



BEST OF  
THE FIELD

# Therapeutic Trends and Genetic Insights Highlighted in Noteworthy Papers in Dementia and Memory

BY NORRA MACREADY

**N**ew data on therapeutic trends and genetic insights are featured in the papers published in 2008 and chosen by John Hart, MD, and David Knopman, MD, for *Neurology Today* as best of the field in memory and dementia.

## BENEFITS OF EXERCISE

Of all the clinical candidates for preserving cognitive function, “one thing that continually comes out a winner is physical exercise,” said Dr. Hart, medical science director of the Center for BrainHealth at the University of Texas at Dallas.

Adding to that growing body of evidence is a study by Nicola T. Lautenschlager, MD, professor of psychiatry of old age at the University of Melbourne in Australia, and colleagues in the Sept. 6, 2008 issue of the *Journal of the American Medical Association*. They reported outcomes of the Fitness for the Aging Brain Study, a randomized, controlled trial conducted between May 2004 and January 2007 at the Royal Perth Hospital in Australia.

The participants were locally recruited volunteers aged 50 or more who reported subjective memory impairment, but did not meet clinical criteria for dementia. Baseline assessment included tests of cognitive function and measurement of the *apolipoprotein E* (APOE) genotype. After that, the volunteers were randomized to a “usual care” control group, which were given information about memory loss, stress management, healthy eating, and other health-oriented messages, or to a 24-week physical activity intervention, in which the subjects were encouraged to engage in 150 minutes of moderately intensive physical activity each week, preferably in the form of three 50-minute weekly sessions. All the participants were assessed six, 12, and 18 months after



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baseline measures were taken.

By the end of the trial, people in the exercise group scored significantly higher on the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), had better delayed recall, and lower Clinical Dementia Rating sum of boxes scores, than people in the control group. The change in ADAS-Cog scores during the study for APOE noncarriers who exercised was significantly better than scores of individuals in the other groups combined.

The difference of 0.69 points in ADAS-Cog scores “is small but potentially important when one considers the relatively modest amount of physical activity

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# Brain Mechanisms Needed to Overcome Addiction are Impaired, New Studies Suggest

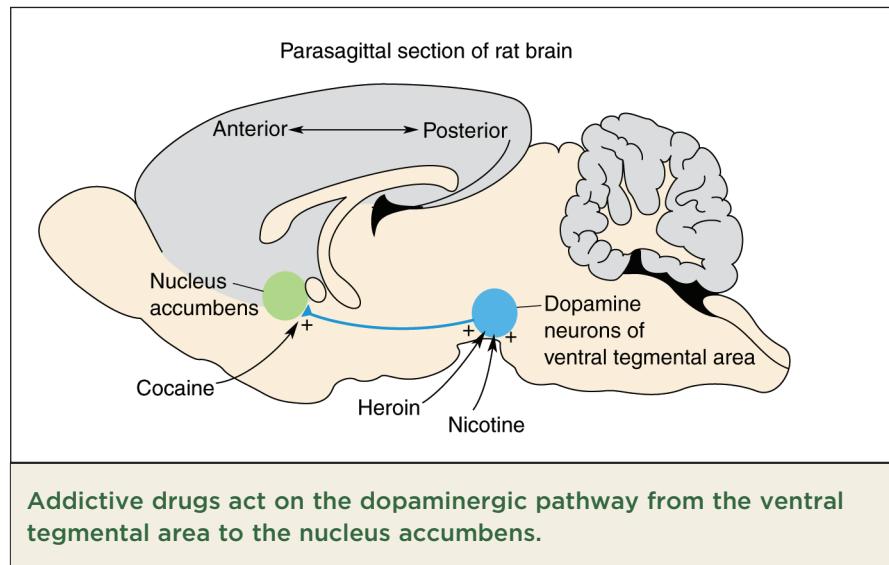
BY TOM VALEO

## ARTICLE IN BRIEF

Investigators discussed the latest data from studies on how impaired brain mechanisms challenge recovery from drug addiction.

**W**ASHINGTON—Drug addiction impairs the very brain mechanisms needed to overcome addiction, according to scientists who described their new work here at the Society for Neuroscience annual meeting in November.

For example, addictive drugs produce changes in long-term potentiation (LTP) of neurons in the ventral tegmental area (VTA), part of the brain's reward circuit that promotes survival-boosting behaviors that include eating and procreation, according to Julie Kauer, PhD, professor of medical science in the department of molecular pharmacology, physiology,



biotechnology, and neuroscience at Brown University.

