Workshop Report:
Translatability of Cognitive Readouts in HD
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MAJOR THEMES

1. To move toward successful clinical trials of HD therapies, it will be important to develop parallel measures (of cognitive or other processes) in humans, rodents, large animal models (such as pigs and sheep), and primates that are sensitive to the disease process and to interventions.
2. An understanding of the "constructs," or neural underpinnings, of a task or measurement would best guide the process. This will include a better understanding of the brain circuits involved in the processes.
3. The language defining the symptoms of HD as a "triad" of cognitive, motor, and emotional symptoms needs to be re-thought. Each of these is a catchall term for complex, multi-faceted, and inter-woven processes (working through brain circuits) that are incompletely understood in HD and even in the normal brain.
4. Likewise, the idea that HD deficits are restricted to frontal-striatal circuits is obsolete. The protein is expressed globally, and the brain is likely affected globally. As symptoms appear, they may result from a failure of compensation rather than a sign of "new" neural dysfunction.

THEME 1: Develop parallel measures in humans and animals

Anne Rosser was struck by the different requirements for various types of translation. The aspects of a task must translate between an animal and a human, but from a drug-discovery perspective, they must be sensitive to both disease process and to intervention. Deborah Harrington pointed out how important it is to be able to fulfill all these requirements. A test that's sensitive to the disease process in an animal might not be altered by an intervention, and would therefore not be useful to a clinical trial—particularly on the short time scale required for trials. Holly Moore suggested we develop tasks at two different levels. In a "developmental pod," tasks don't need to translate so directly between species. These tasks that won't be taken to the

clinic can still be very informative. But at another level, she and others recommend that we identify three tasks that absolutely measure the same processes in rodents, large animals, primates, and humans. These should touch on motor, cognitive, and affective or emotive aspects of HD (but see Theme 3). For each test, the task force (see Action Item 1) should agree about what construct is measured, what it tells us about the disease process, and whether it might be sensitive to a drug or intervention.

Steve Dunnett described some of the difficulties we face in designing tasks to measure cognitive or other neural processes in animals. "You have to adapt your test for the animal in a way that's specifically suitable to their environment," he said. For example, early cognition testing in pigs failed, because people weren't using tasks to properly engage the pig. In the 1960s, the work of Bob Baldwin determined that pigs could be successfully trained for these tasks. Rather than asking pigs to behave as humans or even rodents, he transformed behavioral tasks to focus on rooting in materials, and this thereby transformed what one can ask of a pig—which as an animal model has many advantages over rodents and primates. By designing tasks to properly engage your animal, one can discover much about the underlying cognitive systems required for a task in small as well as large animals.

In effect, the underlying cognitive processes, or neural constructs, are actually remarkably similar, but to reveal this, you need to design tests appropriate for that species. Tim Bussey agreed, and considers these elements in designing his touch screen tasks. For example, he might ask a rat to respond to a stimulus by sniffing at the screen, which the screen can record. Along the way, the rat also learns to take in and discriminate the visual aspects of stimuli as well. Dunnett agreed, saying, "Rodents live in an olfactory and whisker realm." Karen Bales urged researchers to "remember the animal" in developing tests and working with animal models. An animal's husbandry, social context, genetic background, housing during development, and natural history all affect how the animal might respond to a given task or an intervention. Common marmosets should be considered. They're small, but their lifespan is shorter so disease effects would come sooner, and they're more economical to house.

Holly Moore summed up the discussion from the animal's perspective: like us, they live in a world of opportunities, potentials, and contingencies. The best way to "break in" to the animal's world is to consider how they make contact with those contingencies. How does he find out whether something is beneficial or threatening? Rodents in particular "lead with the nose," whether using the olfactory or tactile modality. In primates, visual input may be more prescient. While animals might use a different initial approach—for example pigs using their snout and monkeys using their hand—you can design tasks that are actually quite similar across species. Dani Brunner and others pointed out the dangers inherent trying to take "some very human output and put it on animals," in that you may find an effect on an animal behavior that won't be meaningful in a human population or vice versa. For example, vocalizations in mice are not a meaningful measure when trying to affect behaviors in autistic children, because communication, not vocalization, is the deficit in autism.

