Zachary A. Miller, MD
Leighton B. Hinkley,
PhD

Alex Herman, PhD
Susanne Honma, RT
Anne Findlay, MA
Nikolas Block, BA
Robin Ketelle, RN, MS
Gil Rabinovici, MD
Howard Rosen, MD
Srikantan S. Nagarajan,
PhD

Bruce L. Miller, MD
Maria Luisa
Gorno-Tempini
MD, PhD

ANOMALOUS FUNCTIONAL LANGUAGE LATERALIZATION IN SEMANTIC VARIANT PPA

In 1982, Marsel Mesulam detailed a series of cases with primary progressive aphasia (PPA). Originally defined, PPA was restricted to patients with focal left hemisphere involvement. As cases with right hemisphere disease appeared,^{1–3} an amended theory proposed that PPA arose from a “locus of least resistance” within the dominant language network.⁴ Ultimately, this explanation was unable to account for a specific subtype of semantic variant PPA (svPPA) where pathology first involved the nondominant hemisphere and subsequently attacked the dominant anterior temporal lobe language network.⁵ With the discovery of increased non-right-handedness (nRH) and planum temporale symmetry within our svPPA cohort,⁶ we put forward a refinement of the prevailing hypothesis and suggested that mechanisms of lateralization and neurodevelopment that shape the language network also generate a differential pattern of disease susceptibility within specific PPA variants. We postulated that the increased nRH observed in svPPA might be secondary to an increased incidence of anomalous language laterality. In this report, we describe the magnetoencephalography (MEG) pattern of language lateralization in a single svPPA case with left temporal predominant atrophy despite a clinical presentation of a right temporal syndrome.

Methods. We obtained written patient consent and study approval by the UCSF Institutional Review Board. We performed comprehensive neurologic, neuropsychological, language battery,⁶ brain MRI, FDG and Pittsburgh compound B (PiB) PET imaging, and genetic testing.

MEG data were collected using a 275-channel whole-head biomagnetometer (CTF; Coquitlam, BC, Canada) during an auditory verb generation task.⁷ MEG sensor data were reconstructed in brain source space using a time-frequency optimized adaptive spatial filtering technique (nutmeg.berkeley.edu). Oscillatory power changes in the beta (12–30 Hz) and high-gamma (50–120 Hz) bands were estimated using a pseudo-F statistic, comparing sliding active

windows to an intertrial baseline period. MEG imaging reconstructions were analyzed time locked either to stimulus onset (0 ms = auditory noun presentation) or to response onset (0 ms = vocal verb generation), and a laterality index was derived as a ratio of beta power change between the left and right hemispheres over temporal and frontal regions.⁷

Case report. We present data from a 61-year-old ambidextrous man with 8 years of progressive behavioral changes evidenced by new onset of hyper-religious dogmatism and inability to recognize familiar faces. He developed a new fascination with words, manifested as hyperverbality and obsession with word games, and rigidly sought out specific foods. A year prior to presentation, he began substituting words, “that boy” for “son,” “temper” for “temperature,” and “knob” for “ankle.” On examination, he revealed pressured, fluent speech, and spoke in rhymes and puns. Edinburgh Handedness Inventory corroborated ambidexterity (+0.3). Neuropsychological testing showed intact global cognition (30/30 Folstein Mini-Mental State Examination), verbal memory (average for age on California Verbal Learning Task short form), and visuospatial abilities (15/17 Benson Figure copy). He performed poorly on Stroop interference executive testing and displayed greatest impairments on confrontation naming (8/15 Boston Naming Task) and face recognition (0/12 Famous Faces).

Results. *Genetics.* C9ORF72, GRN, and TDP-43 mutations were absent.

PET/MRI. FDG-PET showed relatively symmetrical hypometabolism in the temporal poles, while PiB-PET was negative for cortical amyloid. T1-weighted MRI revealed prominent, left greater than right, anterior temporal lobe atrophy extending into the insulae without appreciable frontal involvement.

