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Contacts: Kat Snodgrass, (202) 962-4090
Sarah Bates, (202) 962-4087

RESEARCH SHOWS BEHAVIOR GREATLY IMPACTS RECOVERY FROM BRAIN INJURY, ADDICTION, AND OTHER CONDITIONS

Studies explore lifestyle's influence on wellness and brain health

SAN DIEGO — New research is providing a deeper understanding of how individual actions — such as exercising, sensory stimulation, or drinking — influence brain health and outcomes. This new knowledge could ultimately lead to interventions in age-related cognitive declines, drug abuse, stroke, and brain injury, separate from or in combination with traditional pharmacological approaches. These findings were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

Specifically, today's new findings show that:

- Mild sensory stimulation within the first two hours of stroke may be a life-saving intervention before patients reach emergency rooms. Research showed whisker stimulation in rats protected against brain damage and restored function (Ron Frostig, PhD, abstract 14.10, see attached summary).
- Musical training may help mitigate age-related hearing loss, suggesting that the old adage "use it or lose it" applies to hearing (Benjamin Zendel, abstract 481.14, see attached summary).
- Aerobic exercise lessens excessive cocaine use in rats. The findings suggest physical activity may be helpful in treating or preventing drug addiction (Mark A. Smith, PhD, abstract 574.12, see attached summary).
- Being physically fit prior to injury alleviated effects of traumatic brain injury in mice. This finding builds on existing research showing physical exercise after injury improves cognitive function (Jerome Badaut, PhD, abstract 356.7, see attached summary).

Other recent findings discussed show that:

- Behavior and lifestyle interventions can improve brain health and function, and may be effective in slowing or preventing age-related diseases. Both human and animal studies support the effectiveness of physical activity, cognitive training, and other lifestyle changes to benefit brain health, learning, and memory (Carl Cotman, PhD, see attached speaker's summary).

"Evidence indicates that our actions have broader and more complex ties to brain function and health than previously thought," said press conference moderator Carol A. Barnes, PhD, of the Evelyn F. McKnight Brain Institute of the University of Arizona, an expert on the aging brain. "We are learning a great deal about the brain, and today can fully appreciate our own role in keeping it healthy."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 14.10 Summary

Senior author: Ron Frostig, PhD (949) 824-2883
University of California, Irvine rfrostig@uci.edu
Irvine, Calif.

Sensory Stimulation Protects Against Brain Damage Caused by Stroke

Animal study could lead to life-saving treatments for stroke

Mild sensory stimulation given soon after the first symptoms of a stroke can prevent a large area of the brain from becoming damaged, a new animal study shows. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. If applicable to humans, these findings could potentially help protect vulnerable brain tissue in patients with stroke.

"Current treatment options are very limited for people who suffer a stroke," said senior author Ron Frostig, PhD, of the University of California, Irvine. "Our findings suggest a possible new treatment option, one based not on drugs or specialized machinery, but on activating the cortex with a non-invasive, mild sensory stimulation."

Frostig and his colleagues stimulated the whiskers of rats that had undergone a procedure that mimics an ischemic stroke — one caused by an interruption in the blood supply to the brain. This kind of stimulation imitates the exploratory whisker motion made by healthy rats.

The researchers found that 90 minutes of intermittent whisker stimulation led to a full return of cortical function. Furthermore, the whisker stimulation redirected blood flow within the circulatory system of the cortex —effectively compensating for the blockage that had caused the stroke. Timing was crucial, however: whisker stimulation offered protection only when it was given within two hours of the onset of the stroke.

"Our results suggest that mild sensory stimulation is capable of saving the cortex and restoring pre-ischemic levels of function if given right after the stroke begins," Frostig said. "This line of research may eventually add to the arsenal of existing stroke treatments and thus help to ease the high emotional, physical, and economic cost of stroke," he said.

Research supported by the National Institute of Neurological Disease and Stroke.

Scientific Presentation: Saturday, Nov. 13, 3:15–3:30 p.m., Room 24A

14.10, Mild sensory stimulation completely protects the adult rodent cortex from ischemic stroke
C. C. LAY, M. DAVIS, C. CHEN-BEE, **R. FROSTIG**; Neurobio. & Behavior, Univ. of California, Irvine, Irvine, CA