Allan Tobin asked whether tasks that ask animals to use different sensory modalities could really be directly compared. Wouldn't the "labeled lines," or different sensory input circuits, create a very different task when presented through varying sensory experiences? Moore responded, "in some ways yes, and other ways no. A mouse's expectation might be that he's going to find something important with his nose, but meanwhile he's getting information through a visual

modality…even if that's not his initial expectation. You can't parse out the sensory streams so rigidly." Jared Young concurred with this assessment, saying, "although they differ in the way they come in," the important point is, "where do they converge, at which cognitive construct?" Daphna Shohamy also agreed. It's important to know what the animal is interested in, as a way to engage the animal, but it's "less critical to know how it gets in to the brain, and more important to see what happens with that information" once it's in the brain. Participants agreed that when examining neural circuits between rodents, large animals, primates, and humans, the convergence in circuitry is striking. Regardless of how organisms gather information, Shohamy said, species do converge, particularly in the fronto-striatal circuit.

Simon Brooks discussed at length his findings with cognitive tasks in HD mouse models, and the R6/1 mouse in particular. The mouse shows deficits in a test of implied learning, but not on that specific measure of the task. Instead, they showed more basic deficits that indicate a problem of attention and vigilance. The discussion led participants to the consensus that much can be learned from a complex task, even if it has little to do with the specific element the task was designed to measure. The important thing is to agree on what has been learned, and what might be the constructs of any emergent deficit in an animal model. Failures in clinical trials can be avoided, Moore said, if you understand why a particular deficit arose, and then one needs to design other tasks to measure that particular construct. Brooks also stressed how arduous it is to design and validate these complex tasks that measure a particular construct —upwards of 20 years, in some cases. Ralf Reilmann plans to develop a behavioral testing battery for transgenic minipigs. To this end, Reilmann intends to form an advisory board including some Workshop participants. He has begun training pigs in two very simple cognitive tasks.

Relevant tasks in human subjects

Participants who work extensively in the clinical testing domain—including Julie Stout, Sarah Queller, and Deborah Harrington—shared details about specific tasks that show sensitivity to HD, as well as some that were expected to show sensitivity but weren't as useful. They focused on tasks that show sensitivity, regardless of selectivity, for HD, and that had particularly big effects in "near-diagnosis" prodromal and early-diagnosed HD subjects in cross-sectional—not longitudinal—studies. The time-pressure component of many tasks emerged as a common element that reveals effects in HD. Without time pressure, HD subjects can accurately do tasks, and they perform more slowly with more complex tasks. Simon Brooks and other expressed that they hadn't appreciated how little time clinicians have to run tests on people. We can performs tests for hours on animals, but we need to bear in mind the time constraints when developing tests that may go to clinic.

The **University of Pennsylvania Smell Identification Test (UPSIT)** asks subjects to scratch and sniff an odor, and then choose the word that correctly matches the odor from four printed choices. Because of the multiple-choice design, the naming element implicit in the test does not confound results. As with many neurodegenerative diseases, the sense of smell seems to be affected early in HD. The modality of smell itself is the key component in this task. Brunner pointed out that the UPSIT and other tasks discussed are very standardized and widely used, which is an important factor.

Paced tapping requires subjects to use their internal control of timing, which seems to be affected in HD. An evenly paced series of tones gives the subject cues about the timing of the

taps they need to make on a button. They begin tapping with the tone and then use their own estimate of time to continue to tap at that same pace for 32 taps after the pacing tone has been silenced. Variability in tapping time is the instructive outcome. Harrington characterized this task as "excellent" for translation to animals, and it depends intensely on striatal activity. While it may seem like a motor task, it reveals more about internal timing control. Researchers have used a task called **time bisection** in animals to achieve the goal of measuring timing rather than motor aspects. Harrington is now studying a related time-discrimination task for use in pre-HD human subjects.

Speeded tapping is a related task, in which subjects hear a tone, they tap as fast as they can, and then another tone sounds 10 seconds later to indicate they should stop. This task shows very high sensitivity in HD and measures more of the motor component. Although simpler than paced tapping, speeded tapping was more sensitive in the quantitative motor assessments performed by Reilmann's team in the TRACK-HD study – both cross-sectional and longitudinal – delivering the only non-imaging measure that detected progression in all subgroups of TRACK-HD, including the preHD-A group.

