Standardized test battery to aid those with Down syndrome

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Researchers at The University of Arizona are developing a set of standardized tests that could improve the lives of people with Down syndrome.

The condition, which occurs once in every approximately 800 to 1,000 live births, is signaled by the presence of an extra 21st chromosome. Those with Down syndrome often have mild to severe developmental disabilities, and other health issues that include heart defects and the early onset of Alzheimer's dementia. New research also suggests connections between chromosome 21 and other genes point to some of these problems.

For the past 25 years, Lynn Nadel has been studying the cognitive aspects of Down syndrome. Nadel, a Regents' Professor in the UA psychology department, has spent the bulk of his career studying the hippocampus, the area located deep within the brain that is associated with memory and spatial navigation.

Nadel said while some researchers may be involved with Down syndrome, he was drawn to it as an interesting scientific problem. The hippocampus develops later than other parts of the brain, including after birth, and is susceptible to disruptions. Nadel became interested in the possible implications of environmental impacts such as fetal alcohol syndrome, autism, lead and mercury poisoning and others.

"A lot of things that happen early in life have an impact on the

development of this structure because it is still plastic and developing," Nadel said.

"Since the hippocampus is one of the later developing parts of the nervous system, it made sense to think there might be some connection between this late development story and cognitive problems in Down syndrome."

Starting in the mid-1980s, Nadel began to speculate on the possibility that problems with hippocampal development might also contribute to cognitive problems in Down syndrome. He said the existing literature and later research added to the mounting evidence connecting the two. His own neuropsychological work and cognitive testing supported the case.

In the early 1990s, Nadel and his colleagues in Denver decided that in order to make any further progress, they would need a very accurate profile of the cognitive deficits in children with Down syndrome. For a while, their research slowed until Roger Reeves, a heart specialist at Johns Hopkins who had worked on heart problems in Down syndrome, asked about Nadel's research.

Like the hippocampus, there are anatomical features in the heart that develop very late, like the closing of the valves. Reeves wondered if children with Down syndrome were more likely to have late-developing heart problems. On one of his heart projects, Reeves related the probability of heart defects not just to chromosome 21, but other genes that interact with the extra chromosome 21, and had shown the feasability of using that as a predictor.

Nadel thought he could do that for cognitive function, and suggested they team up to determine the best way to profile cognitive deficits to use in combination with genetic and intervention studies. This could be a

way to determine what else contributes to the exact outcome to any particular child with Down syndrome.

Nadel and Reeves brought in genetics experts from Emory University to complete the team.

"We're also planning to bring in researchers in Pittsburgh and setting up two or three sites around the country to increase the sample size to get even more exact data on how to make a direct link between the genetic profile of a given child with Down syndrome and their cognitive outcome. You want to predict as early as possible their likely trajectory, and which kids you should intervene with more aggressively," Nadel said.

Most researchers assume that the range of variability in children with Down syndrome is no different than for the rest of the population. There is a very large range in typically developing children, everything from high-functioning to low-functioning. And there is every reason to assume the same in Down syndrome.

"We're trying to figure out how to most accurately assess as early as possible, within the first year or two of life. What is the likely trajectory. The kids at age 1 you could already predict by looking at their genetic makeup and a few cognitive tests that we're trying to work out that would be sensitive to cognitive function in the first year or two of life."

An accurate assessment of a child's learning trajectory would enable parents and medical and education specialists time to develop appropriate strategies for learning and possible drug therapies.

"The earlier we can make the prediction, the better advice we can give to parents about what they need to do to optimize their kids' development," Nadel said.

The key to finding out where people with Down syndrome are cognitively, he said, is through the use of standardized tests.

"We're working on developing a standardized battery for 8 to 18 year olds, the adolescent range that is easiest to develop tests that have adequate controls for in the developing population. Once we have that figured out for that age range, we want to move in both directions."

That includes tests for much younger children, but also for those in the 25-35 age range. Until a few decades ago, many with Down syndrome died in their 30s and 40s, usually from heart problems. Medical advances have helped stave off heart-related deaths, but it exposed another health risk for this group.

