Cognitive activity and cognitive decline in a biracial community population

R.S. Wilson, PhD; D.A. Bennett, MD; J.L. Bienias, ScD; C.F. Mendes de Leon, PhD; M.C. Morris, ScD; and D.A. Evans, MD

Abstract—*Background:* Frequent participation in cognitively stimulating activities has been associated with reduced risk of AD in several prospective studies. However, the association of cognitive activity with cognitive decline, the principal manifestation of AD, is not well understood. *Methods:* More than 4,000 older residents of a geographically defined biracial community of Chicago were interviewed at approximately 3-year intervals for an average of 5.3 years. Each interview included administration of four cognitive function tests from which a previously established global measure was derived. At baseline, each person rated frequency of participation in cognitively stimulating activities (e.g., reading a magazine) from which a previously established composite measure of cognitive activity was derived. *Results:* Cognitive activity scores ranged from 1 to 5 (mean = 3.14, SD = 0.66), with higher scores indicating more frequent participation. More frequent cognitive activity was associated with reduced cognitive decline during follow-up. In a model that controlled for baseline level of cognition, age, sex, race, and education, a 1-point increase in cognitive activity score was associated with an approximately 19% decrease in annual rate of cognitive decline ($p < 0.001$). This effect remained when we controlled for depressive symptoms and chronic medical conditions ($p < 0.001$), and when we excluded persons with evidence of memory impairment at baseline ($p < 0.001$). *Conclusion:* Frequent participation in cognitively stimulating activities is associated with reduced cognitive decline in older persons.

NEUROLOGY 2003;61:812–816

Frequent participation in cognitively stimulating activities has been associated with reduced risk of developing dementia and Alzheimer disease (AD) in several recent studies.[1-4] Because AD is the leading cause of dementia in older persons and few potentially modifiable risk factors have been identified, understanding the basis of the association of cognitive activity with disease incidence is a matter of substantial public health significance.[5]

The association between frequency of cognitive activity and risk of AD is probably due in part to the correlation between cognitive activity and cognitive function. That is, people who report more frequent participation in cognitive activity tend to perform better on tests of cognitive function than persons who report less frequent activity.[6-9] On average, therefore, those who have been cognitively active are likely to begin old age at a higher level of cognitive function than their less cognitively active peers. As a result, a cognitively active person would need to experience a greater amount of cognitive decline than a less cognitively active person before reaching a level of cognitive dysfunction commensurate with dementia.

Another way in which cognitive activity might influence AD risk is through an association with the principal manifestation of the disease, progressive decline in cognitive function. That is, cognitively active people may not only begin old age with better cognitive skills than less cognitively active persons, but these skills may also be less subject to decline. An association between cognitive activity and cognitive decline would be important because it would imply that cognitive activity, or something associated with it, may modify the functional consequences of AD pathology. In laboratory animals, exposure to complex stimulating environments has been associated with increased neurons and synapses. In a similar fashion, human cognitive activity may give rise to changes that result in some neural systems being less vulnerable to AD pathology.[5,10-12]

There have been few studies of the association of cognitive activity with cognitive decline in old age, and their results have been mixed. Two studies found that frequent cognitive activity was associated with reduced cognitive decline,[3,13] but the effect was present for only one of nine cognitive measures in one study,[13] and both cohorts were selected. By contrast, a population-based study found no association between participation in everyday activities, including several cognitively stimulating ones, and change in several measures of cognitive function.[14]

We examined the relation of cognitive activity to cognitive decline using data from the Chicago Health

From the Rush Alzheimer's Disease Center and Rush Institute for Healthy Aging and Departments of Neurological Sciences (Drs. Wilson, Bennett, and Evans), Psychology (Dr. Wilson), and Internal Medicine (Drs. Bienias, Mendes deLeon, Morris, and Evans), Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.

Supported by National Institute on Aging grants AG-11101 and AG-10161.

Received February 18, 2003. Accepted in final form June 9, 2003.

