

NEWS FROM THE SOCIETY OF NEUROSCIENCE  
ANNUAL MEETING

# The Gift of Gab: Advances in the Field to Decode the Neuropathology of Speech Processing

BY TOM VALEO

## ARTICLE IN BRIEF

 Lecturers at the last Society for Neuroscience annual meeting offer an overview of advances in understanding the underlying neuropathological substrates in impairments in speech processing.

**B**roca's area and "language genes" play a role, of course, but they barely begin to explain the human ability to produce and comprehend speech. That requires an understanding — just beginning to emerge — of brain-wide networks that combine memory, muscle coordination, executive planning, and other neural feats into a complex ballet that can be disrupted in multiple ways, according to new research.

"A lot of talk about language is woefully out of date," said David Poeppel, PhD, professor of psychology and neural science at New York University who has spent his career trying to unravel the complexities of spoken language.

"Any lecture on vision includes an anatomical map showing 30 to 50 areas. A map of the auditory system includes 12 to 14 areas. But go to a talk on language processing and you see the left hemisphere with two blobs — Broca's region and a region at the back of the head that are somehow connected. That's our theory. It's kind of insulting. We can do better."

In one of his first forays into the physiology of speech processing, Dr. Poeppel compared five PET studies that attempted to identify the relevant brain area for spoken language. To his surprise, he found that each study identified a different area. "The experiments implicate distinct, non-overlapping perisylvian areas," Dr. Poeppel dryly concluded in his 1996 paper in *Brain & Language*.

## CORTICAL OSCILLATIONS

The field has come a long way since then. Dr. Poeppel's March 2012 paper in *Nature Neuroscience* focuses on "cortical oscillations and speech processing" — also the theme of his presentation at the last Society for Neuroscience annual meeting in New Orleans. He believes cortical oscillations contribute to cognition by "packaging" information into units that enable the decoding of speech. The low gamma (25–35 Hz), theta (4–8 Hz) and delta (1–3 Hz) oscillations somehow link the "temporal administrivia" needed



**DR. DAVID POEPPEL:** "Any lecture on vision includes an anatomical map showing 30 to 50 areas. A map of the auditory system includes 12 to 14 areas. But go to a talk on language processing and you see the left hemisphere with two blobs — Broca's region and a region at the back of the head that are somehow connected. That's our theory. It's kind of insulting. We can do better."

for speech, according to the hypothesis presented in the paper by Dr. Poeppel and his co-author, Anne-Lise Giraud, PhD, who heads research for the Auditory Language Group of the Cognitive

*Continued on page 14*

## Speech

Continued from page 13

Neuroscience Laboratory at the Ecole Normale Supérieure in Paris.

Dr. Poeppel's overarching goal is to move the field beyond the textbook truism that Broca's region plays the decisive role in speech production.

"The classical view was never right," Dr. Poeppel told *Neurology Today*, "but go to the chapters on language disorders and aphasia in textbooks on neurology and that's the picture you'll find."

In the current view, the decision to speak a word activates regions in the parietal and frontal lobes, and in the auditory system. The motor command results in an "efferent copy" that enables the speaker to assess whether the right sound is coming out of the mouth, according to Dr. Poeppel.

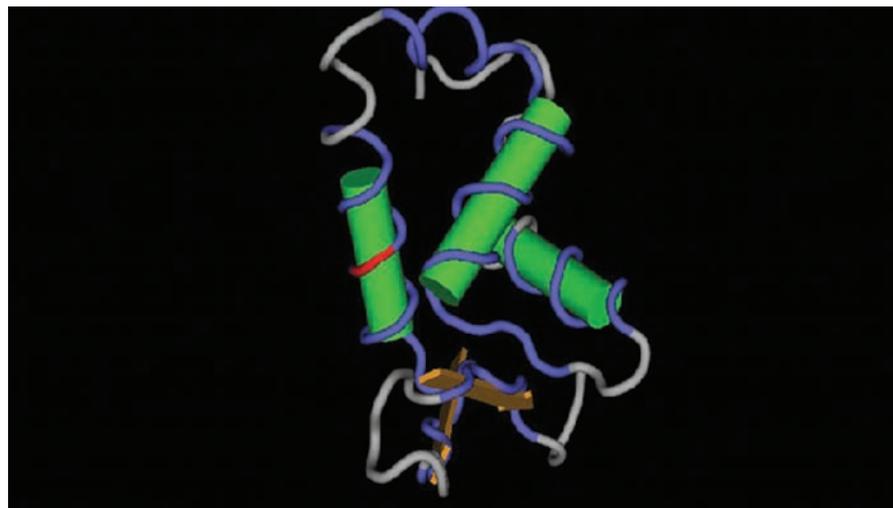
"It's now uncontroversial to say that both hemispheres play a central role in language processing," Dr. Poeppel said.

