



## Turning off stress at the spigot

**S**tress is such a common denominator in depression. Look at any large study of those who had it that aims to uncover a cause for the disease: Whatever the age, race or socioeconomic-whatnot of the group under study, chronic stress is there with its persistent little companion, the molecule cortisol, bathing vulnerable parts of the brain.

While no one doubts that genes can raise the chance of depression—some 40 percent of risk is genetic—we think that “most vulnerability to depression isn’t accounted for by genetic inheritance,” says **Jimmy Potash**, who directs research for Hopkins’ Mood Disorders Center. “And a large body of evidence figures stress into the remaining 60 percent. Stress and genetic vulnerability somehow interact to promote depression.”

It’s the “somehow” that Potash, **Richard Lee** and their team want to define.

In a study recently published in *Endocrinology*, they focused on the HPA axis, the trio of hypothalamus, pituitary and adrenal glands that together manage the body’s stress response. Specifically, the researchers analyzed the structure and workings of five genes known to affect the HPA axis. All five have some tie to the hormone cortisol, an HPA by-product.

Cortisol is typically secreted much as a good mother spoons out cough syrup—sparingly and only when needed. Then it’s useful and crucial in mobilizing the body for fight or flight. But chronic, high levels of the steroid deliver unwanted effects, including anxiety,

depression, irritability and insomnia. And the research’s results suggest how.

In the study, test mice drank the rodent-equivalent of cortisol in their drinking water for a month, then recovered for another. The researchers observed the animals for behavioral and physiological changes. But equally important, Potash analyzed DNA in the five test genes, sampling them from the animals’ white blood cells as well as select brain regions, including the hypothalamus. He’d hoped to see epigenetic changes in the DNA. And in one of the genes, he found them.

Epigenetic changes can decide whether a gene gets expressed or not. As the name implies, they’re “above” genetics; they come about through a cell’s environment. The most common such change bonds methyl chemical groups—or *marks*—onto DNA. The effect is like using the Tab key in a Word document: Marked parts of the DNA are passed over when a gene’s code is translated into cell action.

Potash made two important finds. First, he found fewer marks than usual in the *Fkpb5* gene of the mice with the “spiked” water. Tampering with *Fkpb5* would likely increase cortisol levels even more.

Moreover, the marks persisted weeks after the mice stopped getting the added hormone, suggesting the changes might last. “This gets at a role that epigenetics could play in psy-



Jimmy Potash sees stress effects with an epigeneticist’s eye.

chiatric disease,” Potash says.

Epigenetic marks added through life experience, he explains, may ready animals for future events. “They might prepare you to fight harder or flee faster the next time you’re up against something stressful.” But helpful as those behaviors were in earlier times, they aren’t that way today. “You can’t fight or flee modern stressors like work deadlines. Consequently,” he says, “the chronic cortisol release that epigenetic changes trigger might lead to depression or other mood disorders.”

The idea, though, is that possibly in the near future, doctors will be able to profile epigenetic changes in a patient’s blood cell DNA and then use drugs to add or subtract marks as needed. It’d be tailoring cures from within. ■

For information: 443-287-4135.

## Imaging that will open the brain

Neuroscientist **Christopher Ross** casually offered his brain to science this summer, submitting to several MRI scans, each reflecting a nuance of the structural or functional imaging offered by the new high-powered, 7 tesla scanner installed nearby at the Kennedy Krieger Institute’s Kirby Imaging Center. Ross’s images are part of pilot work to establish ways to assess healthy brain as a baseline for comparing with patients with psychiatric diseases.

The new scanner’s magnetic-field strength leaves earlier 1.5 or 3.0 tesla (the standard unit) versions in the dust. “You can actually feel the force field if you walk by,” says Ross. “But what’s remarkable,” he adds, “is the high resolution that results. You can see every little fold of the cortex so an image looks almost like living brain.”