Trails A and B work much like a child's dot-to-dot puzzle. In Trails A, numbered dots are scattered on a page and need to be sequentially connected. Trails B is slightly more complex; it has numbers and letters interspersed on the page, which need to be connected alternately and sequentially, e.g., 1-a-2-b, etc. Trails B is slightly more sensitive than Trails A, and both are timed.

The **Stroop Task** measures interference and inhibition abilities. There are three conditions to the task: a word shown in black font says "blue" or "red," and subjects have to read the words. The second condition asks subjects to simply name the color of a color patch on the page. In the third condition, called the interference condition, subjects are presented with a list of words that name colors, but the word is printed in a different color. Rather than reading the word, subjects must name the color of the ink. Each condition asks subjects to name the words or colors as fast as possible for 45 seconds. This third condition is thought to measure executive function and had been predicted to be sensitive to HD. It's not very sensitive in premanifest HD, however, and is not the most sensitive of the three conditions. Surprisingly, bigger effects emerged from the first two conditions, which are psychomotor tasks.

The **Symbol-Digit Task** provides subjects with a key at the top of the page, in which each symbol is paired with a number. [E.g., a=1, b=2, c =3 with a, b, c being abstract, meaningless symbols.] Subjects are asked to refer to a key at the top of the page that indicates symbol-digit 'translations' and to translate the symbols into their corresponding digits for the remaining symbols on the page. They must fill the numbers in order they're presented. People who perform well on the task use memory rather than constantly looking back and forth at the key. The task contains an associated-pairs learning element as well as a visual scanning component among others.

A large effect size also emerged in a **Map Search Task**. Subjects are presented with a map on which various icons are scattered about, and they're instructed to circle all the gas stations icons, for example. The icons are embedded in a cluttered display of other map elements and don't appear in orderly rows.

Emotion Recognition Tasks reveal effects in HD. Here, subjects see a face on a screen and they're presented with seven emotional descriptor words (disgust, fear, happy, sad, anger, surprise and neutral). This multiple-choice task asks them to match the word to the face's emotion. Although this task has worked in revealing HD effects, it has limitations. Stout and others agreed that this area needs to be further explored, perhaps using improvements over the current Eckman series of faces, like the Cantab computer-generated faces, in which emotion can be dialed up or down. This task is not timed.

The **Verbal Fluency Task** asks subjects to generate as many words as possible that start with a certain letter in a certain time period. In the **Hopkins Verbal Learning Test – Revised**, a similar verbal learning test that differs between HD and healthy subjects, subjects are read a list of words and are asked immediately recall the words on the list and then are asked again twenty minutes to recall the words on the list. Immediate recall is more sensitive than delayed recall in premanifest and early HD, so the test reveals more about affected retrieval mechanisms in HD than about memory per se.

The **Spot-the-Change** task tests working memory, and it might also be sensitive to visuospatial circuits in the posterior cortex. The subject sees squares of colors on a screen; that image is replaced by an identical image in which one particular square has either changed color or not changed. The square in question is circled, and the subject has to report whether or not it changed color. There's no variability in timing, and no distracter of another square that has changed color.

The circle tracing task is a **motor planning task** that asks subjects to trace an annulus presented on a screen, as fast as possible, with the display of their progress visible either on the screen being traced or on a 2nd screen while the tracing hand is blocked from view. There are three 45-second trials in each of the 2 conditions. The most sensitive measures are the amount of time spent inside the annulus or the amount of ink laid within the annulus. Late premanifest and early HD subjects perform worse than healthy controls. Longitudinal follow-up reveals that Circle Tracing performance improves in controls to a larger extent than in HD and this is a rather different finding that more decline in HD than in controls over time.

Harrington described another task that requires planning called "**Buttons.**" On a touch screen, subjects view two rows of 12 buttons each. As the buttons light up, the subject is asked to push them. As the task progresses, it becomes more difficult, because the buttons light up more rapidly, thereby providing more advance cueing of the response locations. Subjects have to be able to remember and make use of the advance cueing without errors. The task is sensitive in both cross-sectional and longitudinal studies of pre-HD.