Address correspondence and reprint requests to Dr. Robert S. Wilson, Rush Alzheimer's Disease Center, 1645 West Jackson Blvd., Suite 675, Chicago, IL 60612; e-mail: rwilson@rush.edu

Table 1 *Baseline characteristics of 4,392 participants with follow-up data*

Characteristic	Value
Age, y	73.9 (6.5)
Education, y	12.0 (3.7)
Women	62.1
African American	61.7
Cognitive activity score	3.14 (0.66)
Global cognitive score	0.12 (0.78)
CES-D score	1.53 (1.97)
Number of medical conditions	1.05 (0.96)
Disability	10.6

Data are presented as mean (SD) or %. Disability was defined as inability to perform one or more activities of daily living on the Katz scale.

CES-D = Center for Epidemiologic Studies Depression Scale.

and Aging Project, a population-based longitudinal study of aging and AD.[15] More than 4,000 older persons from a biracial community were interviewed at approximately 3-year intervals for a mean of 5.3 years. At baseline, persons rated frequency of participation in seven common cognitive activities from which a previously established composite measure of cognitive activity was derived. At each interview four brief cognitive performance tests were administered and used to form a global measure of cognition. We used random effects regression models to test the association of cognitive activity with annual rate of cognitive decline, controlling for baseline level of cognitive function and selected demographic and clinical variables.

Methods. *Subjects.* From October 1993 to May 1997, all households in a geographically defined area on the south side of Chicago were censused, persons aged 65 years or older were invited to participate in an in-home interview, and 6,158 of 7,826 (79%) eligible persons did so. The interview, which included four brief performance tests of cognitive function, was repeated twice at approximately 3-year intervals. The study was approved by the Institutional Review Board of Rush-Presbyterian-St. Luke's Medical Center.

Of 6,158 persons at baseline, 1,175 died before the first follow-up interview. Of the remaining 4,983 people, 4,392 (88.1%) completed at least one follow-up interview. Analyses are based on this group, which completed a mean of 2.6 interviews per individual during a mean of 5.3 years of observation. Table 1 provides information on demographic characteristics and key study variables in these persons at baseline.

Assessment of cognitive function. Each interview included administration of four brief tests of cognitive function. There were two measures of episodic memory: immediate and delayed recall of 12 ideas contained in the East Boston Story.[16] There was one measure of perceptual speed: the oral version of the Symbol Digit Modalities Test,[17] in which persons match as many digit-symbol pairs as possible in 90 seconds. The fourth test was the Mini-Mental State Examination,[18] a widely used 30-item measure of global cognition.

Because we wanted to minimize floor and ceiling artifacts and other sources of measurement error and because in a previous factor analysis[9] all four tests loaded on a single factor that accounted for about 75% of the variance, we used a composite of all four tests in longitudinal analyses. As previously described,[9] we formed the composite by converting raw scores on each test to z scores, using the baseline mean and SD in the population, and then averaging the z scores.

To identify subgroups with impaired memory at baseline, we used the average score from immediate and delayed recall of the East Boston Story.

Assessment of cognitive activity. We used a previously established composite measure of frequency of participation in cognitively stimulating activities.[9] At the baseline interview, we asked about seven activities that mainly involve seeking or processing information and make minimal physical or social demands: viewing television; listening to radio; reading newspapers; reading magazines; reading books; playing games like cards, checkers, crosswords, or other puzzles; and going to a museum. Persons rated their current frequency of participation in each activity on a five-point scale: 5) every day or about every day; 4) several times a week; 3) several times a month; 2) several times a year; 1) once a year or less. The ratings were averaged to yield the composite measure of cognitive activity, which ranged from 1 to 5, with higher scores indicating more frequent participation.

We used a summary measure of cognitive activity instead of individual activities to reduce floor and ceiling artifacts and other forms of measurement error. As previously reported,[9] participation in each activity is positively related to level of participation in the remaining six, supporting the use of a summary measure. We based the summary score on the average frequency of participation because we found that accounting for differences in the estimated cognitive demand of each activity resulted in a measure nearly identical to a measure based only on frequency, which we chose for reasons of parsimony. In prior research this composite measure has been associated with incident AD[3,4] and, in a different cohort, with rate of cognitive decline.[3]

Assessment of other variables. Depressive symptoms were assessed at the baseline interview with a 10-item form[19,20] of the Center for Epidemiologic Studies Depression (CES-D) scale.[21] The score is the number of symptoms experienced during the last week.

