

NEUROLOGY

**fMRI evidence of compensatory mechanisms in older adults at genetic risk for
Alzheimer disease**

Nikolaos Scarmeas, Yaakov Stern, Mark W. Bondi and S. Duke Han
Neurology 2005;65;1514-1515

This information is current as of March 3, 2006

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://www.neurology.org/cgi/content/full/65/9/1514-a>

Neurology is the official journal of AAN Enterprises, Inc. A bi-monthly publication, it has been published continuously since 1951. Copyright © 2005 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.



Position on Stem Cell Research

To the Editor: The American Academy of Neurology (AAN) and American Neurological Association (ANA) position paper on the use of stem cells in biomedical research is a decision to support destruction of and experimentation on human life at its very earliest stage.

The AAN and ANA justify this position by citing “a strong moral obligation to pursue research that may result in beneficial treatments.” However, using an end to justify a means is dangerous when dealing with human life and was used in the last century to justify increasing encroachment on principles that physicians should hold sacred.¹ Physicians should not be saying, “This research may result in a cure, therefore it is justified.” Physicians should be saying, “If there is any, even the least chance that this research is ethically questionable, we should not go anywhere near it.”

The AAN and ANA should be guardians of the traditional ethics and standards of the neurologic profession and should be conservative and cautious about any new positions they take on behalf of their members.² It is also difficult to understand the motivation of the AAN and ANA to put out an ethical position paper which is decisive in its conclusions when there is ongoing debate and disagreement on this issue throughout the country.

The journal *Neurology* has also not shown balance in publishing two editorials that strongly favor one side of the debate without giving a voice to neurologists who object to using embryonic human stem cells.

Patrick Pullicino, MD, PhD, William J. Burke, MD, PhD, FAAN, Newark, NJ

The institutional affiliations of the signatories are intended for purposes of identification only and in no way imply representation of or endorsement by our respective institutions or departments.

Text of letter sent to Dr. Olson:

April 4th 2005

Dear Dr. Olson: We are writing to raise a major concern about the way in which the President and Board of Directors of the American Academy of Neurology have represented its members in the recent Position Statement regarding the use of embryonic and adult human stem cells in biomedical research. The position taken by the AAN on this issue is a decision to support destruction of human life at its earliest embryonic stage. We and many other neurologists believe that human life starts at conception. We hold the destruction of human embryos for stem cell research to be unethical and an exploitation of society's weakest members. Neurologists have many patients who cannot speak or act for themselves, and more than any other medical specialty, our duty is to protect and champion these weakest members of society. The AAN is a scientific body, not an ethical body. What the AAN Board has done here is to take an ethical position on behalf of all of its members, even though they “recognize that there are differing ethical opinions . . . that cannot be resolved through medical science alone.” The Board has applied what they see as the scientifically-sanctioned ethical view, to the whole AAN membership. The justification given for doing this, that this research “. . . may result in beneficial treatments . . .”, is totally inadequate. Using an end to justify a means is dangerous when dealing with human life, and has many very unsavory historical precedents. Nor is there any possible justification for riding roughshod over members' ethical views. The very least the AAN should have done was to poll its members on their views about this issue before publishing a Position Statement that appears to show unanimous support from the membership. The current Position Statement should be revised to state that a proportion of its members are categorically against it.

William J. Burke, MD, PhD, FAAN, Professor in Neurology, St. Louis University. Diego Cadavid, MD, Assistant Professor of Neurology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey. James Carroll, MD, Professor and Chief, Child Neurology, Medical College of Georgia. Robert E. Cranston, MD, MA, FAAN, Clinical Associate Professor, University of Illinois

Urbana-Champaign. Pierre Giglio, MD, Assistant Professor in Neurology, University of Nebraska. David C. Hess, MD, Professor and Chairman of Neurology, Medical College of Georgia. Catalina Ionita, MD, Neurocritical care fellow, Duke University. Laurence Kinsella, MD, FAAN, Associate Professor, Neurology, Saint Louis University. Patrick Pullicino, MD, PhD, Professor and Chairman of Neurology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey. D. Alan Shewmon, MD, Professor of Neurology, University of California at Los Angeles.

