventually internal states, which will be the real challenge to get at. This is one thing that really did strike home to me. In a number of different instances, people reminded of the importance of considering not just the environmental contexts. In what a set of circumstances is that animal navigating the environment, behaving as it were, but also the social contexts. Part of one's environment is also the con-specifics as well as perhaps predators and prey or other threats or other people or animals around us or around the subject. I think it's really important to reveal the riches of behaviors and of course, we typically don't operate in isolation of our environment or of other co-specifics and others. It was really good reminder for me anyway. Of course, the goal of this workshop is to try to sort out new and different ways of linking neural activity to behavior. Again, what struck home to me was not to think of these circuit struck behavior is linear processors where you have an input circuit and then an output behavior, but really more at the level of a recurrent networks and think more than once people spoke about lessons we might learn from control theory. Another interesting point that was raised was the need to understand the purpose and the goal of behavior. So I would tend to think about you get a sensory input that drives some activity in some specific circuit and that will result in some specific behavior. But it was pointed out that, well, maybe almost certainly it's more of a closed-loop system and that the behavior itself can drive what sensory put one gets. When I'm driving around, I remember driving around town right after I moved to Berkeley. There is a very famous barbecue joint and I actually chemo-navigated myself to that place because my behavior was driving me to. I think of more pleasurable sensory inputs. Just a silly anecdote, but this really was driven home to me. It's hard to overstress the importance of establishing causality. I think through all the studies we do, whether it's direct experimental studies, and especially as we get into a machine-learning techniques where the ground truth can be pretty fuzzy if present at all. We need to keep in mind the importance of driving our science toward developing testable hypotheses and hopefully perturbation experiments that can either validate or falsify this hypothesis and lead to new and better ones. Again, the importance of establishing causality and David Anderson put a nice analogy in the chat yesterday during one of the talks. The subject of species diversity has come up a lot of times. We use the words human research and non-human research comparative studies, what have you. I think the value here is that looking at a variety of different species, each with their own specializations, will help us identify both generalized and specialized strategies for circuit design and ultimately in behavior. My position is just to ask what can evolution teach us? In terms of the evolution I've heard of species, it's been going on for about 500 million years. So there are certainly lessons there to be learned. We can't hope to beat 500 million years of evolution, so what are the lessons we can learn there? Again, just echoing some of the comments that came up in discussion just now as well as in the chat, I think not everything has to be similar for us to understand animal behaviors. I think the differences are at least as useful if we know how to pay attention to them. Final point here is to embrace not a shoe variability. If we understand the drivers of variability in whatever we study, whether it's measured behaviors, gene expression whatever, we can learn a lot about the systems. I think, Marla Murphy made really great point that variability in behavior isn't always just noise, so again, something to pay attention to. We've also came across some ongoing needs. Very, very important is we need theoretical frameworks for both designing and interpreting our investigations, and this again cannot be over-stressed meaning we have some theoretical frameworks. We need more and better ones and again, in order for us to design and test and come up with new ideas. We are looking at an abundance of riches here and we need to develop a data infrastructure to handle, store, analyze, compare, very important, compare and disseminate large and complex data-sets. I think it was mentioned a couple of times that quality control and metadata standards are essential to assure democratization reuse of data. Many instances people have discussed the importance of developing new machine learning and artificial intelligence and approaches to assist us in our studies. From the hardware side, we have several technology needs. I've just put them into a few buckets. I think it's pretty clear we need new and or improved modalities for increased resolution and through both spatial and temporal, no other, these are new recording electrodes, new ways, new video monitoring techniques and modalities. Videos great, we're seeing a lot of great data from that but what are we missing? We pick up more for example, with high-speed video to get a more granular analysis of behaviors. What are we missing by using, in some cases, conventional video or there are other ways of monitoring behaviors besides video? There are a lot of photonics applications out there, infrared, lidar, your iPhone looks at you, what is it doing? It's processing a ton of information, it's not video. So there are a lot of applications there. I think a lot of cool new technologies that just haven't been fully leveraged in this space. Miniaturisation has come up, and not just in terms of size, but also in terms of energy consumption, especially when you're thinking about wearables, not their shoulder beautiful studies with the wearable in a human and the humongous backpack, you're not going to put that backpack on a ramp, so we need to think about these issues. As we get into wireless technologies, the energy consumption really does become a report and asked us bandwidth of getting not just energy in, but signal out. Very, very important, and this is the S in the BBQ or synchronization. We need to find ways to better integrate data from multiple modalities and synchronize them across the board, whether there are physiologic, behavioral or what have you. Then we've started to see closed-loop systems deployed in humans, and this involves on the fly processing, so all the above things will be required to develop