Seven chronic medical conditions were reported by at least 5% of the population at baseline: heart disease, stroke, hypertension, diabetes, cancer, thyroid disease, and shingles or herpes zoster. We used the number of these conditions present at baseline as an indicator of chronic illness, as previously described.[4]

We assessed disability at baseline with the Katz scale.[22] The score is the number of daily activities out of six that the persons reported being unable to perform.

Data analysis. We used random effects models to characterize change in the global measure of cognitive function during the observation period and to test the association of cognitive activity with initial level of cognition and rate of change.[23] In this approach, each individual path of change is assumed to follow the path of the population except for random effects that cause the initial level of function to be higher or lower and the rate of change to be faster or slower. An important advantage of this approach is that baseline level of cognition is explicitly modeled as a source of random variability and a possible correlate of how rapidly people change. Further information on the application of these models to cognitive function data is published elsewhere.[24,25]

The core model included terms for time since baseline in years, cognitive activity score (centered at 3), and the interaction of cognitive activity with time. The term for time indicates the average annual change in the global cognitive score. The term for cognitive activity indicates the effect of one unit of cognitive activity on the baseline global cognitive score. The interaction denotes the effect of one unit of cognitive activity on annual rate of change in global cognition. This and all subsequent models also included terms to account for the potentially confounding effects of age, sex, race (black/non-black), and education on initial level of cognition and rate of change.

We repeated the core model with two additional interaction terms: race × cognitive activity and race × cognitive activity × time. The latter term indicates whether the association of cognitive activity with cognitive decline varied by race. We constructed similar models for age, for sex, and for education.

In subsequent analyses, we repeated the core model excluding persons with evidence of memory impairment at baseline, and then again including terms to control for the effects of depressive symptomatology, ill health, and disability.

Programming was done in SAS.[26] All models were validated

Table 2 Association of cognitive activity with baseline level of global cognition and annual rate of change, estimated from a random effects model adjusted for age, sex, race, and education

Model term	Estimate	SE	*p* Value
Time	−0.064	0.004	<0.001
Cognitive activity	0.294	0.015	<0.001
Cognitive activity × time	0.012	0.003	<0.001

graphically and analytically, and assumptions were judged to be adequately met.

Results. At baseline, the global measure of cognition ranged from −3.497 to 1.541 (mean = 0.124, SD = 0.779), with higher scores indicating better cognitive function. The composite measure of frequency of participation in cognitive activity ranged from 1.00 to 5.00 (mean = 3.14, SD = 0.66), with higher scores indicating more frequent participation. We assessed the relation of frequency of cognitive activity to initial level of cognitive function and rate of cognitive decline in a core random effects model that also included terms to account for the effects of age, sex, education, and race on baseline level of cognition and annual rate of change (table 2). In this model, there was an average decline of 0.064 unit per year on the global measure of cognition, as shown by the term for time. Frequency of cognitive activity was positively correlated with baseline level of cognitive function. On average, for each point on the composite measure of cognitive activity, baseline cognitive score was 0.294 unit higher, as shown by the term for cognitive activity. Frequency of cognitive activity was also associated with rate of cognitive decline, with a reduction of 0.012 unit, or about 19%, for each point on the cognitive activity scale, as shown by the interaction term. Compared to a person with infrequent cognitive activity (score = 2.14, 10th percentile), therefore, rate of global cognitive decline was reduced by about 35% in a person with frequent cognitive activity (score = 4.00, 90th percentile).

Because little is known about factors that may influence the association of cognitive activity with cognitive decline, we conducted further analyses with interaction terms to test whether the association of cognitive activity with cognitive decline varied by age, sex, race, or education. None of these interaction terms was significant, suggesting that the association of cognitive activity with cognitive decline did not vary along demographic lines. This is important because it suggests that all older persons have the potential to benefit from cognitive activity.

We conducted additional analyses to see if the results depended on a subset of persons with very early manifestations of AD. Because impaired episodic memory is an early sign of AD,[27,28] we repeated the core analysis excluding persons whose average immediate and delayed recall of the East Boston Story at baseline was at or below the fifth percentile, and the interaction of cognitive activity with time remained (estimate = 0.014, SE = 0.004, $p < 0.001$). Results were similar when we excluded those with baseline memory at or below the 10th (estimate = 0.014, SE = 0.004, $p < 0.001$) or 15th (estimate = 0.015, SE = 0.004, $p < 0.001$) percentiles.

