



**The Medial Frontal Cortex and the Rapid Processing
of Monetary Gains and Losses**

William J. Gehring, *et al.*
Science **295**, 2279 (2002);
DOI: 10.1126/science.1066893

***The following resources related to this article are available online at
www.sciencemag.org (this information is current as of May 27, 2008):***

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/cgi/content/full/295/5563/2279>

Supporting Online Material can be found at:

<http://www.sciencemag.org/cgi/content/full/295/5563/2279/DC1>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/cgi/content/full/295/5563/2279#related-content>

This article **cites 23 articles**, 6 of which can be accessed for free:

<http://www.sciencemag.org/cgi/content/full/295/5563/2279#otherarticles>

This article has been **cited by** 188 article(s) on the ISI Web of Science.

This article has been **cited by** 31 articles hosted by HighWire Press; see:

<http://www.sciencemag.org/cgi/content/full/295/5563/2279#otherarticles>

This article appears in the following **subject collections**:

Neuroscience

<http://www.sciencemag.org/cgi/collection/neuroscience>

Information about obtaining **reprints** of this article or about obtaining **permission to reproduce this article** in whole or in part can be found at:

<http://www.sciencemag.org/about/permissions.dtl>

development (30). Given the wide distribution of NCS-1 in the nerve terminals (14–18), the activity-dependent I_{pCa} facilitation may be mediated by NCS-1 at various synapses, thereby mediating activity-dependent synaptic facilitation. The residual Ca^{2+} hypothesis for the synaptic facilitation has been widely accepted, but its detailed mechanism is still unknown (31). One of the downstream effects of residual Ca^{2+} is the facilitation of I_{pCa} (3–5). Hence, our results suggest that NCS-1 may be a key molecule for the activity-dependent synaptic facilitation.

References and Notes

1. B. Katz, R. Miledi, *J. Physiol.* **189**, 535 (1967).
2. F. A. Dodge Jr., R. Rahamimoff, *J. Physiol.* **193**, 419 (1967).
3. I. D. Forsythe, T. Tsujimoto, M. Barnes-Davies, M. F. Cuttle, T. Takahashi, *Neuron* **20**, 797 (1998).
4. M. F. Cuttle, T. Tsujimoto, I. D. Forsythe, T. Takahashi, *J. Physiol.* **512**, 723 (1998).
5. J. G. G. Borst, B. Sakmann, *J. Physiol.* **513**, 149 (1998).
6. S. R. Ikeda, *J. Physiol.* **439**, 181 (1991).
7. H. Kasai, *J. Physiol.* **448**, 189 (1992).
8. O. Pongs et al., *Neuron* **11**, 15 (1993).
9. S. Nef, H. Fiumelli, E. De Castro, M. B. Raes, P. Nef, *J. Recept. Signal Transduct. Res.* **15**, 365 (1995).
10. P. Olafsson, T. Wang, B. Lu, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 8001 (1995).
11. E. De Castro et al., *Biochem. Biophys. Res. Commun.* **216**, 133 (1995).
12. J. B. Ames et al., *Biochemistry* **39**, 12149 (2000).
13. Y. Bourne, J. Dannenberg, V. Pollmann, P. Marchot, O. Pongs, *J. Biol. Chem.* **276**, 11949 (2001).
14. P. Olafsson et al., *Mol. Brain Res.* **44**, 73 (1997).
15. N. C. Schaad et al., *Proc. Natl. Acad. Sci. U.S.A.* **93**, 9253 (1996).
16. M. E. Martone, V. M. Edelman, M. H. Ellisman, P. Nef, *Cell Tissue Res.* **295**, 395 (1999).
17. S. Sage, S. Ventéo, A. Jeromin, J. Roder, C. J. Dechesne, *Hearing Res.* **150**, 70 (2000).
18. M. Paterlini, V. Revilla, A. L. Grant, W. Wisden, *Neuroscience* **99**, 205 (2000).
19. R. Rivosecchi, O. Pongs, T. Theli, A. Mallart, *J. Physiol.* **474**, 223 (1994).
20. Supplemental information is available at *Science Online* (www.sciencemag.org/cgi/content/full/295/5563/2276/DC1).
21. H. Taschenberger, H. von Gersdorff, *J. Neurosci.* **20**, 9162 (2000).
22. Y. Kajikawa, N. Saitoh, T. Takahashi, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 8054 (2001).
23. S. Iwasaki, T. Takahashi, *J. Physiol.* **509**, 419 (1998).
24. C. D. DeMaria, T. W. Soong, B. A. Alseikhan, R. S. Alvania, D. T. Yue, *Nature* **411**, 484 (2001).
25. T. Sakaba, E. Neher, *Neuron* **32**, 1119 (2001).
26. C.-Y. Wang et al., *Neuron* **32**, 99 (2001).
27. F. Helmchen, J. G. G. Borst, B. Sakmann, *Biophys. J.* **72**, 1458 (1997).
28. O. D. Uchitel et al., *Proc. Natl. Acad. Sci. U.S.A.* **89**, 3330 (1992).
29. T. Takahashi, A. Momiyama, *Nature* **366**, 156 (1993).
30. S. Iwasaki, A. Momiyama, O. D. Uchitel, T. Takahashi, *J. Neurosci.* **20**, 59 (2000).
31. Y. Tang, T. Schlumpberger, T. Kim, M. Lueker, R. S. Zucker, *Biophys. J.* **78**, 2735 (2000).
32. Supported by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, a research grant from the Mitsubishi Foundation (T.T.), and the Medical Research Council of Canada (A.J., J.C.R.).