The institutional affiliations of the signatories are intended for purposes of identification only and in no way imply representation of or endorsement by our respective institutions or departments.

Reply from the AAN: In the May 24, 2005, issue of *Neurology*, the deliberative process used to create our position statement on embryonic stem cell (ESC) research was explained.³ Coincidentally that same day, the US House of Representatives cast a bipartisan vote in favor of the Castle-DeGette bill, which would expand federal funding for ESC research using embryos left over after in vitro fertilization (IVF) treatment.⁴ The AAN and ANA expect that this bill will restore the use of the 2000 NIH Guidelines to further promote ethical research practices in this field. If this bill fails to become law, ESC research will continue in places where there may or may not be such ethical safeguards. Meanwhile, IVF clinics and their clients will continue to face limited options when deciding the fate of surplus embryos.

As the position statement on ESC research acknowledges, “In consideration of taking a specific position on the use of human embryonic stem cells for research, the AAN and the ANA recognize that strongly held and disparate views exist, and it is thus unlikely they can satisfy the concerns of all their members or the public.”⁵ There may never be unanimous agreement as to when life begins—whether at conception, birth, or any stage between. In our deliberations, physicians, scientists, and ethicists all had a place at the table, and all viewpoints—minority as well as majority—were shared and pondered. Ultimately, we concluded that, as physicians, we have a deep and abiding moral and ethical obligation to support the pursuit of ESC research under carefully considered strictures. We cannot turn our eyes from the possibility that this work may lead to treatments or cures for neurologic disorders.

Drs. Pullicino and Burke attempt to draw a parallel between ESC research and medical experiments during the Third Reich. We all know that knowledge can be applied toward both good and evil ambitions. The horrors of the 1930s and 1940s inflicted in the name of science should never be forgotten. However, harnessing the dark forces of nationalism and racism in pursuit of world domination and “racial hygiene” is starkly different than the AAN and ANA urging federal support and strict ethical oversight for research that may alleviate the suffering of millions of people worldwide—as many as 50 million in the United States alone.

The AAN is not merely a scientific body, but is deeply concerned with a wide range of ethical issues. We advocate for improved health care for people with neurological conditions and fair compensation for neurologists. These too become ethical issues in an economic and political climate that forces heavy competition for the limited number of public dollars available. Every decision we make is inherently an ethical one, and we do our best to reconcile a wide range of member positions. We encourage a continuing dialogue on this topic. We welcome your viewpoint and will keep your concerns in mind as we continue to track this issue and revisit it as research progresses and circumstances require.

Thomas R. Swift, MD, AAN President; Sandra F. Olson, MD, AAN Past President

To the Editor: The editorial by Dr. Goldman cites the role of disease-focused advocacy groups in inflaming the stem cell debate and singles out Alzheimer disease (AD) as a stem cell “cause célèbre” generating “irrational exuberance” about therapeutic potential.⁶ As the largest voluntary health organization working to

eliminate AD and support those affected, the Alzheimer's Association feels compelled to respond.

The Alzheimer's Association would like to clarify that it has never specifically advocated for stem cell research, encouraged others to do so, or nurtured unrealistic expectations. Our science staff and advisors agree with Dr. Goldman that consensus in the field suggests any translation of stem cell research to AD treatment lies far in the future. Our spokespeople have stated repeatedly in public venues that there are numerous strategies more promising than stem cells for treating or preventing AD. Research priorities identified by our medical and scientific advisors and detailed in our annual requests for grant proposals have never included stem cell studies.

On a philosophical level, we oppose any restriction or limitation on human stem cell research, provided that appropriate scientific review and ethical oversight guidelines are in place. Our National Board of Directors has adopted a policy statement to this effect. The Alzheimer's Association would be willing to lend its name to legislation removing barriers to human stem cell research provided the legislation is consistent with our position.

The Alzheimer's Association feels all legitimate paths of inquiry operating within appropriate boundaries should remain open and the decision to follow any particular path should rest with individual scientists as long as they respect those boundaries.