## COMPUTATIONAL NEUROANATOMY

The study of human speech is further complicated by its division into psycholinguistics and the mechanics of motor control, which seldom interact, according to Gregory Hickok, PhD, professor of cognitive sciences and director of the Center for Language Sciences at the University of California, Irvine.

He would like to integrate the two approaches, as he explained in a January 2012 paper in *Nature Reviews Neuroscience* and the theme for his lecture at the Society for Neuroscience meeting.

"Psycholinguistics is interested in figuring out how people put phonemes together to make words, and put words together to make sentences," Dr. Hickok told *Neurology Today*. "The data come from speech errors where people put phonemes in wrong place, or swap phonemes and words. People interested



**FOXP2.** The illustrated portion of the protein binds to and controls genetic information within cells. The red mark shows the position of a mutation in FOXP2 that causes severe speech and language deficits.

in motor control try to figure out how individual muscle forces are applied, so they talk about internal forward models and that sort of thing — the same thing you find in the analysis of pointing, or reaching, or eye movements."

But there's not a meaningful distinction between these two levels of analysis, in Dr. Hickok's view. "In my paper I tried to show that if we integrate these two levels of analysis, things work out quite nicely," he said. "You get insights into motor control and linguistic processing that you wouldn't get otherwise. There's a huge amount of overlap in the two traditions in terms of the principles they've uncovered."

For example, psycholinguists have long known that speech is planned several syllables in advance of actual articulation. Someone who says, for example, "I would like a cuff of coffee" obviously is already thinking about the last word of the sentence while pronouncing "cup," which contributes to the error in motor control.

"Such speech errors are relatively rare in normal speech," Dr. Hickok said, "but more common in some neurological disorders, such as conduction aphasia."

By integrating the motor control and psycholinguistic traditions, Dr. Hickok has been able to develop a model of the brain circuits involved in these disorders.

## THE ROLE OF GENETICS

Language, like every other function of the brain, has a genetic basis, but any talk of a "speech gene" is wildly misleading, according to the man who helped identify FOXP2 — forkhead box protein 2, located on chromosome 7 — the first gene so named.

Now Simon E. Fisher, DPhil, of the Max Planck Institute for Psycholinguistics, has discovered that another gene known as CNTNAP2 (or contactin-associated protein-like 2) may be involved with specific language impairment (SLI) and with language delays in autism.

In his Presidential Special Lecture at the Society for Neuroscience meeting, Dr. Fisher, who holds a professorship at the Radboud University in Nijmegen, Netherlands, attempted to describe how genes actually influence human speech.

"People think there are these direct lines between genes and behavior, but

these direct lines don't exist," he said. "There's no such thing as a gene for language or a gene for grammar."

The brain does speech and language, not the genes, according to Dr. Fisher, but genetic mutations can certainly disrupt the process. Some mutations that result in cerebral palsy, cleft palate, and other overt physical problems produce obvious reasons for language problems. "But sometimes children mysteriously fail to acquire complex language," Dr. Fisher said. "These developmental disorders cluster in families, which hint at a genetic cause. Also, twin studies indicate high heritability."



**DR. GREGORY HICKOK** said the study of human speech is further complicated by its division into psycholinguistics and the mechanics of motor control, which seldom interact, adding he would like to integrate the two approaches.

In a landmark 2001 paper in *Nature* Dr. Fisher and colleagues linked a severe form of SLI in an extended British family known as KE to a mutation in the FOXP2 gene. Those with the mutation — about half the members of the family — have trouble producing the sequence of mouth movements that

Continued on page 15

## EMERGING THERAPIES FOR APHASIA AND OTHER LANGUAGE PROBLEMS

**E**merging insights into the production and comprehension of language are starting to point toward better forms of therapy, according to Peter Turkeltaub, MD, PhD, assistant professor of neurology at Georgetown University and a lead researcher at the newly created Center for Brain Plasticity and Recovery, a collaborative venture between Georgetown and the MedStar National Rehabilitation Network.