MEG. Robust beta-band power suppression was observed over the right hemisphere in the svPPA case in both stimulus-locked and response-locked verb generation tasks, in contrast to the highly left-lateralized activation observed in healthy individuals⁷ (figure). Quantitative comparison of activity across the left and right hemispheres produced a laterality index of -0.46 , indicative of right hemisphere language dominance.

(A) Changes in β band (12–30 Hz) oscillatory activity during the speech reception phase (verb generation task, stimulus-locked) for an average of 18 healthy controls (left column) and the semantic variant primary progressive aphasia (svPPA) case (right column). Increases in beta power suppression during later time windows (550–750 ms, poststimulus) are largely left hemisphere dominant in the control cohort. Increased right hemisphere beta suppression is observed in the svPPA case for the same time windows. (B) Changes in beta band (12–30 Hz) oscillatory activity during the speech production phase (verb generation task, response-locked) for an average of 18 healthy controls (left column) and the svPPA case (right column). Increases in beta power suppression prior to response onset (–550 ms) are largely left hemisphere dominant in the control cohort and right hemisphere dominant in the svPPA case. MEG = magnetoencephalography.

Discussion. We report the functional identification of right hemisphere language dominance in an atypical right temporal svPPA clinical presentation with predominant left-sided anterior temporal lobe atrophy. Previously, anomalous language lateralization was reported in a left-handed PPA patient with right-sided, not left-sided, atrophy.³ In both cases, discordant clinical and radiologic observations prompted functional imaging assessments, and the presence of anomalous language lateralization reconciled these observations. Whether anomalous language activity is secondary to neurodevelopment or is in response to the disease process is uncertain and needs to be addressed in future studies. Nevertheless, the clinical presentation and nRH status of both supports a history of premorbid right hemispheric language dominance. Anomalous language lateralization is suspected in PPA when hypometabolism or atrophy pattern conflicts with clinical predictions.^{1–3} Larger cohort studies may be able to adequately address the issue of whether or not anomalous lateralization is more common in PPA, or specific subtypes of PPA, than the general population. Approaches like MEG (potentially when combined with other noninvasive imaging measures) may be important and effective research tools for investigating the natural history of language lateralization in PPA.

From the UCSF Memory and Aging Center (Z.A.M., N.B., R.K., G.D.R., H.R., B.L.M., M.L.G.-T.) and the UCSF Biomagnetic Imaging Lab (L.B.H., A.H., S.H., A.F., S.S.N.), San Francisco, CA. Author contributions: Zachary A. Miller was responsible for all aspects of this report's design, conceptualization, analysis, interpretation, drafting, and revision. Leighton B. Hinkley

contributed to the design, analysis, interpretation, and revision of this paper. Alex Herman contributed to the analysis and revision of this report. Susanne Honma contributed to the analysis and revision of this report. Anne Findlay contributed to the analysis and revision of this report. Nikolas Block contributed to the design and revision of this paper. Robin Ketelle contributed to the design and revision of this paper. Gil D. Rabinovici contributed to the design, analysis, interpretation, and revision of this report. Howard Rosen contributed to the analysis, interpretation, and revision of this report. Srikantan S. Nagarajan contributed to the design, analysis, interpretation, and revision of this report. Bruce L. Miller contributed to all aspects of this report's design, analysis, interpretation, drafting, and revision. Maria Luisa Gorno-Tempini contributed to all aspects of this report's design, conceptualization, analysis, interpretation, drafting, and revision. Study funding: NIH grants P01 AG19724, P50 AG023501, P50 AG1657303, P50AG16574, R01-AG032306, R01 NS050915-05A1, R01 DC004855, R01DC013979, and UL1 RR024131. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute on Aging or NIH.

Disclosure: Z. Miller, L. Hinkley, A. Herman, S. Honma, A. Findlay, N. Block, and R. Ketelle report no disclosures relevant to the manuscript. G. Rabinovici has received a speaking honorarium from GE Healthcare, has consulted for Eli Lilly, and receives research support from Avid Radiopharmaceuticals. H. Rosen and S. Nagarajan report no disclosures relevant to the manuscript. B. Miller has consulted with grant support from Novartis and has consulted for TauRx, Ltd., Allon Therapeutics, Siemens Inc., Eli Lilly, and the Consortium for Frontotemporal Dementia Research. M. Gorno-Tempini reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 5, 2014. Accepted in final form September 1, 2014. Correspondence to Dr. Miller: zmiller@memory.ucsf.edu

© 2014 American Academy of Neurology

1. Drzezga A, Grimmer T, Siebner H, Minoshima S, Schwaiger M, Kurz A. Prominent hypometabolism of the right temporoparietal and frontal cortex in two left-handed patients with primary progressive aphasia. *J Neurol* 2002;249:1263–1267.

