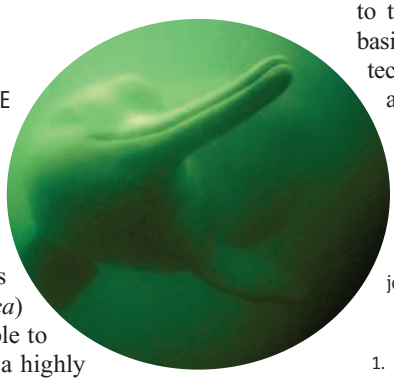
LETTERS

edited by Etta Kavanagh

The Loss of a Valuable Dolphin



JERRY GUO'S ARTICLE "RIVER DOLPHINS DOWN FOR THE count, and perhaps out" (News of the Week, 22 Dec. 2006, p. 1860) revealed no sightings of a baiji dolphin (*Lipotes vexillifer*) during a recent comprehensive survey. If, as expected, this species is truly extinct, then the loss to both the natural and physical sciences is more profound than most realize. This animal is one of only two species of river dolphins (the other being the Ganges river dolphin, *Platanista gangetica*) that, although bereft of vision and olfactory sense, are able to migrate, locate prey, and find mates while navigating in a highly dynamic riverine environment (*1*). The biology of both species is poorly known. However, insight into their biology could be expected to lead to advancements in acoustic-based sensors, geolocation, and navigation in extreme environments, as well as the development of technologies to assist vision-impaired persons.

The loss of this organism highlights the need for unbiased prioritization of conservation biology projects within the scientific community. Broader scientific potential contributions need to be considered in addition to general ecosystem health. Perhaps, other species at risk would receive more attention if the ramifications of their demise were better presented to the public.

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Reference

1. See http://nationalzoo.si.edu/Publications/ZooGoer/2003/5/RiverDolphins.cfm.

The Ethics of Transcranial Magnetic Stimulation

WHEN *SCIENCE* PUBLISHES RESEARCH USING healthy human subjects, one assumes there was minimal risk and/or vital clinical value. This does not appear to be the case for the work by D. Knoch and colleagues ("Diminishing reciprocal fairness by disrupting the right prefrontal cortex," Reports, 3 Nov. 2006, p. 829). Their results on the dorsolateral prefrontal cortex's role in judgments of fairness and self-interest are interesting, but they largely validated what was already suspected.

Experimental subjects received repetitive transcranial magnetic stimulation (rTMS) for 15 min to produce "suppression of activity in the stimulated brain region." The rTMS generated an electric maelstrom powerful enough to disrupt all activity for 7 min. Animal rTMS research (with overexposure as in LD50 drug toxicity studies) shows that anything studied (e.g., receptor levels) is modified. For rTMS in humans, known risks range from headaches to, more rarely, seizures or psychosis (*1*). Long-term occult changes and self-reported symptoms in healthy subjects have not been studied, and rTMS continues to be used for studies both fascinating and frivolous (just check the literature).

The use of rTMS on healthy subjects does not meet the definition of "minimal risk" (45 CFR section 46.102: risks… "not greater … than those … encountered in daily life"). We know that healthy subjects don't risk seizures or psychosis in their "daily life." What we don't know is what the residual effects of this activity-swamping tsunami of electrical current are. The Report demonstrates a naiveté about the possibility of rTMS having long-term or negative consequences. Oddly, some of these authors have used rTMS to treat neuropsychiatric disorders on the basis of its long-lasting effects (*2*). Roentgen's technology was also once thought harmless, and x-rays were used to check shoe sizes (*3*). We know better now.

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Response

WE THANK JONES FOR HER LETTER, WHICH offers the opportunity to discuss the safety of transcranial magnetic stimulation (TMS) and the ethics of TMS research in humans and to address common prejudices about its application in healthy subjects. Research on human subjects should indeed be done with utmost attention to the protection of all participants. An international workshop on the safety of TMS held at the National Institutes of Health in June 1996 concluded that the risks of single-pulse, paired-pulse, and slow repetitive TMS (≤1 Hz) are minimal for populations without certain predisposing conditions, provided that appropriate safety guidelines and precautions are followed (*1*). In our study, we applied slow, 1-Hz repetitive TMS (rTMS) in strict adherence to the recommended guidelines (*1*), which have been endorsed by the International Federation for Clinical Neurophysiology (*2*).