"More knowledge about the subprocesses that go into understanding and producing speech can help in developing new speech therapies for aphasia and other language problems," he said.

For example, Dr. Turkeltaub is starting a three-year clinical trial using transcranial direct-current stimulation to enhance activity in the left frontal lobe.

"There's a fair amount of evidence that the best recoveries from aphasia occur when people use the same areas they used to use in the left hemisphere, or nearby areas," he said. "We don't know why that is. It may be that right hemisphere is not as efficient, or maybe the right hemisphere is impairing recovery somehow, so our approach is to reduce right hemisphere activity and increase left hemisphere activity."

Dr. Turkeltaub, who recently received a \$486,000 award from the Doris Duke Charitable Foundation, is also exploring the use of the Alzheimer medications donepezil and memantine for the treatment of aphasia. "I've had anecdotal reports about the promising effects of these medications, so I think it's worth further study," he said. "So far they've been used by themselves, but they might work in synergy with tDCS and TMS (transcranial magnetic stimulation)."

—Tom Valeo



**DR. PETER TURKELTAUB**

## Speech

Continued from page 14

result in precise enunciation. Recordings of family members that Dr. Fisher played could barely be understood without subtitles.

How does a mutation in FOXP2 result in this condition? FOXP2 is a gene highly conserved in mammals, with functions that extend far beyond speech, such as sensory processing, sensory-motor integration, and the learning of motor skills. The chimpanzee version of FOXP2 resembles the mouse version, and the two amino acid changes in humans emerged after humans split from chimpanzees five million years ago.

“FOXP2 must have had an ancient role, but it is not restricted to brain,” Dr. Fisher said. “FOXP2 is also involved with the lungs, gut, and heart. FOXP2 likes to moonlight. It’s not there just to give our species language.”

In humans FOXP2 produces a transcription factor involved in the regulation of gene expression, and this appears to malfunction in members of the KE family who display the distinctive form of SLI.



**DR. SIMON E. FISHER:**  
**“People think there are these direct lines between genes and behavior, but these direct lines don’t exist. There’s no such thing as a gene for language or a gene for grammar.”**

“Most of the time FOXP2 acts like a dimmer switch,” Dr. Fisher said. “A section in the middle of protein known as the Fox domain likes to stick to DNA. Affected members of the KE family carry a single nucleotide change of G to A in one point. This changes an arginine

residue into histidine. Then the protein can’t stick to DNA, and that messes with the function of the protein.”

FOXP2 binds to CNTNAP2, a gene that encodes a neuroligin expressed in the developing cortex. Certain polymorphisms of CNTNAP2 are associated with SLI and language delays in children with autism, and certain alleles correlate with delayed language in the general population, Dr. Fisher said.

FOXP2 also regulates gene networks involved in neurite outgrowth in primary neurons in the developing brain, according to a poster presented at the Society for Neuroscience meeting by Sonja C. Vernes, DPhil, one of Dr. Fisher’s co-authors on a 2011 paper in *PLoS Genetics* on the subject.

And a recent examination of white matter in six members of the KE family who carry the FOXP2 mutation found reduced tract volume in the right arcuate fasciculus. In a presentation at the Society for Neuroscience meeting, Kate E. Watkins, PhD, explained how she and her colleagues used diffusion tensor imaging to detect the reduced volume, which indicates white matter disorganization in pathways underlying speech and language, and motor cortical

areas — changes that are consistent with the speech difficulties of affected members of the KE family. •

### FOR FURTHER READING:

- Poeppel D. A critical review of PET studies of phonological processing. *Brain Lang* 1996;55:317-351.
- Poeppel D, Giraud AL. Cortical oscillations and speech processing: emerging computational principles and operations. *Nature Neurosci* 2012;15(4):511-517.
- Hickok G. Computational neuroanatomy of speech production. *Nature Rev Neurosci* 2012;13(2):135-145.
- Lai CS, Fisher SE, Monaco AP, et al. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 2001;413:519-523.
- Fisher SE et al. CNTNAP2 variants affect early language development in the general population. *Gene, Brain Behav* 2011;10:451-456.
- Vernes SC, Oliver PL, Fisher SE, et al. Foxp2 regulates gene networks implicated in neurite outgrowth in the developing brain. *PLoS Genet* 2011;7(7):e1002145