Brunner described her findings with the R6/2 and Q175 mice in various tasks. The go-no go task shows a deficit in the HD model mice, as do some other tasks that suggest a deficit in reversal learning. She described some of the findings as suggesting the mice perseverate, although the term perseverate can be defined in several different ways. Brooks said that his results in various mouse models of HD do not suggest perseveration. "Inertia" might be a good description of some of the deficits seen in HD animals, which also matches well with some findings in human HD and PD patients. Bussey has already seen species translation in one touch-screen paired-associate learning task. The task was "profoundly impaired" in R6/1 mice and in pre-manifest HD humans. He feels optimistic that tasks can be identified and used in multiple species.

Graham Williams and Stacy Castner described some of the tasks that could potentially be used in monkeys. Reaching for an object presents the most technically simple task design, but touch screen and even occulomotor tasks can be used for more sophisticated questions. Castner suggested developing a spot-change task on a touch screen like that used with HD patients that could be used in monkeys.

Finally, Ken Serbin urged participants to be aware of the different psychological elements of testing for patients vs. animals. HD gene-positive subjects have a very conscious incentive to perform well (to prove they're not symptomatic) whereas animals might have more of a rote practice effect from performing tasks repeatedly.

THEME 2: Identify the neural processes underlying tasks affected by HD.

Brunner and others noted that, once the construct of a task is understood, it could be tied to real neuropathology. The best approach to better understanding the neural underpinnings of a task may be to identify biomarkers or surrogate measures in parallel with testing—such as imaging—that can be used in animals and people. This parallel approach is now possible in behaving animals. The aim is actually different from the goal of identifying biomarkers of HD in general, although biomarkers of cognitive tasks could inform the overall search for biomarkers of HD. In order to be useful to a clinical trial, a test must be sensitive to both disease process and to intervention. Knowing at least some of the neural substrates of the processes employed by a particular task will be greatly informative. It might also prevent mysterious negative results; if a task measures a process not affected by HD, task performance won't be affected. Harrington suggested that diffusion tensor imaging (DTI) and tractography might provide additional insights, especially when combined with functional imaging (e.g., fMRI, EEG, MEG, PET), because one should consider whether functional changes might be related to microstructural changes in white matter. Disease-modifying and symptomatic therapies will have different requirements in terms of development and assessment; they should be pursued in parallel. By understanding the constructs, the best tasks can be chosen for the application.

Karen Bales explained the difference between homology and analogy. Analogous structures might look and even function in similar ways but have come from drastically different evolutionary lineages, for example fins in fish and flukes in whales. Homologous structures or behaviors in contrast also share a common evolutionary background, whether or not they perform the same function, for example the flipper of a dolphin and the human arm. In animals used as disease models, phenomena that may look the same may have different evolutionary backgrounds.

Jared Young outlined the main types of validity to consider in comparing human and animal models. **Face validity** describes a phenomenon or behavior that simply looks in an animal model like it does in a human; for example, an HD mouse and human both develop chorea. Face validity is the least rigorous from of validity, because it refers to the surface appearance, regardless of its underpinnings. Young pointed out, "if it walks like a duck and quacks like a duck, it might be a platypus." Face validity of a model is "a place to start, not to hang your hat on."

Construct validity takes into account the neurobiological underpinnings of a behavior or phenomenon. For example, reversal learning, the process of learning something new once you've already learned something, depends on the orbitofrontal cortex in humans, rodents, and nonhuman primates. The requirement for a common structure means it has some degree of construct validity, but that doesn't necessarily mean the learning process also shares the same neurotransmitter signaling, just the same brain structure. So there are different levels of construct validity. This becomes an important consideration in drug development, because even if a process occurs in the same structure, if a molecular drug target (like a neurotransmitter receptor) doesn't underlie the process in both species, it won't hold up.