21 November 2001; accepted 14 February 2002

The Medial Frontal Cortex and the Rapid Processing of Monetary Gains and Losses

William J. Gehring* and Adrian R. Willoughby

We report the observation of neural processing that occurs within 265 milliseconds after outcome stimuli that inform human participants about gains and losses in a gambling task. A negative-polarity event-related brain potential, probably generated by a medial-frontal region in or near the anterior cingulate cortex, was greater in amplitude when a participant's choice between two alternatives resulted in a loss than when it resulted in a gain. The sensitivity to losses was not simply a reflection of detecting an error; gains did not elicit the medial-frontal activity when the alternative choice would have yielded a greater gain, and losses elicited the activity even when the alternative choice would have yielded a greater loss. Choices made after losses were riskier and were associated with greater loss-related activity than choices made after gains. It follows that medial-frontal computations may contribute to mental states that participate in higher level decisions, including economic choices.

A fighter pilot monitoring cockpit indicators, a stock-exchange trader checking prices, and a gambler playing blackjack in a casino all evaluate quickly whether events are good or bad and make rapid decisions on the basis of those events. Recent research indicates that such evaluations can take place quickly, automatically, and without conscious deliberation (1–3). In addition, there is growing knowledge about the neural systems that mediate such processing, in particular those concerned with reward and punishment (4–7). Yet there is still little direct evidence for neural processing in humans that is not only

fast enough to reflect this evaluation but also is directly related to choice behavior.

Here, we report the observation of neurophysiological activity with characteristics that are consistent with its involvement in rapidly evaluating the motivational impact of events and in guiding choice behavior. The activity responds to the monetary outcome signified by an event, operates on a short time scale, and covaries with the riskiness of people's choices in a gambling task. To investigate evaluative neural activity, we recorded event-related brain potentials (ERPs) from human participants as they performed a monetary gambling task (Fig. 1). Participants' choices were followed by outcome events signifying both the monetary gain or loss that resulted from their choice and the gain or loss that would have resulted from making the other choice.

An important objective of our experimental design was to separate processing related to monetary gains and losses from other possible confounding factors. Our analyses compared results from conditions under which the physical characteristics of the stimuli were equivalent, ruling out the possibility that effects arose from processing related to physical differences between the stimuli. Moreover, the probabilities of the outcomes were equivalent, making the statistical expected value of the monetary outcome zero on each trial and ruling out potential confounding influences with the differential probability of a gain or loss (8).

Twelve participants (six males and six females, ranging in age from 19 to 30 years old) completed 768 trials of this gambling task while the electroencephalogram (EEG) was recorded from 42 scalp electrodes (9). The experimental session for each participant was divided into 24 blocks of 32 trials, and cumulative monetary awards were given at the end of each block (10). ERPs were computed by averaging the EEG records associated with each type of outcome stimulus (11).