TECHNICAL ABSTRACT: Mild sensory stimulation following permanent occlusion of the middle cerebral artery (pMCAO) has been shown to be completely neuroprotective 24 hours after ischemic onset in an animal model of stroke (Lay et al. 2010), but precisely when functional recovery took place during the post-occlusion 24hr period remained unclear. Here, we quantify the return of cortical function immediately following ischemic onset using intrinsic signal optical imaging, electrophysiological recording, laser speckle imaging of blood flow, and histological analysis in order to assess the relationship between protective sensory stimulation, recovery of cortical function, and reperfusion within the ischemic territory. By examining cortical function (i.e. the spatial extent and amplitude of whisker functional representation) within the somatosensory cortex, we determined that 90 minutes of intermittent whisker stimulation delivered within 2 hours following pMCAO resulted in a return of function to pre-occlusion levels, and was accompanied by a significant reperfusion of the ischemic region via collateral vessels. In contrast, animals which received the identical whisker stimulation three hours after pMCAO never regained cortical function and sustained a major cortical infarct. Therefore, complete protection from impending ischemic stroke is possible within two hours of stroke onset whereas irreversible damage occurs when whisker stimulation is initiated three hours post-pMCAO. In summary, we found that the return of cortical function to pre-pMCAO levels by single whisker stimulation occurred 90 minutes following pMCAO, and was accompanied by a reperfusion of the imperiled region. These findings demonstrate the existence of a stimulus-induced neurovascular plasticity that confers complete protection of the ischemic territory; and that sensory induced protection is bounded within the first two hours (acute phase) of ischemia.

Abstract 481.14 Summary

Lead author: Benjamin Zendel (416)785-2500
University of Toronto b.zendel@utoronto.ca
Toronto, Canada

Musicians Less Likely to Experience Age-Related Changes in the Auditory Cortex

Human study suggests musical training may help mitigate age-related hearing loss

The old adage "use it or lose it" applies to hearing, suggests a new study. Older musicians do not experience certain changes in the auditory cortex — the part of the brain involved with hearing — that are associated with aging, according to research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"This finding is important because it suggests that age-related changes in the auditory cortex that contribute to decline in auditory perception may be mitigated by musical training," said Benjamin Zendel, a doctoral student who co-authored the study with Claude Alain, PhD, of the University of Toronto.

Zendel and Alain presented participants with complex sounds under two conditions: active, in which they focused on the sounds, and passive, while they were doing another activity. During these tests, the researchers used electroencephalography to measure the participants' brain waves — electrical activity caused by the firing of brain cells.

During periods of attentive listening, the auditory cortices of older musicians responded the same as those of younger adults, whereas older non-musicians showed typical age-related changes. The researchers note that the musicians spend much of their time paying attention to the details of sound, and this experience may be important for sparing auditory cortex responses.

"Our findings suggest that musical training, which is widely available, may enhance neural connections in the auditory cortex and thus might be useful in preventing age-related changes that contribute to hearing difficulties," Zendel said.

Research supported by the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada.

Scientific Presentation: Monday, Nov. 15, 2–3 p.m., Halls B–H

481.14, Age-related changes in the auditory evoked response are mitigated by musical training
B. R. ZENDEL, C. ALAIN; Rotman Res. Inst., Univ. of Toronto, Toronto, ON, Canada

TECHNICAL ABSTRACT: It is well established that hearing abilities decline with age. Some of this age-related decline can be accounted for by physical changes in the cochlea, however, there is also evidence that part of the decline in hearing abilities is due to an independent change at the central level. Paralleling this age-related decline in hearing ability, functional measures of the auditory cortex (i.e. auditory evoked responses) have also been shown to change with age. Auditory evoked responses (AER) represent a phase locked neural response to a transient auditory stimulus. Long latency responses (P1-N1-P2-N2) are known to originate from sources in the auditory cortex, and along the superior temporal plane. These responses are sensitive to both stimulus characteristics (e.g. amplitude, frequency, etc...) as well as subjective state (e.g. attention); with later responses being more influenced by attention than earlier responses. With age, the P1-N1-P2 responses tend to get larger, while the N2 response tends to diminish. In addition to age-related changes in the auditory evoked response, components of the AER are enhanced in musicians due to long-term training induced plastic changes in the auditory cortex. In musicians earlier responses, such as the N1 are enhanced when the evoking stimulus is musical, such as a piano sound, while later responses, such as the N1c or P2 are enhanced even when the stimulus is a pure tone. It is unknown how age and musical training interact to influence the auditory evoked response. To test this we presented four groups of listeners (older musicians and non-musicians & younger musicians and non-musicians, N = 14 per group), with complex sounds (F0 = 220 Hz + 5 harmonics, 150 ms duration) in two listening conditions (active & passive), while monitoring brain activity using EEG. In passive listening, both musicians and non-musicians demonstrated age-related increases in P1 & P2 amplitude and a decrease of N2 amplitude, which is consistent with previous age-related findings. In active listening, N1c and P2 amplitude interacted with both age and musical training. That is, in older musicians during active listening, the N1c and P2 amplitude were similar to younger adults, while in older non-musicians the typical age-related pattern of change in the AER was observed. These results suggest that aspects of age-related change in the auditory cortex can be mitigated through long-term training and focused attention.