Perhaps the primary goal in therapeutic development is **predictive validity**: If a drug has an effect in an animal model, it should have the same effect in humans. Similarly, a cognitive or other measure can have predictive validity: if one changes the parameters of a test in a way that produces certain performance outcomes, it should affect the animal and human in the same way. However, predictive validity can occur without construct validity. For example, scopolamine treatment changes animal and human behaviors in similar ways, but the neural underpinnings are not necessarily shared. Ideally, one should strive for both predictive and construct validity—even if one comes before the other—and let face validity fall by the wayside.

Finally, **etiological validity** should be considered in HD. At least on the surface, animal models and humans share the same etiology of disease—an elevated number of CAG repeats in the huntingtin gene. The etiological validity of HD models can be greatly improved by using animals with a physiologically relevant number of CAG repeats rather than the much higher number in currently used models.

Participants discussed the ways that the various forms of validity can be applied to the search for HD therapies. Drugs or therapies can be developed or discovered in two main ways: serendipitously, in which there was no prior knowledge of the construct underlying drug action, and rationally, in which a drug is designed based on its construct. Beth B pointed out that the vast majority of drug successes have come from serendipitous discovery, which might suggest that there is no point in trying to understand construct validity a priori. Brunner brought up another example in which a drug was developed entirely built on the construct of understanding the way ribosomes process RNA, in which the ribosome was "fooled" into ignoring a mutant RNA. Hugo Geerts pointed out that a drug could fail for two reasons: (1) it doesn't engage the target, or (2) it does, and the target fails in the sense that no emergent properties arise in the circuit—it has no effect. Participants agreed that therapeutics should be developed from both directions. Clinical observations of humans might be as valuable as molecular, hypothesis-driven drug development, and in fact can be used for reverse translation to guide rational design. For example, imaging studies of people with HD might guide us to what properties might emerge from drug interventions.

Brunner crystallized the situation facing CHDI and others in the search for HD therapies. If you're after a disease-modifying therapy, then the target is genetic. In that case, the construct of individual measures or phenomena matters very little, because you know you're targeting the disease etiology: mutant huntingtin. (However, construct might matter even for mHTT-lowering strategies in terms of where within the brain to target the therapy, for example.) If you're pursuing a symptomatic therapy, construct becomes very important, and rational, molecularly targeted drug therapy is a likely path to success. We should not be deterred by the lack of

success in this realm for neurological disorders, because it's early days in drug development for such conditions.

In discussing the animal models, David Howland raised the common point that "all models are wrong; some are useful." About 99% of all work in animal models has been done with high CAG repeat numbers, which means they don't have good etiological validity (aside from a basic disruption of *Htt*). These models, however, can be informative. Although the animals don't have HD, they act as "amplifiers" of some aspects of HD. Ethan Signer pointed out, though, that an amplifier is only instructive if it amplifies a signal at the right frequency—that is, an effect of HD that is present in human disease. Primate models with a human disease-like CAG repeat number (around 40) are not yet technically possible to make. Rodent models with lower CAG numbers are available, but are so far "grossly under-studied." Closer examination of these animals, with imaging, electrophysiology, and perhaps sensitive behavioral tests, might reveal disease-sensitive processes within the animal's lifespan.

THEME 3: Redefine the "triad" of HD symptoms (motor, cognitive, and affective)

Neither tasks nor symptoms should be parsed out according to rigid categories. Geerts believes that a way toward a therapy may be to look at circuit phenotypes and to attempt to reverse them with multi-target pharmacology. This "tall order" will rely heavily on what you can learn about the circuits in preclinical models and in humans. This effort is progressing as more refined iterations of Quantitative Systems Pharmacology with regard to CNS diseases that rely on the simulation of a humanized environments are becoming available. Jared Young noted that three years ago he thought that HD would best be assessed with very complicated tasks in animals such as the intradimensional/ extradimensional set-shift task (ID/ED), but now he realizes that tests of executive function are likely not the way to go for HD. Simpler processes are affected in HD, which speaks to the inter-relatedness of the three "domains" commonly assigned to HD. For example, the early deficits seen in emotion recognition and other affective aspects of HD provide powerful tools. Simon Brooks said that HD meetings often focus on non-specific motor functions, but here he saw a focus on very disease-specific processes. In trying to understand this underlying circuitry, Queller suggested that we "work backward" from the large body of behavioral and clinical observations in parallel with the molecular approaches that mainly rely on animal work. Similarly, she responded to the question, "What can we learn from one (transgenic) monkey?" You can learn when you see disease-relevant behaviors; in other words, symptoms or deficits seen in a few HD patients or a few monkeys might indicate areas that would be fruitful for further thought and exploration. However, a lack of symptoms or test sensitivity in a single patient or a single monkey is just not informative. There is always some level of overlap in performance levels of HD subjects and healthy control subjects and only properly powered studies can provide us with a reasonable level of confidence that a task in insensitive or a symptom is absent in the HD monkey population. Graham Williams pointed out that the "timing" aspects of tasks and of neural processing that are affected in HD and in the models might suggest a cortico-cortical processing or synchronization deficit.