In predisposed patients, e.g., those on certain medications or with underlying neuropsychiatric conditions, there is a rare possibility for serious adverse effects, most notably a seizure or the induction of psychotic symptoms (*3*). However, these have never occurred with slow rTMS in healthy subjects. In addition, in all our studies, each subject partici-

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pated voluntarily and on the basis of the provision of all relevant information. The experimental nature of the intended procedure was made clear at the outset, and all participants were fully informed of any reasonably foreseeable risks or discomforts and about the fact that they would not derive any direct benefit from their participation in the study. This included notification of the possibility of seizures.

Contrary to the opinion expressed by Jones, we firmly believe that the findings of our study provide novel insights into the role of the right dorsolateral prefrontal cortex (DLPFC) in the control of self-centered motives and in overriding economic temptations. Such findings may have profound applications for a variety of neuropsychiatric conditions. For example, increasing the level of activity in the right DLPFC might promote the inhibitory control of prepotent, impulsive responses and therefore diminish excessive risk-taking behavior in patients with impulse control disorders. If so, such an intervention might, for example, prove useful in clinical populations with drug or nonsubstance addictions (e.g., pathological gambling), in which impairments of decision-making seem to reflect a breakdown of these control processes (*4*). Preliminary findings in cocaine addicts reveal that high-frequency rTMS to the right DLPFC, which is thought to increase cortical excitability in the targeted brain region, reduces craving (*5*).

The ethical principles discussed in relation to TMS research in human subjects were initially articulated by Green *et al.* (*6*), and subsequent discussions and updates have appeared (*7*, *8*). We believe that our study followed these articulated high standards and thus disagree with Jones's implications about the appropriateness of our experiment.

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Comparing Neanderthal and Human Genomes

THE RECENT SEQUENCING OF SUBSTANTIAL parts of Neanderthal DNA ["Sequencing and analysis of Neanderthal genomic DNA," J. P. Noonan *et al.*, Research Article, 17 Nov. 2006, p. 1113; (*1*)] was preceded by releases of drafts of the chimpanzee and human genomes in 2005 and 2001, respectively. Green *et al.* (*1*) expect recovery of the complete Neanderthal genome within the next 2 years, which, it is hoped, will allow comparison of all three genomes to examine the genetic basis of functional differences between the species. With regard to many evolutionary questions, Lambert and Millar (*2*) suggested that analyzing differences between Neanderthal and human brains would be of great interest.

However, although such comparisons are of interest, it is not the static genome but rather the dynamic proteome that determines the phenotype of an organism. Salient examples include the caterpillar and the tadpole, which share genomes with the butterfly and frog, respectively, but which have very different proteomes making them into very different organisms. Thus, rather than performing untargeted comparisons of sizable genomes, we suggest that it might be more useful to address this question using a standard hypothesis-driven approach. One such avenue might be the "fat utilization" hypothesis, which holds that the key mutations that differentiate us from Neanderthals and great apes are in the genes coding for proteins regulating fat metabolism, in particular, those regulating the phospholipids in brain synapses (*3*, *4*). A specific search for variations in genomic DNA or gene expression related to lipid biochemistry and metabolism could be carried out.

Charles Darwin was once asked if he thought that natural historians should collect data without the prejudice of a preformed hypothesis, or whether they should be observing nature with a particular theory in mind (*5*). In a stinging reply to his friend, the economist Henry Fawcett, Darwin wrote that they may as well "go into a gravel-pit and count the pebbles and describe the colours" (*6*). Plus ça change…

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Response

ERREN *ET AL.* APPEAR TO HAVE NO TECHNICAL objections to our study, but rather put forth a general philosophical objection to whole-genome analysis. They would prefer that we search for the molecular basis of human-specific traits by focusing on particular classes of genes speculated to contribute to some biological difference between humans and other species. We fail to see the advantage of this approach over unbiased whole-genome comparisons. The reason such candidate gene strategies were used in the past was due to the lack of genomic data sets. The sequencing of multiple genomes, including human and chimpanzee, has removed this obstacle. We do not know in advance which genes or other functional elements have changed in human evolution. It therefore seems shortsighted to guess that mutations in lipid genes, to cite the authors' example, are responsible for functional differences between human and Neanderthal brains. If changes in genes regulating fat metabolism do contribute to human-specific traits, a whole-genome approach will efficiently detect that signal, as well as all the other genes that the authors' "lipid-centric" approach would miss.