We also considered whether depressive symptomatology or chronic illness contributed to the association of cognitive activity with cognitive decline. We repeated the core model with terms added for number of depressive symptoms on the CES-D scale and for the number of chronic medical conditions. In this analysis, the association of cognitive activity with cognitive decline was comparable to the original model (estimate = 0.012, SE = 0.003, $p < 0.001$). Results were unchanged in subsequent analyses that controlled for specific chronic illnesses instead of the total number present (data not shown). Because chronic illness can lead to disability, we constructed a final model with terms for disability, number of medical conditions, CES-D score, age, sex, race, and education. In this analysis, frequent cognitive activity continued to be related to reduced cognitive decline (estimate = 0.010, SE = 0.004, $p = 0.003$).

Discussion. In a biracial community of more than 4,000 older persons, we found that frequent participation in cognitively stimulating activities was associated with reduced cognitive decline during a mean of about 5 years of observation. On average, persons with frequent cognitive activity (90th percentile) experienced about 35% less cognitive decline than persons with infrequent cognitive activity (10th percentile). The findings suggest that frequent cognitive activity is associated with reduced cognitive decline in old age.

These results are in agreement with two previous studies of selected groups of highly educated, mostly white participants,[3,13] suggesting that the association of cognitive activity with cognitive decline is generalizable. By contrast, a recent population-based study did not find an association between participation in everyday activities and cognitive decline.[14] In the latter study, however, individual cognitive tests rather than composite measures were used in analyses and very little decline was evident. In addition, cognitive activities were not analyzed as a group but were instead grouped with noncognitive activities into developmental (i.e., following an educational course grouped with doing outdoor sports) and experiential (i.e., visiting a cultural institution grouped with visiting a restaurant) categories.

The current results suggest that cognitive activity contributes to reduced risk of AD not only by an association with level of premorbid cognitive function but also by an association with rate of cognitive decline. The basis of the association of cognitive activity with cognitive decline is uncertain, however. In clinical trials, cognitive training has been shown to have beneficial and long-lasting effects on cognitive function in older persons,[29] supporting the idea that the association between cognitive activity and cognitive decline may be causal. The benefits of cognitive training are restricted to the skill being trained, and evidence of this specificity can also be found in observational studies,[5] suggesting that repetition is an important component of skill building.

The neurobiological mechanisms linking cognitive activity with cognitive decline are unknown. Environmental complexity has been related to a variety of neuroplastic responses in adult animals, including the formation of new neurons and synapses, in brain regions that are critically involved in cognitive functioning.[30,31] In people, therefore, frequent mental activity may contribute to structural and functional reorganization that makes neural systems involved in the activity less vulnerable to disruption by AD pathology.[5,32] Support for this hypothesis comes from a recent clinicopathologic study in which the deleterious impact of AD pathology on cognitive function proximate to death was reduced in persons with more education compared to those with less education.[33] Further clinicopathologic research will be needed to identify the structural, biochemical, and molecular mechanisms that underlie the brain's ability to tolerate AD pathology.

Assessment of cognitive activity is difficult. Most activities involve some degree of cognitive function, but it is uncertain how best to quantify that degree or individual differences, particularly in persons with diverse cultural and socioeconomic backgrounds. The measure used in this study focused on activities in which information processing is central and that make minimal physical or social demands. In previous research, the items on the scale have been shown to be correlated with each other and the total score has been related to education and cognitive function, supporting the construct validity of the scale.[9] We acknowledge, however, that this brief scale is unlikely to capture the full spectrum of individual differences in participation in cognitively stimulating activities and that improved methods of assessing participation in cognitive activity are needed.[8]

Several factors increase confidence in these findings. We studied a geographically defined population of older persons, making it likely that there was a broad spectrum of cognitive activity and cognitive function. We used composite measures of cognitive activity and cognitive function that were previously established in cross-sectional analyses.[9] Analyses controlled for baseline level of cognitive function and excluding persons with baseline memory impairment did not alter results, making it unlikely that the association of cognitive activity with cognitive decline is due to pre-existing cognitive impairment or early AD.

Two study limitations should be noted. We used a global measure of cognition whereas prior research suggests that cognitive activity effects are strongest on processing abilities like working memory.[3,13] Thus, the current results may slightly underestimate the strength of the association between cognitive activity and cognitive decline. In addition, because we used brief measures of depressive symptoms and ill health, the possibility remains that some residual confounding by these variables could have occurred.