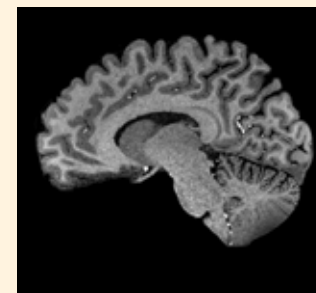
For Ross, who’s done seminal work in Huntington’s disease (HD), an immediate use is clear. With colleagues in Hopkins Psychiatry, Radiology and at Kennedy Krieger, he’ll more accurately describe brain changes in the caudate nucleus, the cerebral cortex and other areas affected in presymptomatic HD patients. The 7T could pick up early structural shifts deeper in the brain, metabolic changes and even differences in specific biochemicals that signal a downhill path—all useful HD biomarkers to track how the disease progresses and, ideally, the benefits of potential therapy.

“But the 7T will be even more useful, we suspect, for depression, schizophrenia and bipolar disorder where the brain changes can be more subtle. “The 7T,” he adds, “puts us at the forefront of imaging.” ■



### See Chris Ross.

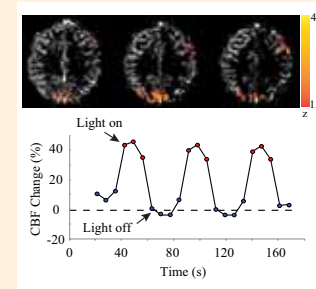
Christopher Ross directs Psychiatry’s division of neurobiology.



Craig Jones

### See Chris Ross’s brain.

Ross’s MRI scan adds to other healthy controls, providing a needed comparison for clinical studies.



Manus Donahue/Jun Hua

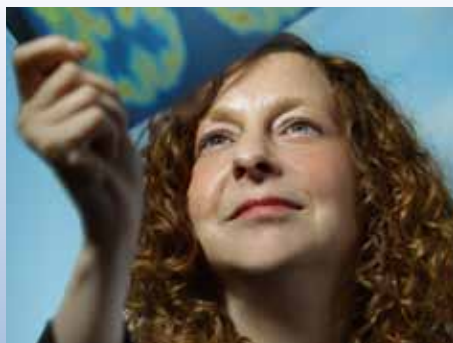
### Look, Chris, look.

Subtle shifts in brain blood flow reflect changes in brain activity as Ross views a flashing light.

### A Deep Prod for Alzheimers

Could DBS right the brain?

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### Save the Synapses

Why a shift to study a common schizophrenia path makes sense

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# DBS for Alzheimer's

*A turnaround in metabolism seems to be real. But will it do any good?*

Deep brain stimulation can ease chronic pain as well as troubling symptoms of Parkinson's disease. More recently, the technique has lifted the dark cloud of intractable depression in some patients in clinical trials. But now another use is flirting with possibility. Last summer, with a new pilot study, a research team that included Hopkins neuropsychologist **Gwenn Smith** raised the idea of using DBS early in Alzheimer's disease.

It was a small trial but an intriguing one, especially given the lack of good therapy for an illness poised over baby boomers like a tidal wave.

In the study, surgeons implanted a fine electrode able to deliver a low-grade electrical pulse close to the fornix, a key nerve tract in brain memory circuits. The researchers—most with the University of Toronto—reported few side effects in the six patients they tested. But more interesting, says Smith, was seeing DBS reverse a downturn in brain metabolism that typically comes with Alzheimer's.

DBS has been thought of for dementias—which, like Parkinson's disease, are not

only localized in the brain but likely engage larger brain circuitry. But what actually sparked the research was unusual: It began with a very obese man in Toronto who'd joined a trial of DBS for an eating pathology.\* The stimulation did him no harm but, unexpectedly, his verbal memory, as measured by standard tests, jumped significantly. Inspired, the scientists held on for two years of rigorous ethical and scientific approval and patient recruitment before an Alzheimer's phase I safety study could begin.