Abstract 574.12 Summary

Senior author: Mark A. Smith, PhD (704) 894-2470
Davidson College masmith@davidson.edu
Davidson, N.C.

Aerobic Exercise May Reduce Excessive Cocaine Use

Animal study suggests that exercise could be an effective intervention for substance abuse prevention and treatment

Aerobic exercise may protect against binge-like patterns of cocaine use, suggests a new study. Rats allowed access to running wheels self-administered less cocaine than did rats that were not. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our findings represent the first demonstration that exercise reduces binge-like patterns of cocaine intake," said senior author Mark A. Smith, PhD, of Davidson College. "This adds to a growing number of studies reporting that physical activity may have beneficial effects on maladaptive patterns of drug use," he said.

Drug addiction is often characterized by episodes of brief but excessive drug intake, during which individuals exhibit compulsive patterns of drug use. Such "binges" are associated with negative outcomes, including criminal activity, visits to hospital emergency rooms, and high-risk sexual behavior. Interventions that reduce either the duration or severity of these binges could therefore have a significant impact on public health.

"Although randomized clinical trials examining aerobic exercise have not yet been conducted, recent studies report that individuals who participate in exercise-related activities during a formal treatment program maintain higher abstinence rates," Smith said. "Our findings also support the expanded use of exercise-based interventions in drug addiction treatment."

Research supported by the National Institute on Drug Abuse.

Scientific Presentation: Tuesday, Nov. 16, 11–12 p.m., Halls B–H

574.12, Aerobic exercise decreases binge-like patterns of excessive cocaine intake under unlimited-access conditions
K. C. LANG, **M. A. SMITH**; Davidson Col., DAVIDSON, NC

TECHNICAL ABSTRACT: Episodes of brief but excessive drug intake, during which an individual exhibits highly dysregulated and compulsive patterns of drug use, are especially problematic from a public health standpoint. These "binges" of excessive drug intake are associated with a number of negative outcomes and are a leading cause of mortality in substance-abusing populations. The purpose of the present study was to examine the effects of aerobic exercise on binge-like patterns of excessive cocaine intake under unlimited-access conditions. To this end, female Long-Evans rats were obtained at weaning and divided into sedentary and exercise groups immediately upon arrival. Sedentary rats were housed in standard laboratory cages that permitted no exercise beyond normal cage ambulation; exercising rats were housed in cages of equal dimensions but with running wheels affixed to the interior of the cage. After 6 weeks, rats were surgically implanted with venous catheters and allowed to self-administer cocaine during 23-hour periods of unlimited drug access. Sedentary rats self-administered significantly more cocaine than exercising rats under these conditions, and this effect was apparent at both low and high doses of cocaine. In contrast, no differences in responding were observed between sedentary and exercising rats when test sessions were limited to 2 hours. These data suggest that aerobic exercise protects against binge-like patterns of excessive drug intake under unlimited-access conditions and may be an effective intervention in substance abuse prevention and treatment programs.

Abstract 356.7 Summary

Senior author: Jerome Badaut, PhD (800) 422-4558
Loma Linda University jbadaut@llu.edu
Loma Linda, Calif.

Pre-injury Exercise May Mitigate the Effects of Traumatic Brain Injury in Mice

Preliminary study suggests physically fit people may experience easier recoveries

Being physically fit before a traumatic brain injury (TBI) might improve recovery, preliminary findings suggest. After TBI, mice bred for running behavior exhibited smaller brain lesions and engaged in more extensive post-injury activity than did mice that had been sedentary before the injury. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Engaging in physical exercise *after* TBI is known to improve cognitive outcome. "Our findings suggest that people who are already physically fit will have a better recovery profile than sedentary people," said senior author Jerome Badaut, PhD, at Loma Linda University.

In a preliminary study, Badaut and his colleagues compared four mice genetically selected for running behavior with five control mice. The runner mice were allowed to run on wheels for two weeks before undergoing a procedure that mimics a TBI; the sedentary mice were not.

Magnetic resonance imaging revealed that the brain lesions in the exercising mice were 34 percent smaller in volume than those in the sedentary mice. In addition, the exercising mice spent more time on a balance beam task, indicating that the smaller lesions contributed to improved behavior. They also gradually increased their activity after injury, while the sedentary mice decreased theirs.

Research supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Science Foundation, Department of Defense, and the Swiss National Science Foundation.