Serbin shared his experiences as someone who has tested positive for HD but is not yet symptomatic. Serbin's mother was diagnosed with HD after her chorea manifested around age 52, but in retrospect, other aspects of HD affected her several years earlier. As a bank teller, Mrs.

Serbin would have trouble balancing her accounts, which might suggest cognitive or executive functional deficits. But more striking were the emotional difficulties that came with that. She would be upset and even inconsolable in response to her perceived failings at work. Similar to many patients' experience, the Serbins found that the cognitive and emotional changes were far more difficult to cope with compared to the chorea. As a clinician, Reilmann concurred that patients face many challenges, the least of which is chorea. "Bring on the chorea," said Serbin, "just don't mess with my brain." A further consideration in treating the symptoms of HD—including chorea, depression, and anxiety—is that the medications can introduce further cognitive and affective symptoms. Eventually, Serbin's mother couldn't care for herself and required help with grooming, bathing, and feeding; "she acted very childlike," said Serbin. It's hard to separate the psychological and affective changes from the cognitive, because the mix ultimately results in a loss of function. "She became a mere shadow of herself." Serbin described a common saying in the HD community: the disease results in two deaths. First, there's the loss of the person you once were, which tragically happens in the prime of life. Perhaps many years later, the final, real death occurs.

Serbin also described HD as "the devil of all diseases," not only for what it does to the patient but in the way it affects entire families across generations. There are significant psychological considerations when thinking about the way people are affected by HD. When a parent tests positive for HD, their children are faced not only with the diagnosis of their parent but also with their own potential disease. The decision to openly discuss the disease and its genetic nature, the decision to get tested, and to test one's children (or have children) can all weigh heavily on family members. The frightening and stressful nature of these decisions and realities in themselves might affect one's cognitive and affective behaviors. Reilmann shared his perception that patients with access to an experienced HD clinician and to more information, perhaps at an HD-specific center, find it easier to face testing. Patients often find they are relieved to have diagnosis and a clear understanding of what's happening. Serbin agreed that this free exchange of information and becoming part of an HD social network is "part of providing hope...and getting people out of the woods when they're still in denial." Allan Tobin related a moving moment in a previous workshop shared by an HD family. A woman whose husband had tested positive for HD expressed her relief, because she thought his behaviors arose "because he didn't love me."

By re-thinking the "triad" of HD symptoms, we also face the opportunity to examine the constructs of some of the processes and properties that emerge from HD. For example, although the disease was long thought of as "striatal," this view no longer holds true. Holly Moore suggested that we consider the rich neuroanatomical literature as we learn more about the brain-wide effects of the disease. Deborah Harrington pointed out that the striatum has abundant connections to prefrontal cortical (PFC) areas, but that other areas of inter-connectivity need to be considered in HD. The striatum and basal ganglia structures are also highly connected with posterior cortical areas, the hippocampus, and even the cerebellum. In human healthy subjects, functional imaging is now being used to understand the vital element of connectivity. Cognition depends on active circuits, not just on isolated, regional activation. In preclinical HD, many posterior cortical areas show changes, which play a role in white-matter function and in multisensory integration. Some morphometric analyses show that the biggest changes—like cortical thinning—occur in occipital-parietal areas in prodromal HD patients.