"By age 35, and certainly by age 40, just about everyone with Down syndrome has characteristic neuropathology associated with Alzheimer's," Nadel said. "Every individual with Down syndrome who has died past that age all have this pathology.

"What we also know is that for individuals with Down syndrome who are alive past age 35, about 35 to 40 percent actually seem to have early Alzheimer's. They all have mental retardation, either high or low functioning, but they don't seem to have dementia of the Alzheimer's type. This itself presents another interesting scientific question. Why do they have what appears to be the pathology associated with Alzheimer's disease, but don't have it? Given that they all have the neuropathology, we need another indicator, like behavior testing, to find out which ones have dementia or are more likely to get it."

Developing tests requires a large number of subjects. Several dozen have been tested in Tucson, Baltimore and Atlanta. Nadel is creating a fixed battery of nine or 10 tests that can be useful worldwide.

The test battery has to be precise in its ability to tell researchers about a particular brain structure. Three of these tests are targeted as assays, like blood tests that detect the presence of blood sugar. Performance on a cognitive test indicates how well the subject's hippocampus or the prefrontal cortex, another structure thought to be compromised in Down syndrome, are functioning.

"The battery has to be designed to be quite specific to only assay one particular structure and not be affected by the function of other structures," Nadel said.

"They have to be targeted and precise. They also have to be fairly short. All kids have a short attention span, so we want tests that are precise and targeted and short. They typically are computer based, but not always.

"They also are portable. We want to be able to test not only on kids or individuals who can make it into a university or hospital laboratory, but in schools and homes," he said.

Nadel said a number of criteria constrain the development of this battery but the goal is to have something that is repeatable, to test subjects initially and then bring it back a month later and still get reliable results.

Down syndrome also cuts across languages and cultures, so tests have to work the same way anywhere in the world.

"Luckily, we're based in Tucson, where there is a substantial Hispanic population. A number of students working on the project speak both English and Spanish fluently, so they were able to help us navigate testing kids who come from Spanish-speaking families. So we've been able to jump that hurdle," Nadel said.

Nadel and his group are now establishing contacts with colleagues in

Barcelona, Spain. One of his students is going to do her study-abroad semester in Argentina and will look into what is happening there. The family of another student runs a home for kids with developmental disabilities in Indonesia.

"There are cultural differences in how people with developmental disabilities are treated. But worldwide Down is emerging from the closet and kids are being mainstreamed and treated as educable and worth doing something for. That's happened over the last 20 or so years as a function of what we're learning about it."

Nadel said the test battery is near completion, likely in 2009, after a year and a half in development and presentations at meetings. A journal article is near as well.

"We're pretty much there, and should have a finished product that we will be happy to share with others doing the same thing around the world who want to use this standardized approach. People are pretty much waiting on us to finish."

Standardized tests, he said, will also aid other researchers working on drug treatments and other kinds of early stimulation, especially for clinical trials that require before-and-after comparisons.

Nadel also has found popular support from the parents of children with Down syndrome. The research testing was developed so that the children would enjoy it. There are boring parts, but Nadel said they try to work around those.

"The parents in Tucson and Denver and wherever I've worked with these groups are enormously positive and cooperative about the work. Most of our research is from private foundations that get their money from families with kids with Down syndrome and want to see this research go

forward."

"What it will make possible is a way of assessing kids, but also for assessing the efficacy of clinical trials. That's been missing. There's always been lots of anecdotal stories about the value of ginkgo or vitamin E. What has been lacking in the field has been some sort of solid scientific way of assessing the virtues of and value of things. So, parents are very excited that we're getting close to having this kind of measurement tool."

The research has also drawn interest from UA students. Nadel said this avenue of research is an area where the rewards are obvious.

"One of the most exciting things is how many students want to work on this project. Six or seven right now. It's been an immediate hit. This is good and interesting science and connects to the real world and they can sink their teeth into it and make a difference. It's been a magnet for undergraduate students who want to get involved in research, in something connected to the world."

"This one of those perfect examples of how teaching and research mesh completely. In the classroom you talk about brain development and cognition and how it goes right and how it goes wrong. Here is the opportunity for undergrads to actually go in and discover something about that process and make a difference."

Source: University of Arizona