Acknowledgment

The authors thank the residents of Morgan Park, Washington Heights, and Beverly who participated in the study. They also thank Ann Marie Lane for community development and oversight of project coordination, Michelle Bos, Holly Hadden, Flavio LaMorticella, and Jennifer Tarpey for coordination of the study, Todd Beck for analytic programming, and the staff of the Rush Institute for Healthy Aging.

References

1. Scarmeas N, Levy G, Tang M-X, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 2001;57:2236–2242.
2. Wang, H-X, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen Project. Am J Epidemiol 2002;155:1081–1087.
3. Wilson RS, Mendes de Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer's disease. JAMA 2002;287:742–748.
4. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and incident AD in a population-based sample of older persons. Neurology 2002;59:1910–1914.
5. Wilson RS, Bennett DA. Cognitive activity and risk of Alzheimer's disease. Curr Direct Psychol Sci 2003;12:87–91.
6. Christensen H, Mackinnon A. The association between mental, social, and physical activity and cognitive performance in young and old subjects. Age Ageing 1993;22:175–182.
7. Hultsch DF, Hammer M, Small BJ. Age differences in cognitive performance in later life: relationships to self-reported health and activity life style. J Gerontol Psych Sci 1993;48:P1–P11.
8. Wilson RS, Barnes LL, Bennett DA. Assessment of lifetime participation in cognitively stimulating activities. J Clin Exp Neuropsychol 2003;25:634–642.
9. Wilson RS, Bennett DA, Beckett LA, et al. Cognitive activity in older persons from a geographically defined population. J Gerontol Psych Sci 1999;54:P155–P160.
10. Friedland RP. Epidemiology, education, and the ecology of Alzheimer's disease. Neurology 1993;43:246–249.
11. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology 1993;43:13–20.
12. Mortimer JA. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics 1997;52(suppl 2):S50–S53.
13. Hultsch D, Hertzog C, Small B, Dixon R. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychol Aging 1999;14:245–263.
14. Aartsen MJ, Smits CHM, van Tilburg T, Knipscheer KCPM, Deeg DJH. Activity in older adults: cause or consequence of cognitive functioning? A longitudinal study of everyday activities and cognitive performance in older adults. J Gerontol Psych Sci 2002;57B:P153–P162.
15. Evans DA, Bennett DA, Wilson RS, et al. Incidence of Alzheimer's disease in a biracial urban community: relation to apolipoprotein E allele status. Arch Neurol 2003;60:185–189.
16. Albert MS, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Int J Neurosci 1991;57:167–178.
17. Smith A. Symbol Digit Modalities Test manual–revised. Los Angeles, CA: Western Psychological Press, 1982.
18. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State. A practical method for grading the mental state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
19. Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). Arch Intern Med 1999;159:1701–1704.
20. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D depression symptoms index. J Aging Health 1993;5:179–193.
21. Radloff LS. The CES-D scale: a self report depression scale for research in the general population. Appl Pyschol Meas 1977;1:385–401.
22. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–923.
23. Laird N, Ware J. Random-effects models for longitudinal data. Biometrics 1982;36:963–973.
24. Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychol Aging 2002;17:179–193.
25. Wilson RS, Gilley DW, Bennett DA, Beckett LA, Evans DA. Person-specific paths of cognitive decline in Alzheimer's disease and their relation to age. Psychol Aging 2000;15:18–28.
26. SAS Institute Inc. SAS/STAT user's guide, version 8. Cary, NC: SAS Institute, 2000.
27. Bowen J, Teri L, Kukull W, McCormick W, McCurry SM, Larson EB. Progression to dementia in patients with isolated memory loss. Lancet 1997;349:763–765.

28. Howieson DB, Dame A, Camicioli R, Sexton G, Payami H, Kaye JA. Cognitive markers preceding Alzheimer's dementia in the healthy oldest old. J Am Geriatr Soc 1997;45:584–589.
29. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled clinical trial. JAMA 2002;288:2271–2281.
30. Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Ann Neurol 2002;52:135–143.
31. Shors T, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved in the formation of trace memories. Nature 2001;410:372–376.
32. Cummings J, Vinters H, Cole G, Khachaturian Z. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. Neurology 1998;51(suppl 1):S2–S17.
33. Bennett DA, Wilson RS, Schneider JA, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 2003 (in press).

Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD

T. Hershey, PhD; F.J. Revilla, MD; A.R. Wernle, BSN; L. McGee-Minnich, BSN; J.V. Antenor, MPH; T.O. Videen, PhD; J.L. Dowling, MD; J.W. Mink, MD, PhD; and J.S. Perlmutter, MD

Abstract—*Objective:* To assess whether subthalamic nuclei (STN) stimulation's primary mechanism of action is to drive or inhibit output neurons. *Methods:* Cerebral blood flow responses to STN stimulation were measured using PET in 13 patients with Parkinson disease. Patients were scanned with stimulators off and on (six scans each condition). Clinical ratings, EMG, and videotaping of movements were obtained at each scan. Scans with observable tremor or movement were eliminated from analysis. Brain regions where STN stimulation significantly altered blood flow were identified. *Results:* STN stimulation increased blood flow in midbrain (including STN), globus pallidus, and thalamus, primarily on the left side, but reduced blood flow bilaterally in frontal, parietal, and temporal cortex. *Conclusions:* These data suggest that STN stimulation increases firing of STN output neurons, which increases inhibition of thalamocortical projections, ultimately decreasing blood flow in cortical targets. STN stimulation appears to drive, rather than inhibit, STN output neurons.

NEUROLOGY 2003;61:816–821

Despite the clinical benefit of deep brain stimulation (DBS) of the subthalamic nuclei (STN), the fundamental effects of DBS on brain activity remain unclear. DBS could alter neuronal function via at least three different mechanisms: 1) by blocking local neuronal activity ("conduction block"); 2) by preferentially activating local inhibitory axon terminals, thus inhibiting output neurons from the target structure; or 3) by directly exciting output neurons, increasing their firing rate. These options may not be mutually exclusive. The net output from the stimulated area may be a key element in determining how DBS alters brain function.

In this investigation, PET measurements of blood flow were used to determine whether DBS of the STN stimulates or inhibits output neurons from the STN. By measuring blood flow in targets of STN projection neurons and cortex, it can be determined whether these projection neurons are increasing or decreasing their activity with stimulation. The underlying assumption of this approach is that changes in local blood flow reflect changes in neuronal activity in target synaptic fields, including local interneurons, rather than changes in efferent activity.[1-3]

If DBS drives efferent axons from STN, blood flow would increase in SN, GPi, and thalamus, but decrease in the cortical targets of thalamic nuclei. If DBS reduces output from STN, blood flow would decrease in GPi and thalamus, but increase in cortical regions. This study found that DBS of STN increases blood flow in midbrain and thalamus yet decreases blood flow in several cortical areas, suggesting that DBS drives STN output neurons.

Materials and methods. *Subjects.* Thirteen patients with Parkinson disease (PD) with bilateral STN stimulators implanted at least 2 months earlier were studied. Patients met the diagnostic criteria for clinically definite PD[4,5] and were excluded for a

From the Departments of Psychiatry (Dr. Hershey), Neurology (Drs. Hershey, Revilla, Videen, and Perlmutter, and A.R. Wernle, L. McGee-Minnich, and J.V. Antenor), Neurological Surgery (Drs. Revilla and Dowling), Radiology (Drs. Videen and Perlmutter), and Anatomy and Neurobiology (Dr. Perlmutter), Washington University School of Medicine, St. Louis, MO; and Departments of Neurology, Neurobiology, and Pediatrics (Dr. Mink), University of Rochester Medical Center, Rochester, NY.

Supported by the Greater St. Louis Chapter of the American Parkinson Disease Association (APDA), NIH (NS41248; NS41509), American Academy of Neurology, APDA Advanced Center for PD Research at Washington University, the Sam & Barbara Murphy Fund, and the Barnes-Jewish Hospital Foundation.

Received March 3, 2003. Accepted in final form May 21, 2003.

Address correspondence and reprint requests to Dr. J.S. Perlmutter, Campus Box 8111, Washington University School of Medicine, 4525 Scott Avenue, St. Louis, MO 63110; e-mail: joel@npg.wustl.edu