Smith was brought in because of her expertise in mapping the brain's glucose metabolism in aging and psychiatric disease. It was Smith's earlier analysis of Alzheimer's patients' PET scans that revealed their distinct pattern of lowered brain metabolism. The hippocampus, where Alzheimer's earliest pathology surfaces, and specific parts of the temporal and parietal cerebral cortex—memory network areas—became increasingly sluggish with time.

In the DBS trial, checking glucose metabolism would give an extra measure that participants weren't harmed. But, even better, the opposite seemed true. "To our surprise,



Gwenn Smith caught a move toward more normal metabolism in Alzheimer's.

we found a striking increase in metabolism in those areas implicated in Alzheimer's disease," says Smith.

Interestingly, areas that improved with DBS are sites where the illness's hallmark amyloid protein collects.

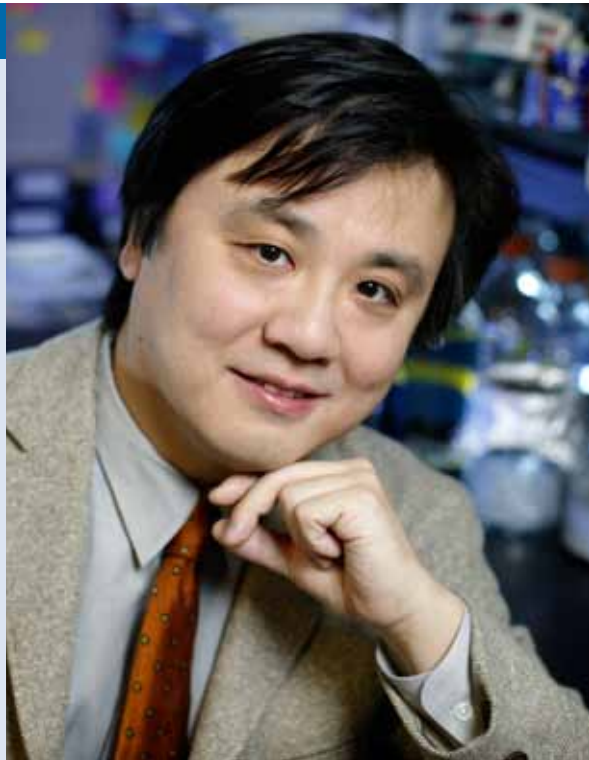
That's not to say that DBS cures or even

slows Alzheimer's disease. "If, in step with what we'd found, patients definitely improved in the cognitive tests that they took, or at least didn't lose ground," she says, "then we could say we'd slowed the progression of Alzheimer's." But in a trial designed to measure safety, easing cognitive loss is hard to show. Still, that loss appeared to slow in one or two in the study, team members say, as did the slump in quality of life.

What this means is that more study is called for. And Hopkins colleagues agree. Says Smith: "We're moving forward with a follow-up trial." ■

For information: 410-550-8696

\*Andres Lozano, the principal investigator in both studies, is known for his novel explorations of DBS. All studies have been carefully examined by ethical and scientific review boards.



Akira Sawa's focusing new effort on a brain pathway gone awry in schizophrenia, bipolar disorder and major depression.

The brain undergoes a massive overhaul in late adolescence—something that developmental biologists have long known and that teenagers, fortunately, can't feel. In the late teens, there's a grand pruning of "disposable" synapses, while Nature reinforces those she wants to keep.

The fact that schizophrenia symptoms surface at that same time of life has struck neuroscientists as no coincidence. Since the early 1990s, the idea's been around that what trips the disease's onset may be an overzealous reorganizing of critical synapses. And now, as better techniques add support to schizophrenia-as-a-synaptic-sickness, signs point to a revolution in the field.

INSIGHTS: AKIRA SAWA

## Schizophrenia: War to save the synapses

We've asked psychiatrist/neuroscientist **Akira Sawa**, a key figure in the field, for some perspective. He also explains his thoughts—they approach optimism—that the brain might be salvaged from schizophrenia's worst effects.