Shohamy shared her insights from working in the field of Parkinson's disease (PD) and its parallels to HD. Like HD, in the last ten years there has been a major shift in viewing PD as a psychomotor and emotional disease rather than a strictly—or even primarily—motor problem. The conclusion from the field when trying to differentiate cognitive from motor deficits is that "it doesn't make sense to distinguish them," and that the striatum plays an important role in their integration. One way that she and others have examined the deficits in PD is by using tasks that measure motivation for obtaining rewards and avoiding losses—processes that can now be differentiated with specific tasks. Many of the tasks lend themselves to animal research with measures of approach and avoidance, and even optogenetics research has provided valuable information across species. Some experimental results in PD subjects in tasks on or off their L-Dopa medications –and in animals using optogenetics—suggest that tasks can differentiate the direct from indirect dopaminergic pathways.

THEME 4: Consider the global nature of HD and the possibility of compensatory vs. primary deficits.

Mutant huntingtin (mHtt) is expressed in every cell from conception until death.
HD pathology does not originate in the striatum, although the symptoms appear in a way that might suggest that. Queller characterized HD pathology as a needle in a haystack, which will be crucial to find in order to normalize. Ethan Signer reminded us that HD has a long prodromal period, during which you don't have any information about pathology, even though something is happening. It's possible that symptoms finally arise as failures in compensation. What's the compensation that's allowing the disease signs not to show up, and how does it become compromised?
Castner and Brunner raised the issue that because of the long premanifest period, HD arises in a middle-aged brain, where certain processes are already declining (and which we know very little about). It may be better to work in monkeys and rodents of an age that approximates a 40-year-old human rather than a young adult.

Signer posed this question: How can a cell express mHtt for decades and then suddenly fail after 40 or 50 years? One possibility is that mHtt introduces a mild insult that gets worse and worse until it reaches a threshold. A second possibility is that the insult is constant rather than cumulative, but that compensation is changing. Concomitant with aging, the proteostasis network tends to decrease in efficacy over time. That is, the network that protects chaperone proteins and monitors protein production declines with age, so more errors and failures occur. From that perspective, HD might not be a cumulative insult but rather a progressive failure of compensation. There may be a third possibility, but the compensation issue must be held in mind.

Beth Borowsky and others emphasized the need for caution in what we try to correct therapeutically in HD. An anomaly that arises in HD patients might reflect not a primary defect but perhaps the last compensatory change that's keeping that patient functional, which would be the last thing you want to target for change. Serbin also brought up the issue of "decompensation." HD patients often undergo drastic changes in disease course—for better or worse—after significant life or health events, such as a car accident, surgery, or severe stress. Serbin and others in the community are wary of these events because of their possible ramifications. In addition, within the human HD population, there is tremendous heterogeneity

in terms of genetics, development and experience, which can all affect the course of disease and the response to any particular treatment.

Another compensatory issue to consider, particularly when envisioning clinical trials of therapies, is the other medications that HD patients might be taking, for motor, cognitive or affective issues. For example, a cognitive-enhancing drug might fail in trials if all the patients were concurrently—and even chronically—taking antidepressants. Long-term use of some meds prescribed for HD might lead to neuroplastic changes in the brain on top of disease compensation.

ACTION ITEMS

1. Create working group or task force with a subset of CHDI and Workshop participants (with both clinical and preclinical expertise) to "pave a road to translation."
2. Identify three tasks that can effectively and reliably be used in multiple species. CHDI is working with Julie Stout and Sarah Tabrizi to develop new tasks, and these might provide a valuable resource in this aim.
3. Identify the "gaps" in our assessment of HD outcomes. PREDICT HD now includes a pilot study of a three-hour battery to investigate these "gap" areas, according to Harrington.
4. In order to really understand what a given task measures, Young suggested one become a test subject in every test given to human subjects. This might help in designing counterparts for animals. This could be a job for task-force members.

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Tim Bussey	University of Cambridge
Stacy Castner	Yale University
Steve Dunnett	Cardiff University
Hugo Geerts	In Silico Biosciences
Deborah Harrington	University of California, San Diego
Dan Hutcheson	Maccine
Holly Moore	Columbia University
Sarah Queller	Queller Consulting
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Anne Rosser	Cardiff University
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Beth Borowsky	CHDI
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