

will purchase and benefit from their products, and to avoid harming patients.)

The pediatric rule further increases the already high costs of drugs to consumers and puts them at greater risk.

HENRY I. MILLER*

The Hoover Institution, Stanford, CA 94305-6010, USA. E-mail: miller@hoover.stanford.edu

*Miller was an official at the FDA from 1979 to 1994.

Medial Prefrontal Cortex and Error Potentials

WILLIAM J. GEHRING AND ADRIAN R.

Willoughby ("The medial frontal cortex and the rapid processing of monetary gains and losses," Reports, 22 March, p. 2279) report that a "medial-frontal negativity" (MFN), a negative-going deflection in the human event-related brain potential (ERP), was elicited by feedback stimuli indicating monetary gains or losses. The MFN was greater in amplitude following losses than following gains and was attributed to activity in medial frontal cortex. Previous studies have identified a similar negative deflection in the ERP that occurs following incorrect responses in speeded reaction time tasks (1, 2) and following feedback stimuli that indicate

incorrect performance (3). Both of these response and feedback "error-related negativities" (ERNs) were thought to be produced in medial frontal cortex by a mechanism for error detection (1-3). As Gehring and Willoughby note, the MFN and the feedback-related ERN share identical scalp distributions and latencies, suggesting that they are the same phenomenon. Importantly, however, Gehring and Willoughby emphasize that the MFN/feedback ERN is sensitive to the "utilitarian" (gain or loss) value of feedback, rather than to the "performance" (correct or incorrect) value of feedback. In so doing, they dissociate that component from the response-related ERN and its associated function, error detection.

We have proposed a unifying theory that explains the response- and feedback-related ERNs in terms of a single neural mechanism for reward prediction (4-7). This theory renders the distinction between utilitarian and performance feedback artificial by highlighting a shared functional property: the reinforcement of adaptive behavior. Our argument holds that both types of ERN are elicited by the impact of phasic activity of mesencephalic dopamine neurons—a system associated with the computation of utility—on medial frontal cortex. This phasic signal, representing

changes in expected reward, is used by medial frontal cortex to select behaviors that elicit reward. Application of a reinforcement learning algorithm previously used to describe phasic dopamine activity (8) predicts an inverse relationship between the amplitudes of the response and feedback ERNs (4-7). This result is what we find empirically (6, 7).

CLAY B. HOLROYD,¹ MICHAEL G. H. COLES,²
SANDER NIEUWENHUIS¹

¹Princeton University, Department of Psychology, Princeton, NJ 08544-1010, USA. E-mail: cholroyd@princeton.edu, snieuwen@princeton.edu. ²F. C. Donders Centre for Cognitive Neuroimaging, 6500 HB Nijmegen, Netherlands, and Department of Psychology, University of Illinois, Champaign, IL 61820, USA. E-mail: mcoles@s.psych.uiuc.edu

References

1. M. Falkenstein, J. Hohnsbein, J. Hoormann, L. Blanke, in *Psychophysiological Brain Research*, C. Brunia, A. Gaillard, A. Kok, Eds. (Tilburg Univ. Press, Tilburg, Netherlands, 1990), pp. 192-195.
2. W. J. Gehring, B. Goss, M. G. H. Coles, D. E. Meyer, E. Donchin, *Psychol. Sci.* **4**, 385 (1993).
3. W. H. R. Miltner, C. H. Braun, M. G. H. Coles, *J. Cognit. Neurosci.* **9**, 788 (1997).
4. C. Holroyd, J. Reichler, M. G. H. Coles, in *Proceedings of the Second International Conference on Cognitive and Neural Systems* (Boston University, Boston, 1998), p. 114.
5. C. Holroyd, J. Reichler, M. G. H. Coles, in *Cognitive Neuroscience Society 1999 Annual Meeting Abstract Program* (MIT Press, Cambridge, MA, 1999), p. 45.
6. C. B. Holroyd, M. G. H. Coles, *Psychol. Rev.*, in press.

Western Blotting

Price. Sensitive.


Twice the signal intensity for up to half the price!

You can't do better than Pierce SuperSignal® West Pico Chemiluminescent Substrate.

(Product #s 34080 and 34077)

- Low picogram/attomole detection
- Intense signal duration of 6-8 hours
- Room temperature stable

For more information, visit us at www.SuperSignalWest.com or call.



PIERCE
a brand of **QIAGEN**

3747 N. Meridian Rd. • PO Box 117 • Rockford, IL 61105 U.S.A. • Tel: 815-968-0747 or 800-874-3723 • Fax: 815-968-7316
 Technical Assistance E-mail: TA@piercenet.com • Customer Assistance E-mail: CS@piercenet.com • Internet: www.piercenet.com
 © Pierce Chemical Company, 2001. Printed in the U.S.A. A Perbio Science Company
 SuperSignal® is a trademark of Pierce Chemical Company. Patent pending on SuperSignal technology.

SCIENCE'S COMPASS

7. S. Nieuwenhuis *et al.*, *J. Cognit. Affective Behav. Neurosci.*, in press.
8. W. Schultz, P. Dayan, P. R. Montague, *Science* **275**, 1593 (1997).

Response

WE THANK HOLROYD, COLES, AND Nieuwenhuis for suggesting that their computational model of the error-related negativity (ERN) (1) predicts the response of the medial-frontal negativity (MFN) to monetary losses (2). Their model is an important exploration of the role that phasic changes in dopaminergic activity could play in generating event-related potential responses to motivationally significant events such as errors and monetary losses.