Scientific Presentation: Monday, Nov. 15, 10–11 a.m., Halls B–H

356.7, Biological effects of pre-injury exercise administration in mice receiving TBI
V. POP[1], J. S. COATS[2], D. SORENSEN[3], R. E. HARTMAN[4], T. GARLAND, Jr[5], A. OBENAUS[2], **J. BADAUT**[1]; [1]Pediatric Res., [2]Radiation Medicine, Radiology, Biophysics and Bioengineering, [3]Basic Sci., [4]Psychology, Loma Linda Univ., Loma Linda, CA; [5]Biol., Univ. of California, Riverside, Riverside, CA

TECHNICAL ABSTRACT: Exercise regimens following traumatic brain injury (TBI) can provide cognitive benefits in humans and improve behavioral outcomes in rodents. Pre-injury exercise effects have not been studied in TBI. Using adult control (CTL) and genetically selected high-runner (HR) mice, we evaluated behavioral and histological outcomes following moderate TBI. CTL mice were kept sedentary throughout the study period while HR mice received two weeks of pre-injury exercise in cages with attached wheels for voluntary running. A subset of each group of animals received a moderate controlled cortical impact (CCI) TBI injury (5 mm craniotomy, 3 mm impact diameter, 1.5 mm depth, 5 m/sec speed, 100 msec dwell time) at the level of the hippocampal formation. In the first week post-injury, T2-weighted (T2WI) magnetic resonance imaging (MRI) revealed a significant 34% reduction in TBI lesion volume in HR compared to sedentary CTL mice ($p=0.003$). We also found a significant negative correlation of lesion volume and time spent on a balance beam task ($p=0.011$), indicating that smaller lesions may contribute to improved behavioral performance. Histological analyses, comparing CTL and HR animals from the TBI and non-TBI groups, investigated the cellular and molecular mechanisms responsible for reduced lesion volume and improved behavioral indices in mice receiving pre-injury exercise.

Speaker's Summary

Speaker: Carl Cotman, PhD (949) 824-5847
University of California Irvine cwcotman@uci.edu
Irvine, Calif.

Mechanisms of Experience Dependent Neuroplasticity and the Role of Neurotrophic Factors in Animal Models of Alzheimer's Disease (311.2)

Symposium: Experience-Dependent Synaptic Plasticity and Neurogenesis in the Degenerating and Injured Brain
Monday, Nov. 15, 8:35–9:10, San Diego Convention Center, Room 6B

Recent evidence reveals that behavioral and lifestyle interventions are effective at preventing or slowing normal age-related declines as well as age-related neurodegenerative diseases. The approach for improving brain function through behavioral/lifestyle changes represents a paradigm shift from previous research, which has been dominated by pharmacological approaches. Behavioral strategies include exercise/physical activity, cognitive training, and the combination of the interventions. The data supporting the efficacy of exercise come from both animal and clinical studies. In animal studies, exercise increases levels of neurotrophic factors, including BDNF, which helps maintain neuronal health, facilitates synaptic plasticity, and improves learning and memory. A number of other growth factors are induced in the brain in response to exercise, including VEGF, IGF-1, FGF2, NGF, GDNF, among others.

Induction of BDNF appears to be a final common endpoint that is critical for mediating the benefits of exercise on cognitive function. In addition to growth factors, exercise increases neurogenesis in the hippocampus, and increases dendritic complexity and synapse density in both hippocampus and cortex. Further, exercise improves cerebral blood flow and stimulates angiogenesis in the brain. Thus, exercise hits a variety of targets, which act synergistically to improve cognitive health and function.

Exercise can even improve brain health and function in transgenic mouse models of Alzheimer's disease. In APP animals, exercise improves cognition, reduces the accumulation of beta-amyloid, and slows the overall rate of degeneration. The benefits of exercise are most effective at reducing brain pathology when initiated before advanced age, e.g. by mid-life, however exercise can still be effective even if initiated when pathology is well-developed.
An often posed question regards the frequency and amount of exercise that are needed to obtain brain benefits. Animal studies reveal that exercise on alternating days is as effective as daily exercise to benefit the brain. Further benefits of exercise to brain biology and cognition endure several weeks after exercise ends, indicating that the effects of exercise are long-lasting.

In humans, exercise is similarly associated with benefits to brain function. For example, individuals who score high on fitness measures show less age-related brain atrophy, particularly in brain structures such as the hippocampus, and in general maintain higher cognitive performance. Controlled clinical trials are adding to the growing field demonstrating benefits to humans. Various studies demonstrate that exercise (various durations from six months to two years, generally three to five times per week, one hour per day) improves executive function and cognitive performance in humans, paralleling predictions from animal studies. Because pharmacological studies in animals often do not translate to clinical efficacy in humans, it is particularly exciting and encouraging that studies on exercise and behavioral interventions from animal studies are paralleled by similar benefits in humans.