**Q. There's good evidence that both genes and environmental insults are at work in schizophrenia (SZ). And you've looked most, so far, at genes' effects.**

A. Yes. Though risk genes likely disturb how the brain develops in utero and just after birth, the minor abnormalities they create continue as the cortex ages. We think it possible, for example, that in the *prodromal* stage—before SZ's full-blown onset—the very mild signs that people first show reflect an increasingly disturbed brain also undergoing natural synaptic remodeling. It's not hard to believe such abnormal structure can then change a person's thoughts and behavior!

**Q. Many of your studies focus on DISC1—a mutant gene that did all but blow a trumpet to announce itself a decade ago as raising risk of the disease in a Scottish family. You've found firsthand how far-reaching that gene's effects are.**

A. DISC1 is far more important than we first realized. It plays a part in early growth of neurons, how they migrate in the brain, in the connections they make. Our lab has been following one DISC1 pathway, for example, that ends

in forming synaptic spines important to learning and memory.

**Q. You have a roadmap for your coming research with DISC1, but it looks more like a battle plan for you and Hopkins colleagues. War on schizophrenia.**

A. I'm not married to DISC1. There are other genes too. But for now, it makes an excellent system to follow. We think at least four developmental pathways—birth through young adulthood—are differently touched by mutant DISC1. Someone needs to map each one; see what happens, see where it's vulnerable to injury and, perhaps, to being made right.

**Q. And then?**

A. Ah. The most exciting part. Our lab believes those abnormal developmental routes merge to disturb a common pathway—one where glutamate-based conversations take place between inhibitory and excitatory neurons. It's also the path most affected just before the onset of symptoms.

**Q. Isn't it also the target of PCP, the street drug that can make users psychotic and show other symptoms of schizophrenia?**

A. Yes. Changes in this common path, we think, create the synaptic problems that underlie schizophrenia's disordered behavior. And even slight adjustments to the path, with drugs, might offset the worst of the disease. Right now, we're studying an agent in lab cultures that appears to right some of the wrongs. ■

## Our variety's showing: A sampler of new work



### When Miss Daisy changes lanes

Lane-changing is one of the most dangerous maneuvers in ordinary driving; more than 250,000 U.S. road accidents occur yearly from errors in what looks like a simple move-over.

For drivers of any age, not paying enough attention sets them up for trouble. But cognitive neuropsychologist **Cynthia Munro** was interested specifically in seniors. She and collaborators studied more than a thousand drivers over age 67 who participated in a Maryland longitudinal study of vision, cognition, mood and driving.

Car monitors tracked their driving performance. And, as well as measures of mood, visual acuity and field perception, the researchers gave drivers cognitive tests, including the Mini-Mental State Exam (for overall cognition), the Brief Test of Attention and the Beery-Buktenicka Test of Visual-Motor Integration (for auditory attention and visual perception).

What was most important? Surprisingly, not the drivers' state of stress or their overall cognitive function. Safe lane-changing apparently mostly lies in the ability to apply what your visual perception tells you (visuoconstruction) and—surprisingly—in your auditory attentiveness. For information: 410-614-7785.

### A “benzo” without drawbacks?

When benzodiazepines like Librium or Valium came out in the 1960s, they seemed nothing short of heaven-sent for anxiety: They worked—quickly—were well-tolerated and overdose wasn't a particular worry. Yet their downside in having a high potential for abuse and dependence not only marked them as a controlled substance but, after two decades, made physicians wary. So the search has been on for an agent with benzodiazepines' calming effect but fewer or no drawbacks. In a recent issue of *The Journal of Pharmacology and Experimental Therapeutics*, **Nancy Ator** and colleagues reported primate-testing TPA023—a compound more selective in the subtypes of GABA receptors it stimulates than prescribed benzodiazepines. Not only did the drug appear non-addictive, but the animals could ease off it with only a shadow of withdrawal. “This warrants more study,” says Ator. For information: 410-550-2773.