Sam Gandy, MD, PhD, *Philadelphia, PA*

Reply from the Author: Pullicino and Burke's criticisms of both the AAN/ANA position on stem cell research and my editorial are no doubt sincere, but I believe misguided, and to my mind antithetical to the role of treating physicians. First, Pullicino and Burke's statement that if there is "even the least chance that this research is ethically questionable, we should not go anywhere near it" presumes that stem cell research is in fact ethically questionable. Yet in making this statement, the respondents presume to inhabit a moral high ground to which they are not necessarily entitled. Fundamentally, they assume that the means involved in pursuing stem cell-based treatment strategies—the destruction of blastocysts—are inherently so amoral as to ethically preclude the development of cell-based therapies. At issue here, on the one hand, are unused and barely macroscopic collections of cells destined for destruction, from which no living being would ever develop, and on the other hand, sick patients, inestimable numbers of children and adults of both this and future generations, who stand to meaningfully benefit from their use. By what—or whose—moral imperative can treatment reasonably be denied these patients, in the absence of demonstrable harm? I would suggest that the respondents need to justify the ethics of their own position, which strikes me as inimical to the physicians' role as healer. Ultimately, whatever their belief system, how can prac-

ticing clinicians claim a moral prerogative not to treat, not to attempt to heal, when the only affront is to the essentially philosophical sensibilities of a relative few?

Second, and even more concerning to me, is Pullicino and Burke's implicit comparison of stem cell research to historic abuses of human rights, as manifested in their reference to Shevell's commentary on Hallevorden's beliefs on racial hygiene. By making this reference, the authors implicitly equate stem cell research with the racist ideologies of Hallevorden. This is a specifically noxious argument and an affront to the great numbers of scientists and clinicians whose common and sole goal in stem cell research is the alleviation of human suffering. Unfortunately, this type of rhetorical equation of contemporary stem cell science with malevolent pseudoscience has become an increasingly frequent device of the far right. In the past few weeks, particular angst has been stirred by comments attributed to James Dobson, leader of Focus on the Family, comparing the actions of stem cell biologists to Nazi physicians. Need we now to look to our own, fellow neurologists who should share our common goal of treating the sick and healing the afflicted, for fomenting the same type of extremism? Such spurious equations serve only to poison rather than inform intelligent debate.

At the other end of the spectrum, I was puzzled by Gandy's spirited if unnecessary defense of the Alzheimer's Association and its policy regarding stem cell science. Dr. Gandy appears to take offense at my position that advocacy groups risk overstating the near-term benefits of stem cell research, and in thereby degrading the long-term public support of this research. The Alzheimer's Association has been a responsible and important advocate for research into the causes and treatments of Alzheimer disease. It has voiced no doctrinal position on stem cell research and was not the target of my comments. Not all disease-oriented research advocates have been so responsible.

Steven A. Goldman, MD, PhD, *Rochester, NY*

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Shevell M. Racial hygiene, active euthanasia, and Julius Hallevorden. *Neurology* 1992;42:2214–2219.
2. Burke WJ, Cadavid D, Carroll J, et al. Letter to Dr. Olson, President of the American Academy of Neurology. April, 2005.
3. American Academy of Neurology development of a position on stem cell research. *Neurology* 2005;64:1674.
4. Stem Cell Research Enhancement Act of 2005, HR 810 EH, passed by the US House of Representatives, 109th Congress, May 24, 2005.
5. Position statement regarding the use of embryonic and adult human stem cells in biomedical research, American Academy of Neurology and American Neurological Association. *Neurology* 2005;64:1679–1680.
6. Goldman SA. Neurology and the stem cell debate. *Neurology* 2005;64:1675–1676.