Figure 2 compares the ERPs from gain trials and loss trials. It shows a negative-polarity ERP, beginning at about 200 ms after the outcome stimulus. The potential was larger on loss trials than on gain trials ($P = 0.0098$). As shown by the topographic map of scalp electrical activity in Fig. 2, the potential was largest at the medial-frontal scalp location Fz, ($P = 0.00022$) (9). We used dipole modeling to identify which cortical region was most likely to generate the pattern of loss-related electrical activity observed at the scalp. The results of the modeling were consistent with a source in the medial frontal cortex, in or near the anterior cingulate cortex (ACC) (Fig. 2) (9, 12). For convenience, we

Department of Psychology, University of Michigan, 525 East University, Ann Arbor, MI 48109–1109, USA.

*To whom correspondence should be addressed. E-mail: wgehring@umich.edu

REPORTS

refer to this potential as the medial-frontal negativity (MFN).

A possible explanation for the MFN is that it simply reflects error detection—a signal that the person's response was not correct. Such an explanation is plausible, because medial-frontal scalp-recorded electrical activity known as the error-related negativity (ERN or Ne) is associated with errors (13–15), and converging evidence suggests that the ACC and nearby cortical areas generate the ERN (15–18). The design of our study, however, allowed us to demonstrate that the MFN did not reflect error detection. A loss of 5, when the unchosen alternative was a loss of 25, actually corresponded to the “correct” choice; it was the better of the two outcomes. Furthermore, a gain of 5, when the unchosen alternative was a gain of 25, corresponded to the incorrect (“error”) choice—the chosen response was less consistent than the alternative with the overall goal of maximizing gains and minimizing losses. In addition to these “loss-and-correct” and “gain-and-error” conditions were “loss-and-error” and “gain-and-correct” conditions. By comparing these four conditions, we could test whether the primary cause of the MFN effect was the occurrence of a loss or the occurrence of an error. As Fig. 3 shows, the MFN did not reflect error detection. The primary determinant of the MFN was the direction of the outcome (its status as a loss or a gain), not the relative correctness of the response. The loss-gain status significantly influenced the MFN response ($P = 0.00076$), whereas the error-correct status did not ($P = 0.23$) (9).

Although there was no rule they could learn that would yield rewards, participants exhibited particular patterns of risk-taking and risk-avoiding behavior. The alternatives encountered by each participant varied in their degree of risk (19, 20). In half the trials, the participant was forced to choose between two equivalent alternatives, so one can consider the [25][25] trials as forced high-risk choices and the [5][5] trials as forced low-risk choices. On the [25][5] and [5][25] trials, however, participants could choose the level of risk; choosing 25 was more risky than choosing 5, because the potential loss was 25¢ (25 U.S. cents) in the former case and only 5¢ in the latter. Participants differed in the overall riskiness of their choices. The proportion of [5][25] and [25][5] trials on which a participant chose the high-risk option ranged from 0.37 to 0.71 (mean \pm SD, 0.52 ± 0.10).

Taking a closer look at this behavior, we found that participants' predominant strategy was to begin each block of 32 trials with risky choices and gradually shift to more cautious choices. For the first quarter of the block, the mean proportion of risky choices was 0.58. This proportion decreased to 0.48 by the last

Fig 1. Sequence of stimulus and response events in the gambling task. Participants viewed two squares, each of which contained the numeral 5 or 25 (Alternatives). Participants chose one of the squares by pressing the corresponding button (Choice response). One second after the choice, each square turned red or green (Outcome). If the chosen square turned green, then the amount indicated by the chosen numeral (in U.S. cents) was added to the total amount awarded to the individual at the end of a block of trials. If the chosen stimulus turned red, then the amount indicated was subtracted from the total. The square that the participant did not choose turned red or green at the same moment that the chosen square turned red or green. As a result, participants not only discovered their gain or loss but they also discovered what they would have gained or lost had they chosen the other square (25). In the example, the chosen square turns green, indicating a gain of 25¢. The other square turns red, indicating that the participant would have lost 5¢ if he or she had chosen that square. Half of the subjects were assigned red as the gain color, and half were assigned green as the gain color. The color and amount appearing in each square were determined randomly, so the monetary value corresponding to the unchosen square could differ from the chosen square in both magnitude and direction.