### Heart risk: Not just depression

Pointing out the tie between depression and cardiovascular disease has been much in the news lately. And a few studies say it's not just depression that raises the risk of circulatory troubles: Some suggest a similar link with bipolar disorder. But if the latter's true, asks psychiatrist **Hochang Lee**, is it because of the depression that bipolar patients suffer? The mania? Both? Neither?

For answers, Lee used the same large, ongoing survey of Baltimore residents that Hopkins colleagues analyzed for the earlier depression-alone work—the Baltimore Epidemiologic Catchment Area Follow-up Study. His team noted incidence of heart attacks or congestive heart failure in those with a history of mania or hypomania, those who'd had major depression alone or those with neither. The result? Having mood highs also appears linked with risk to the heart—possibly more than major depression. E-mail: [Hochang@jhmi.edu](mailto:Hochang@jhmi.edu)

### Drugs and dicey decisions

Should I have unprotected sex or use a condom? When some people make that decision, they show a thought process not so different from one food-foraging animals use, explains behavioral psychologist **Matthew Johnson**. He's been studying decision-making in the cocaine-addicted—a group with high HIV rates. In the pattern, *hyperbolic delay discounting*, waiting for a distant but preferable option gets harder the closer you are to a tempting but less-beneficial one. When temptation draws near, you're more likely to jettison your resolve to wait. But this animal-like way of deciding, which cocaine-users can adopt to “a drastic degree,” means sabotage for responsible sex practices says Johnson. He's the first to apply decision studies to sexual behavior in people dependent on cocaine; his insights could help tailor education to prevent HIV. E-mail: [mwj@jhu.edu](mailto:mwj@jhu.edu)

### Giving the brain a different buzz

Transcranial magnetic stimulation (TMS) is already proving itself in Hopkins' new clinic for patients with resistant depression. But now another noninvasive way to deliver therapy for that disorder and other specific psychiatric illness is showing potential, though it's still on the workbench. Transcranial *direct current* stimulation (tDCS) employs weak electrical energy, rather than magnetic, applied to the scalp via electrodes. “We think tDCS works by altering the resting potential of large numbers of brain neurons,” says **David Schretlen**, who partnered with **Tracy Vannorsdall** to study the technique.

Unlike TMS, tDCS doesn't directly prompt neurons' firing, but shifts their excitability up or down, depending on the polarity of the current and where it's placed. The resulting brain changes aren't tightly focused but are likely broader in effect.

The research group—it's headed by Neurology's Barry Gordon—is using tDCS to explore the basics of language production. The hint that it improves types of verbal fluency in healthy adults is prompting studies in patients with autism or post-stroke speech loss. For information: 410-955-3268.



### Catastrophizers: A way out is delayed

People with chronic pain know intuitively that distractions are a help. And science at Hopkins and elsewhere backs this up. In experiments that mete out some surface skin pain to healthy volunteers—often via capsaicin, the chili pepper molecule—distracting mental tasks can bring significant relief. The analgesia also holds for patients in chronic pain. Further, brain imaging shows there's an underlying biology to distraction; it may tap the body's native opioid system.

But Psychiatry's Claudia Campbell has found that personality can add a layer of complexity. People who “catastrophize”—a not-uncommon group with an especially negative set of thought and emotional responses to pain—may respond differently. In Campbell's study, healthy subjects were exposed, in random order, to capsaicin while they played video games like PacMan, to capsaicin skin cream alone, and to the games alone. High catastrophizers reported, expectedly, that their pain increased with time. And though they, too, benefitted from distraction, it took longer to kick in. For information: 410-550-7989.



### Having a biomarker for Alzheimer's disease (AD) that you could sample from blood would beat out newer icons of the illness—seen in neuroimaging or spinal fluid—by being far less costly and invasive.