better, closer systems for eventual application in humans. I just want us to consider a few things as next steps for the future. For you folks, as researchers in the field, but also on the part of the funders in the room. Most important thing is for us to talk to each other. This has been a great workshop, I regret that we couldn't do this in person because I imagine there would've been some really great discussions at the brakes and in the evenings at the bar and over dinner. But it's really important that we find complimentary areas of expertise in order to break down both technical as well as conceptual barriers that are keeping us from getting deeper into solving this really difficult problems. We should ask ourselves what new disciplines and players can we bring into the party to help us reinvent our own scientific ecosystem? Can we create a new field out of existing ones? Because just by bringing people in the heavy and they considered the topics that we've discussed over the last two days. This is a huge benefit to public private partnerships. This just came up a few minutes ago, and this little thing that I've put in here, I have to credit a Keith Yamamoto. He put this up at a talk I once went to where the combination, the partnership between academic institutions, non-profits, I forgot the aurochs, sorry, non-profits, org. Industry and government really leads to great innovation in New York's to gain than something. Very importantly, we need to consider the ethical legal societal impacts or LC issues at the outset, not afterwards. It really and the very beginning when we start thinking about the studies you want to conduct, we need to be thinking about the implications of who's going to benefit? What are the risks and costs? Why we're doing this? How can we justify doing experiments, whether it's an animal very critically, when it's in humans? Very critically, we need to consider who is in the room. Who is in the room will determine what questions are addressed and therefore, who stands to benefit, so let's not just count the very critical need to consider the diversity of perspectives on the part of people who were doing the work, and on the part of the people that are deciding what is being done. There was a bit of discussion about, given the enormity of the problem of understanding how neural circuits underlie behavior, is this a big science problem? Higgs boson was given as an example of entailing the efforts and were 5,000 scientists. That's a great question. What I pose to you is the following, one could think about standing up assembly line like factories and these are great for cranking out a ton of data. But you need a question in mind. You need to go online. It doesn't make sense just to throw thousands of people at a problem if you don't have a framework to start with. Another way of thinking about this, is the idea of establishing collaborative consortia, where we have smaller groups of people focused on specific problems, but with a common goal shared with others in the consortium. Where we can foster and share ideas. We can test them together, where the final output will be greater than the sum of the parts. I think there's a lot of space between individual labs, small labs, and these gigantic factory forming efforts. I was fortunate to be involved in the Brain Initiative Cell Census Network and one of the papers that we published together back in October had over 250 investigators, researchers on that. But it really was a coming together of multiple groups working together with a shared goal of trying to solve a larger problem where no one group was powerful as some of these groups might have been, could have done it on their own. The issue of assigning credit is a big one, is certainly a work in progress. It's going to take a paradigm shift not just on the part of grant reviewers, but actually on us. The enemy is us. It's the folks here that are in the academic and industrial spirit. It's you folks who are running the proposals, it's you folks who are reviewing grants and reviewing promotion cases and reviewing journal articles. Some of us we're covering academics and government we're also looking at ways of trying to assign credit where it's not quite as obvious as it might've been, say, 20 years ago. But I think there's a path forward. The great reward is we can all do a lot better science by collaborating and working together. Very, very importantly, this ties in to the importance of mentoring and promoting the next generation of leaders. The heart and soul of most labs is in the students and postdocs. These are the ones that we need to mentor very carefully, cultivate. Because these are the folks who are really going to be taking the fruits of our labor today and really making a huge impacts of tomorrow. I would just say stay tuned. Again, talk to each other. Hopefully if nothing else, some of the folks made some connections. Think about doing projects together you might not have otherwise before. There are a number of current funding opportunities not only a Brain initiative but elsewhere at NIH as well as NSF that you folks might find yourself well aligned to. Stay tuned for future of those coming out of the Brain Initiative space. Again, just going back to a point that I raised before that we have organized this symposium, this workshop in terms of human and organism or comparative research. But really, the overall goal is to have a lot of crosstalk between these groups because we stand a lot to learn from each other. So with that, I just want to thank everybody here, all the participants, for the great discussion, for talking about some really great ideas and great science and to the organizers who put together, a terrific workshop. I will stop here and turn it back over to Dana.

Holly Moore: Dana. Thank you.

Dana: Yes. Terrific. Thank you so much, John. How excited I've been about this effort in pushing this forward. This has been a terrific workshop. It has definitely given us at NIH, as well as our sister agencies some great information, rich information for us to go off on. What I also want to say is that we are really scratching the tip of this big question. We really see this as a workshop that is the large umbrella. We will have more focused efforts, workshops or working groups coming out of this as well. So please stay tuned. Again, thank you so much for your participation, and I hope you all have a wonderful day and have enjoyed the workshop as much as I have.