Risedronate therapy for prevention of hip fracture after stroke in elderly women

To the Editor: The article by Sato et al.¹ reported a reduction in hip fractures following stroke using oral risedronate. Fractures following stroke are recognized and intervention studies necessary,² but there are several omissions in this article which are a barrier to assessing the validity and applicability of these results.³

There are no details regarding how the sample size was determined, particularly important in hip fracture intervention trials where the event rate is low. Secondly, without details of baseline stroke severity, Barthel index (BI), and stroke classification, it is difficult for clinicians to know which stroke patients may benefit from the intervention, given the heterogeneity of the disease. The patients presumably had mild disability because those unable to stand or swallow were excluded. Males, those with dysphasia (based on the assumption that written informed consent was required) and those on anticoagulants, were also excluded.

In our acute stroke service with a catchment area of 500,000, <10% of admissions would fulfill these criteria (n=15 in four months) and yet the authors recruited 374 patients in this period. Formal description of the flow of patients through each stage of the study³ would provide information on inclusion rates and acceptance rates. The definition of "fallers" is open to misinterpreta-

tion, since someone who fell once is not distinguished from a recurrent faller. Although the total number of falls was equivalent between groups, the number of falls per patient is crucial in assessing whether the lower fracture rate is due solely to the efficacy of the intervention. Recurrent falls are common after stroke. In one study, 19% of patients fell once within a year but 29% fell repeatedly.⁴

Finally, the radiographic prevalence of vertebral fractures in unselected postmenopausal Japanese women (mean age 65.4 ± 9.8) was 9.5% in one series,⁵ so the assertion that 187 postmenopausal women had no evidence of vertebral abnormalities raises concerns about the accuracy of assessment or how representative the sample was. This study is potentially of great importance given the scale of the problem of hip fractures following stroke and the paucity of interventions to date, and we congratulate the authors on their achievement. The concerns we raise can be addressed simply, since the relevant details were recorded. By providing this information, the impact of this study on clinical practice and further research will be enhanced.

Kenneth E.S. Poole, BM, MRCP, Elizabeth A. Warburton, MA, DM, MRCP, Jonathan Reeve, DM, BSc, FRCP, *Cambridge, UK*

Reply from the Authors: We appreciate the comments from Poole et al. regarding our study¹ on efficacy of risedronate therapy on hip fracture following an acute stroke. Although we did not perform power calculation, we thought a trial size of 374 was appropriate due to our previous experience in a cohort study on hip fractures in stroke patients.⁶

Baseline stroke severity (degree of hand paralysis according to Scandinavian Stroke Scale [SSS]) and BI in the placebo and risedronate groups were 3.1 ± 1.7 , 3.1 ± 1.2 SSS, and 78 ± 24 , 77 ± 24 BI, respectively. The numbers of patients with cerebral hemorrhage and infarction in the placebo and risedronate groups were 40/147 and 41/146. Patients with dysphagia and those receiving anticoagulants were excluded.

Our hospital treats mild acute stroke patients with clear consciousness, but acute stroke patients with impaired consciousness are transferred to other hospitals. Thus, limited to women, many patients meet the inclusion criteria leading to high inclusion rates (71%) and acceptance rates. Our hospital is a specialized center for acute stroke, and we treat about 2,800 stroke patients per year.

We agree that the definition of "fallers" can be misinterpreted, and it needs to be more specific since repeated falls may enhance the risk of fractures. However, there may not be any evidence that those who fell once are a different group of patients than those who fell more than once. This point has to be addressed in future studies.

We recruited 212 age-matched volunteers from the community,

and 25 volunteers (12%) had vertebral abnormalities in spinal radiological examinations. Thus, we employed 187 postmenopausal women as the comparison group to discriminate bone mineral density variations related to the treatment from those related to methods of measurement.

Yoshihiro Sato, MD, Jun Iwamoto, MD, Tomohiro Kanoko, PhD, Kei Satoh, MD, *Tagawa, Japan*

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women. *Neurology* 2005;64:811–816.
2. Poole KE, Reeve J, Warburton EA. Falls, fractures, and osteoporosis after stroke: time to think about protection? *Stroke* 2002;33:1432–1436.
3. Moher D, Schulz KF, Altman DG. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 2001;357:1191–1194.
4. Lamb SE, Ferrucci L, Volapto S, Fried LP, Guralnik JM. Risk factors for falling in home-dwelling older women with stroke: The women's health and aging study. *Stroke* 2003;34:494–501.
5. Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M. Fracture prediction from bone mineral density in Japanese men and women. *J Bone Miner Res* 2003;18:1547–1553.
6. Sato Y, Asoh T, Kaji M, Oizumi K. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *J Bone Miner Res* 2000;15:2487–2494.