Now a study by **Michelle Mielke** and colleagues showed that blood plasma levels of particular ceramides—long chain lipid molecules—can clearly mark the onset and progress of AD. The team tested healthy people with mild cognitive impairment and those with early, probable Alzheimer's. Unusual ceramide levels in the mildly impaired group predicted a downhill turn a year later. A further bonus is that altered ceramides probably reflect early events in AD—just what you want in a biomarker. E-mail: [mmielke1@jhmi.edu](mailto:mmielke1@jhmi.edu)

### Jennifer Payne's team wanted to see if adoptive mothers experience any of the same signs of depression as post-partum women.

At three different intervals, they studied 112 adoptive mothers of infants less than a year old, using a standard depression scale and questionnaire on medical and psychiatric history. Roughly a quarter of the mothers showed depressive symptoms in the first month after adoption, largely due to stress. Call: 410-502-2586

### Some 44 percent of patients with Alzheimer's suffer sleep disturbances and insomnia—a sad fact both for them and their caregivers. What approach offers the most help?

**Vani Rao** and colleagues reviewed research on 38 sleep-promoting options, from medications to bright light therapy (BLT), holding each to high evidence-based medicine criteria. No treatment brought huge relief, including antidepressants or antipsychotics. Melatonin helped some, apparently. But the methods of choice were non-drug-based therapies such as better sleep hygiene and BLT; improvement there came with a low risk of side effects. Call: 410-550-0019

Autism spectrum disorder (ASD) reflects a derailment of childhood mental development that, in adults, can bring problems with social sensitivity, attention and aggression, among others. Risperidone, the only approved medication, has significant side effects. Now, **Eric Samstad** is conducting trials of **memantine, a more benign, anti-Alzheimer's drug, in adults with ASD**. Certain brain circuits in Alzheimer's and autism likely overlap. Earlier tests suggested memantine benefited children with ASD. The drug may improve social behavior and language, areas untouched by risperidone. Call: 410-913-3216

Should I drink that cocktail? Eat that donut? **Intuition tells us psychiatric illnesses that turn on decision-making, like alcoholism or anorexia, should be less under genes' influence** than those whose symptoms seem to surface spontaneously, like mania or schizophrenia. But **Joseph Bienvenu** took advantage of the many genetic epidemiological studies on psychiatric disease now ripe for review and they suggest otherwise. His surveys of studies of twins suggest “behavioral” ills are every bit as grounded in biology. It's just that gene effects on temperament, reward systems, sensation-seeking and the like are harder to pin down. Call: 410-614-9063

## The well-used prescription pad—a hazard?

Prescribing more than one medication for psychiatric illness can be as valuable as shooting steamed milk into espresso: The whole comes out significantly better than the parts. So, for example, using the second antidepressant bupropion to boost the “almost there” effect of citalopram can ease depression—it’s an approach that’s both tested in trials and anecdotally sound. The same holds for giving someone who’s depressed and hearing voices an antipsychotic agent along with an antidepressant.

But what about taking several antipsychotics for schizophrenia? Prescribing another antidepressant for someone chronically depressed and already on one SSRI and valium? “It’s the mixing of psychoactive drugs without a basis in good clinical trials that worries a lot of us,” says psychiatrist **Ramin Mojtabai**, “and it appears to be a trend.”

Recently Mojtabai reported a large-scale study of psychiatrists’ prescribing patterns. He and a colleague reviewed data from 1996 to 2006 on more than 13,000 visits to mostly private psychiatrists, as gathered in a national medical care survey. The study is the largest of its kind. And it shows, he says, that “we’re combining psychotropic medicines more while our knowledge of whether that’s a good idea hasn’t kept pace.”

The number of patient visits in which psychotropic drugs were prescribed, for example, increased about 13 percent. And visits in which two or more medications were prescribed increased roughly 17 percent.