2. Perry R, Rosen H, Kramer J, Beer J, Levenson R, Miller B. Hemispheric dominance for emotions, empathy and social behaviour: evidence from right and left handers with fronto-temporal dementia. *Neurocase* 2001;7:145–160.
3. Mesulam M, Weintraub S, Parrish T, Gitelman D. Primary progressive aphasia: reversed asymmetry of atrophy and right hemisphere language dominance. *Neurology* 2005;64:556–557.
4. Alberca R, Montes E, Russell E, Gil-Neciga E, Mesulam M. Left hemispheric hypoplasia in 2 patients with primary progressive aphasia. *Arch Neurol* 2004;61:265.
5. Seeley W, Bauer A, Miller B, et al. The natural history of temporal variant frontotemporal dementia. *Neurology* 2005;64:1384–1390.
6. Miller ZA, Mandelli ML, Rankin KP, et al. Handedness and language learning disability differentially distribute in progressive aphasia variants. *Brain* 2013;136:3461–3473.
7. Findlay AM, Ambrose JB, Cahn-Weiner DA, et al. Dynamics of hemispheric dominance for language assessed by magnetoencephalographic imaging. *Ann Neurol* 2012;71:668–686.

Kenneth S. Kosik, MD
 Claudia Muñoz
 Liliana Lopez
 Mary Luz Arcila, PhD
 Gloria García
 Lucía Madrigal, PhD
 Sonia Moreno
 Silvia Ríos Romenets, MD
 Hugo Lopez
 Madelyn Gutierrez
 Jessica B. Langbaum, PhD
 William Cho, MD
 Shehnaaz Suliman, MD
 Pierre N. Tariot, MD
 Carole Ho, MD, PhD
 Eric M. Reiman, MD
 Francisco Lopera, MD

HOMOZYGOSITY OF THE AUTOSOMAL DOMINANT ALZHEIMER DISEASE PRESENILIN 1 E280A MUTATION

We identified several families in Antioquia, Colombia, with early-onset Alzheimer disease (AD) due to the mendelian autosomal dominant inheritance of a *PSEN1* E280A gene mutation. Extended family members were interviewed and parish baptism certificates in Antioquian municipalities examined.¹ The size of these extended families (including carriers and noncarriers) approaches 5,000 individuals. Full genomes in carriers proved a single founder.² To support an AD

prevention clinical trial, we established a registry in 2010 of all family members over age 8 years.³ Since then we genotyped 3,407 family members and identified 823 (24%) carriers of the *PSEN1* E280A mutation. The Comité de Bioética de la Sede de Investigación Universitaria, SIU Universidad de Antioquia, approved this study. All participants provided written informed consent. Despite the size of this exceptionally large family and frequent consanguinity, homozygosity at this gene locus had not been reported. The apparent absence of homozygous *PSEN1* mutations led to the speculation that E280A homozygosity

Figure Genotype analysis

(A) *PSEN1* was amplified using the following primers—forward AACAGCTCAGGAGAGGAATG3, reverse TGAACAGAGTAG—around the mutation site. We used 40 ng of PCR product for restriction digestion with 0.5 units of Mva12691 (Fermentas, Vilnius, Lithuania) for 16 hours at 37°C, and cleaned digestion products using the Qiagen clean up reaction kit. We ran the products on a Bioanalyzer DNA chip (Agilent, Santa Clara, CA). (B) In one patient, we confirmed the mutation by sequencing 20 ng of PCR product (sent to UCLA genotyping and sequencing core). The reported sequences were analyzed using Sequence scanner v1.0 (Applied Biosystems, Foster City, CA).