We respectfully disagree, however, with a few of their points. First, the MFN and the feedback- and response-related ERNs do not share identical scalp distributions (although they are similar), and thus they should not be considered identical phenomena. The feedback- and response-related ERNs have more posterior scalp foci than the MFN (1, 3, 4), and even the two types of ERN differ in their cortical origins (5). It is unlikely that a single cortical source (and single computation) accounts for all of these phenomena. If a common source contributes to the ERNs and the MFN, it is likely that other concurrent, over-

lapping sources also make differential contributions in each case (5).

Moreover, evidence suggests that the distinction between utilitarian and performance feedback is not artificial. There are a number of ways in which an event can be motivationally relevant (6), and different cortical systems may code for different motivational attributes of an event (7). In particular, neurophysiological evidence supports the distinction between the absolute status of a reward as a gain or a loss and its status relative to other alternatives. Some reward-sensitive neurons in the orbitofrontal cortex do not code the absolute desirability of a reward, but, instead, its desirability relative to other alternatives in a particular context (8). Numerous behavioral studies of human decision-making have demonstrated that utilities are affected by a comparison between the obtained outcome and unobtainable alternatives (9).

Finally, because the Holroyd *et al.* model does not distinguish between utilitarian and performance feedback, it is unclear whether the model necessarily predicts our results. The model could do so, but it could just as plausibly predict outcomes contrary to our results, such as an error signal sensitive to the value of the chosen response relative to that of the response that was not chosen. For this

reason, our data do not support the model in its current form. Further testing of the model will require its assumptions to be constrained more definitively.

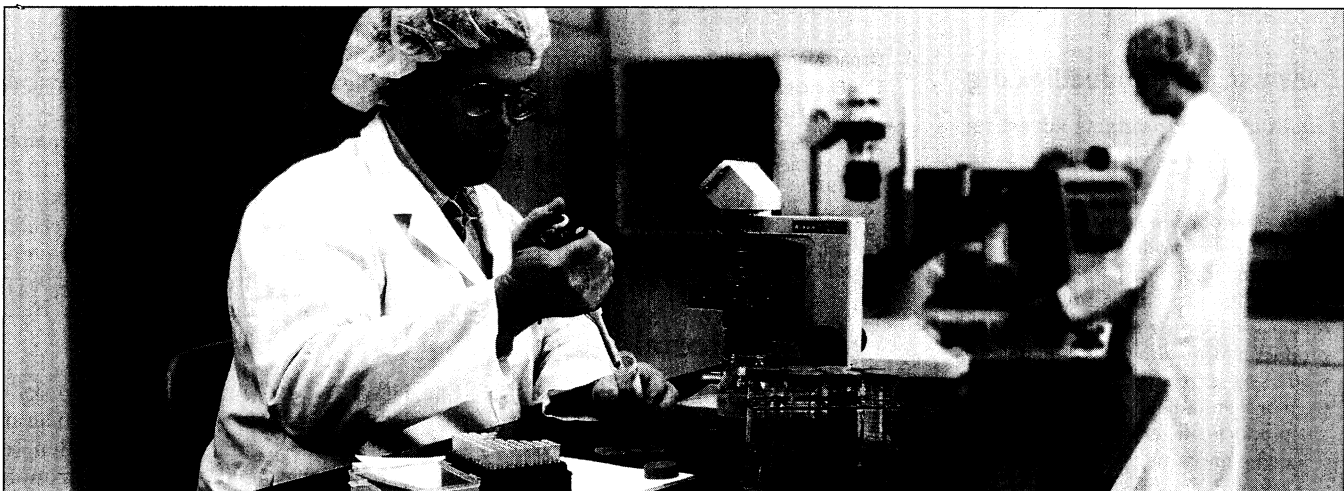
WILLIAM J. GEHRING AND ADRIAN R. WILLOUGHBY
Department of Psychology, University of Michigan, Ann Arbor, MI 48109-1109, USA. E-mail: wgehring@umich.edu, awilloug@umich.edu

References

1. C. B. Holroyd, M. G. H. Coles, *Psychol. Rev.*, in press.
2. W. J. Gehring, A. R. Willoughby, *Science* **295**, 2279 (2002).
3. W. H. R. Miltner, C. H. Braun, M. G. H. Coles, *J. Cognit. Neurosci.* **9**, 788 (1997).
4. R. Badgaiyan, M. I. Posner, *Neuroimage* **7**, 255 (1998).
5. P. Luu, D. M. Tucker, D. Derryberry, M. Reed, C. Poulsen, *Psychol. Sci.*, in press.
6. K. C. Berridge, in *The Psychology of Learning and Motivation*, D. L. Medin, Ed. (Academic Press, New York, 2001), pp. 223-278.
7. W. Schultz, *Nature Rev. Neurosci.* **1**, 199 (2000).
8. L. Tremblay, W. Schultz, *Nature* **398**, 704 (1999).
9. B. A. Mellers, *Psychol. Bull.* **126**, 910 (2000).

DNA Replication and Traintracks

THE PRESCIENT WORK OF THE RUSSIAN theoretician Alexei Olovnikov (1, 2) was omitted from Jean Marx's News Focus article "Chromosome end game draws a crowd" (29 March, p. 2348).



We're In It For The Science

The **National Cell Culture Center** is a non-profit resource sponsored by the NIH to support basic research by providing access to cell culture services at minimal cost. Working with the Center, your cell line or custom protocol is adapted for larger scale production. Cells or cell secreted proteins are delivered in the quantity and frequency you desire, enabling you to focus more of your valuable resources on fundamental research problems.

Thousands of scientists from every major research institution throughout the country have accessed the Center for their cell culture needs. Let us help you with your research. *Visit us on the web at www.nccc.com*

Sponsored by the National Center for Research Resources, National Institutes of Health.

National Cell Culture Center 
Dedicated to Supporting the Biomedical Research Community