“I don’t want to discourage polypharmacy—having combinations—when it’s needed,” Mojtabai emphasizes. “But when it isn’t evidence-based, we can’t predict what side effects to anticipate as drugs interact,” he says, “nor are we sure enough of the benefits, especially when the added drugs are costly.” Also, he says, the more complex the drug regimen, “the more missed doses and noncompliance you see.”

What underlies the upswing? “It might be that the newer antidepressants and antipsychotics lack the florid side effects of earlier ones,” says Mojtabai, “and that makes combining drugs seem low risk.” SSRI antidepressants, for example, are especially perceived as benign, he adds. Also, more new drugs are on the



“I think twice about adding a new medication. I think more about what I can do to maximize one I already have on board,” says Ramin Mojtabai, who’s with both Hopkins Psychiatry and Public Health.

market, and physicians may be sold on promises of added benefits. This spills over to patient demands. “One of my patients with bipolar disorder recently asked me for ‘the butterfly medication’ for his insomnia.”

But most polypharmacy, Mojtabai believes, comes out of the not-uncommon situation when one medication is only partially successful and there’s no guideline for what should happen next. “Say a patient improves on the first drug, but responds even better to a second. Should you taper off the first one? Sometimes you do that and the patient declines, so you have them stay on the first. And that’s how accumulation can start.”

How to remedy? “We need clinical trials on combinations!” he says. “And the FDA should instigate them, since those aren’t likely to be industry-sponsored.” Also, even something as simple as prompting greater use of online medical records would tell what’s helped a forgetful patient in the past and lessen the likelihood of additions.

But perhaps more primal change is needed: Mojtabai cites studies that show a dip in U.S. psychiatrists’ use of psychotherapy. Because today’s view of mental disorders and treatments emphasize biology, he says, “that supports medications in general and may indirectly foster polypharmacy.” A greater openness to add tested behavioral approaches, he says, might be in order. ■

## Tightening the DSM

It’s a bit like hearing Moses was on his way with the two stone tablets. You can’t have much to do with psychiatry and not know that the DSM-5, the latest version of the *Diagnostic and Statistical Manual of Mental Disorders* comes out in May 2013.

There’ll be all manner of revisions to reflect advances in neuroscience, brain imaging and genetics. But one key difference in this DSM is that creators see it as more than a catalogue of disorders: It’s also a vehicle to improve clinicians’ grasp of how patients experience their illness.

Recently, psychiatrist **Bernadette Cullen** and psychiatric epidemiologist **Holly Wilcox** saw how that might work. This fall, they directed some short-but-necessary research—a precursor to the upcoming field trials of the DSM changes. “You need to ensure the method’s right before rolling out what’s new into larger studies,” says Cullen. The upcoming trials at 11 academic medical centers will involve some 3,000 patients.

The Hopkins “pilot pilot study” recruited 70 patients being seen at the East Baltimore Community Psychiatric Program that Cullen heads. It was more complicated than this, but basically, the patients, on two separate occasions, filled out a DSM-generated survey and then were interviewed by a new clinician. In an unusual move, each clinician used the surveys during interviews—something the DSM folks hope to encourage.

The surveys weren’t typical. Patients—iPads in hand—tapped out answers to “cross-cutting” questionnaires that cover symptoms in a variety of disorders, explains Cullen. Exploring mood, concentration, signs of psychosis, anxiety levels and present health—all were there.

“As clinicians, we’d use the surveys to flag where most of a patient’s symptoms lie,” she adds, “and then, following the interview, turn to an online, tentative DSM-5 to choose our diagnosis.” That version, for the first time, reflects illness severity.

Then, diagnoses made by the two new clinicians were compared.

With fine-tuning, the whole process should transfer well to the field trials. But was the new approach of survey and online checklist a keeper? “I’m not sure doing this would change a diagnosis I would have made,” says Cullen, “but it does increase your awareness of severity. And patients really like the surveys; they feel more engaged.” ■

## Hopkins BrainWise

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