Heads down: Flat positioning improves blood flow velocity in acute ischemic stroke

To the Editor: I read with great interest the article by Wojner-Alexander et al.¹ regarding down head positioning promoting higher flow velocities in median cerebral artery. The authors should provide the information regarding the length of the effectiveness of this positioning. By ensuring a higher velocity, there may be more blood coming toward the cerebral tissue, but should all the blood volume be coming out?

Increasing cerebral blood volume content may later increase intracranial pressure but this was not assessed within the observation period. Further studies are needed to confirm the safety of this procedure. If this ultimately proves effective, lying down will certainly be part of acute stroke measures when acute stroke patients are admitted.

Wladimir K. de Paula, MD, *Brasalia, Brazil*

Reply from the Author: Acute stroke patients may show some clinical improvement in neurologic dysfunction when placed flat, but the question for how long this position should be maintained remains unclear. We individualize the approach to positioning,

and some patients are kept in a flat position for the first 24 hours following admission. We emphasize rotation from side-to-side for these patients to minimize risk of aspiration.

For patients with concurrent cardiopulmonary compromise (e.g. congestive heart failure) that do not tolerate flat positioning, we utilize 15-degree head elevation. We have not systematically evaluated use of the Trendelenburg position, but basic physics would suggest that this position may further augment mean flow velocity. Lastly, we consider patients with fluctuating presentation for blood pressure, volume augmentation, or both and this practice is best guided by thorough systemic hemodynamic assessment to avoid fluid volume overload or significant left ventricular afterload promoting cardiac failure. We agree that follow-up studies are needed to determine long-term benefit.

Anne W. Wojner-Alexandrov, PhD, RN, CCRN, FAAN, *Houston, TX*

Copyright © 2005 by AAN Enterprises, Inc.

Reference

1. Wojner-Alexandrov A, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: Flat positioning improves blood flow velocity in acute ischemic stroke. *Neurology* 2005;64:1354–1357.

fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease

To the Editor: We read the recent article by Bondi et al.¹ with great interest. The authors review previous studies suggesting that blood oxygenation level dependent (BOLD) brain responses during performance of memory tasks are of greater magnitude and more diffuse in patients with early Alzheimer disease (AD) than in normal older individuals. They also review previous studies demonstrating an increase in the intensity and extent of brain activation for non-demented E4 carriers.

Using an elegant fMRI experiment, they conclude that elderly E4 carriers require additional cognitive effort to achieve comparable performance levels on tests of episodic memory encoding. The authors suggest that the observed greater magnitude and extent of activations is consistent with the compensatory hypothesis.

There is also strong evidence for reporting brain regions with decreased activation in E4 carriers. Using $H_2^{15}O$ PET, we have demonstrated decreased activation for healthy young (Scarmeas et al. *JNNP*, in press), healthy elderly² and AD³ E4 carriers during non-verbal memory tasks. Decreased activation for E4 carriers has been also demonstrated with fMRI by other investigators dur-

ing visual naming and verbal fluency tasks.^{4,5} Even in Bondi et al.'s study, there were clusters in the left hippocampal and parahippocampal areas where E4 carriers had lower activation, as compared to their E3 counterparts. The interpretation of either increased or decreased activation is not straightforward, as it is not always readily apparent which directionality reflects the "optimal" response. Decreased activation for E4 carriers may be equally important.

In many previous studies involving either AD patients or healthy elderly, decreased activation in certain brain regions has been associated with more efficient processing while an increase has been associated with less effective cognitive strategies. Demonstration of significant correlations with aspects of task performance is one way to determine whether increased or decreased activation constitutes a beneficial or compensatory response.