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Letters to the Editor

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What the Scientific Community Can Do

IN HIS EDITORIAL "SHOW US THE MONEY" (8 Dec. 2006, p. 1515), Donald Kennedy suggests that the scientific community should tell the Administration, the public, and Congress what it can accomplish for our society. As chairman and member of the executive committee of the Association of American Universities and as president of Northwestern University, which has made large investments in human and physical capital over the last decade, especially in the life and nano sciences, I want to do just that.

We can list many research-to-bedside accomplishments. A discovery in our chemistry labs by Richard Silverman led to the drug Lyrica, licensed to Pfizer, which has proved an effective neuropathic pain reliever for tens of thousands of patients. Many other universities can also point to new therapies and diagnostics that were discovered or developed in their lab.

The economic benefits of biomedical research are equally striking. One only has to look at the jobs created in the construction industry when we built the Robert H. Lurie Medical Research Center, the creation of many new biotech companies from our research efforts, or the mobilizing of private-donor support to see the economic benefits. The Chicago area has benefited mightily from our efforts, as Atlanta has benefited from Emory's efforts and Baltimore from those of John Hopkins.

Elias Zerhouni, director of NIH, is correct to note that we in the research community often take for granted the extraordinary return on investments in NIH ("NIH in the post-doubling era: realities and strategies," Policy Forum, 17 Nov. 2006, p. 1088). He refers to scientific and health care benefits. I can also point to the economic returns expressed in job creation and multiple effects of investment from the partnerships among the federal government, private donors, and the research universities.

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Why Are There So Many Species of Herbivorous Insects in Tropical Rainforests?"

David A. Norton and Raphael K. Didham

Novotny *et al*. (Reports, 25 August 2006, p. 1115) argued that higher herbivore diversity in tropical forests results from greater phylogenetic diversity of host plants, not from higher host specificity. However, if host specificity is related to host abundance, differences in relative host abundance between tropical and temperate regions may limit any general conclusion that herbivore diversity scales directly with host-plant diversity.

Full text at www.sciencemag.org/cgi/content/full/315/5819/1666b

RESPONSE TO COMMENT ON "Why Are There So Many Species of Herbivorous Insects in Tropical Rainforests?"

Vojtech Novotny, Pavel Drozd, Scott E. Miller, Miroslav Kulfan, Milan Janda, Yves Basset, George D. Weiblen

Norton and Didham suggest that differences in plant abundance between tropical and temperate forests may influence the host specificity of herbivores in these forests. We agree in principle but show that this is likely only for very rare plant species in tropical forests. Studies of herbivores hosted by rare plant species would help our understanding of tropical plant-insect interactions.

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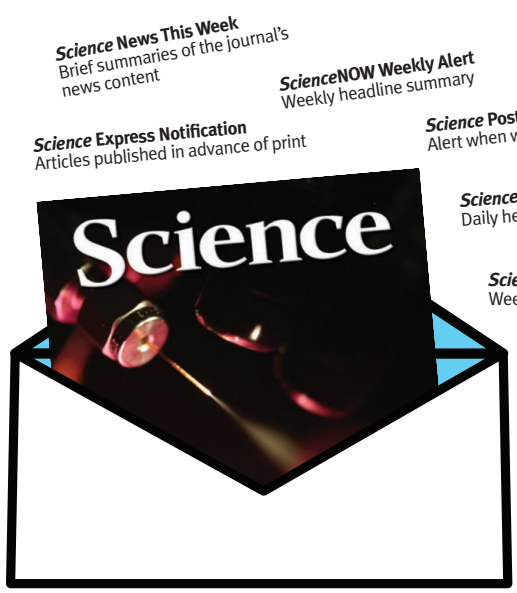

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