Normally LTP creates strong synaptic connections essential for learning and memory, but addictive drugs stifle the

VTA neurons that produce gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that prevents the overproduction of dopamine. Without GABA to apply the brakes, dopamine release

proceeds unabated, and the brain, in effect, learns to crave drugs.

"We injected animals either with saline or morphine and looked at the GABAergic synapses 24 hours later," Dr. Kauer said. "In animals treated with morphine, there was essentially no LTP at VTA GABAergic synapses 24 hours later. Within five days the response returns to normal, but we think in this time period the loss of this inhibitory brake could contribute to excessive firing of the dopamine neurons downstream. The synaptic response can become and stay potentiated for a long time."

Nitric oxide, one of two molecules necessary for the long-term potentiation of GABA, stops performing this function after exposure to morphine, Dr. Kauer said, either because of a loss of the enzyme guanylate cyclase, or because guanylate cyclase becomes insensitive to nitric oxide. Restoring guanylate cyclase

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## Best of the Field

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undertaken by participants in the study," the authors wrote. "This paper shows that, at the end of the day, physical fitness seems to stave off cognitive decline to some degree," Dr. Hart said.

## INTRANASAL INSULIN

Intranasal insulin was associated with better memory and attention span than placebo in a randomized, double-blind pilot study of 25 people with AD or its precursor, mild cognitive impairment with amnesic features. The patients took medication or a placebo twice a day for 21 days. Memory retention among the insulin-treated group was significantly better on day 21 than at baseline, than the placebo group ( $p=0.0374$ ). Patients who received insulin also performed better on measures of selective attention. Insulin administration was associated with higher amyloid beta (A $\beta$ ) 40/42 ratios — measured in plasma — than the placebo; a lower ratio is considered a risk factor for AD, wrote the authors, led by Mark A. Reger, PhD, of the University of Washington, Seattle, in the Feb. 5, 2008, *Neurology*.

This study was not definitive, Dr. Hart noted. In addition to the small number of subjects, baseline postprandial insulin levels were quite a bit higher in the insulin-treated group, despite randomization. Also, baseline scores of memory and selective attention were not ideally equated. Still, the results imply that hormones and hormone-related changes play an important role in developing therapies for these patients, along with "the individual variability that every patient brings to the table," he said. "You can't just assume that everyone is the same."

## NO EFFECT OF IMMUNIZATION

Dr. Knopman, professor of neurology at the Mayo Clinic in Rochester, MN, chose one study because of its disappointing results. In a randomized, placebo-controlled, phase I clinical trial, Clive Holmes, MD, PhD, professor in the Memory Assessment and Research Centre at Moorgreen Hospital, and colleagues at the University of Southampton, UK, studied the effect of A $\beta$  42 immunization on 80 patients with AD. From 2003 to 2006, they followed the patients until death or severe dementia occurred. Neuropathologic examination of the deceased patients showed a significantly lower

A $\beta$  42 load in the brains of those who were immunized ( $p=0.02$ ), they reported in the July 29, 2008, *Lancet*. Yet "seven of the eight immunized patients who had an autopsy, including those with virtually complete plaque removal, had had severe end-stage dementia before death," the authors wrote. Also, immunization did not prolong survival or delay the onset of severe dementia. Dr. Knopman said this finding was "troubling," adding, "It has caused some to doubt the amyloid hypothesis of Alzheimer disease."

## ALS GENE STUDIED

Another of Dr. Knopman's selections produced more encouraging data. A May 2008 paper in *Nature Genetics* delved deeper into the relationship between mutations in the gene for the TAR DNA binding protein (TDP-43) and the occurrence of amyotrophic lateral sclerosis (ALS). Edor Kabashi, PhD, a post-doctoral fellow, and colleagues at McGill University in Montreal, Canada, reported on eight missense mutations in the TDP-43 gene in six people with sporadic ALS, and three with familial ALS.

"The demonstration that mutations in TDP-43 cause ALS, which sometimes appears with FTD, strongly suggests that TDP-43 is directly related to the pathol-

ogy of both ALS and FTD," Dr. Knopman said. He added that abnormal TDP-43 has been detected in motor neurons of almost everyone with sporadic ALS, "suggesting that it is involved directly in the death of motor neurons." •

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