Nikolaos Scarmeas, MD, Yaakov Stern, PhD, *New York, NY*

Reply from the Authors: We thank Drs. Scarmeas and Stern for their interest in our study¹ and cogent commentary. They point out that interpretation of directionality of activation in functional imaging studies is not straightforward. In other words, "optimal"

performance may be reflected either in decreases or increases in activation within a given region.

Although not explicitly stated by Scarmeas and Stern, another implication is that both may occur within a functional system such as episodic memory encoding. That is, an increase in one region may be best complemented by a decrease in activation within another region of this cognitive system.⁶ Advancing methodologies in functional connectivity, including efforts to combine different imaging techniques, will help elucidate such relationships.⁷

The authors close by suggesting that demonstration of significant correlations with aspects of task performance is one way to determine whether increased or decreased activation may constitute a beneficial or compensatory response. Again, we agree and refer back to our article's correlations of brain response in the hippocampi with two different measures of task performance: (a) recognition memory for the pictures and (b) the California Verbal Learning Test's⁸ summary learning variable. Both measures demonstrated different patterns of correlation between the two *APOE* genotype groups. The *APOE* E3 group demonstrated positive associations between BOLD response in the hippocampus and task performance, whereas the *APOE* E4 group demonstrated either negative or no associations.

Based on these correlations, we suggested that the *APOE* E4 group may be invoking bilateral medial temporal brain resources in an aberrant manner as an attempt to facilitate encoding.

Although we fully acknowledge that these correlations are preliminary, they anchor the BOLD response to behavioral measures of interest. In response to Scarmeas and Stern's review of visual naming and verbal fluency studies suggesting a different pattern of activation according to *APOE* genotype, we argue that tasks of episodic memory, such as the one employed for the current study, would differentially activate hippocampal and other regions

within a broadly distributed network and thus are difficult to compare to one another.

Scarmeas and Stern are correct to stress the cautionary stance with which investigators should approach directionality of activation within fMRI research. Given our preliminary evidence supporting a compensation hypothesis, more studies are needed to further clarify the underlying mechanisms of such a phenomenon.

Mark W. Bondi, PhD, S. Duke Han, PhD, *San Diego, CA*

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology* 2005;64:501–508.
2. Scarmeas N, Habeck C, Anderson KE, et al. Altered PET functional brain responses in cognitively intact elderly persons at risk for Alzheimer disease (carriers of the E4 allele). *Am J Geriatr Psychiatry* 2004;12:596–605.
3. Scarmeas N, Anderson KE, Hilton J, et al. APOE-dependent PET patterns of brain activation in Alzheimer disease. *Neurology* 2004;63:913–915.
4. Smith CD, Andersen AH, Kryscio RJ, et al. Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. *Neurology* 1999;53:1391–1396.
5. Smith CD, Andersen AH, Kryscio RJ, et al. Women at risk for AD show increased parietal activation during a fluency task. *Neurology* 2002;58:1197–1202.
6. Ragland JD, Gur RC, Valdez J, et al. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. *Am J of Psychiatry* 2004;161:1004–1015.
7. Ramnani N, Behrens TE, Penny W, Matthews PM. New approaches for exploring anatomical and functional connectivity in the human brain. *Biol Psychiatry* 2004;56:613–619.
8. Delis DC, Kramer JH, Kaplan E, Ober BA. The California Verbal Learning Test. 1987. New York: Psychological Corporation.

**fMRI evidence of compensatory mechanisms in older adults at genetic risk for
Alzheimer disease**

Nikolaos Scarmeas, Yaakov Stern, Mark W. Bondi and S. Duke Han
Neurology 2005;65;1514-1515

This information is current as of March 3, 2006

**Updated Information
& Services**

including high-resolution figures, can be found at:
<http://www.neurology.org/cgi/content/full/65/9/1514-a>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables)
or in its entirety can be found online at:
<http://www.neurology.org/misc/Permissions.shtml>

Reprints

Information about ordering reprints can be found online:
<http://www.neurology.org/misc/reprints.shtml>