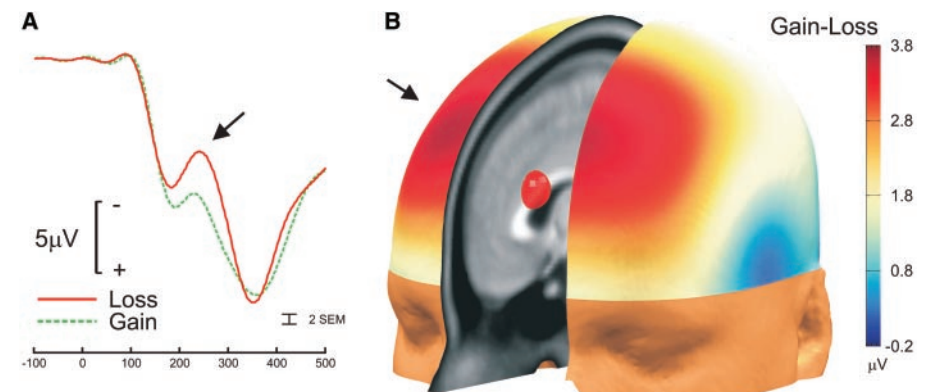
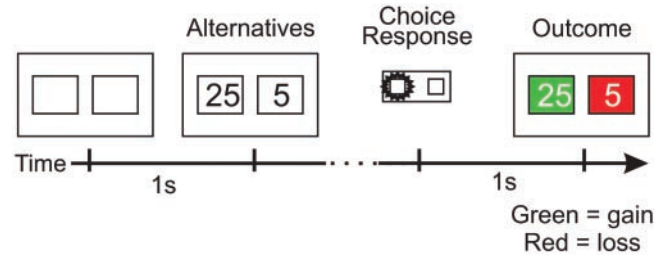


Fig. 2. ERP waveforms, scalp topography, and likely neural generator of the MFN. (A) The waveforms are shown at the Fz (frontal) electrode site. The solid red line corresponds to the average ERP waveform for all trials in which the participant lost money. The dashed green line corresponds to those trials in which the participant gained money. The MFN is indicated by the arrow. The error bar represents two standard errors of the mean, based on the mean squared error from the ANOVA (9). (B) The map of scalp activity shows the voltages, derived by subtracting the loss-trial waveform from the gain-trial waveform, computed at 265 ms after the onset of the outcome stimulus. Larger positive values correspond to a greater MFN effect. The MFN is indicated by the focus of activity at the Fz electrode (designated by the arrow). The best-fitting dipole model of the generator of the MFN is shown as a red sphere centered in the ACC on a canonical magnetic resonance imaging template of the human head (9).

quarter of the block ($P = 0.038$) (9). Such a strategy would enable a participant to preserve gains acquired in the early part of the block.

Further analysis revealed other factors that influenced whether participants made risky or cautious choices. Because studies of decision making have shown that a context in which losses are salient tends to result in risk-seeking behavior (21), we compared the choices that followed losses to those that followed gains. The proportion of trials on which an individual chose the risky option was greater when the previous trial was a loss than when it was a gain ($P = 0.00051$). Moreover, the effect of the previous outcome was greater when the previous value was 25¢ than when it was 5¢ ($P = 0.038$). Figure 4 shows that these effects resulted in the mean

proportion of risky choices bearing a linear relation to the value of the preceding outcome (in the test of the linear trend, $P = 0.0017$) (9).

If, as these proportions suggest, individuals change their preferences according to the history of gains and losses, then the motivational impact of an outcome should vary in a similar manner. We examined the MFN for signs that it too was influenced by the previous outcome. We computed the average difference between the gain-trial amplitude and the loss-trial amplitude as a measure of MFN activity on the trials after the four kinds of outcomes depicted in Fig. 4. The figure suggests that the influence of earlier gains and losses on MFN activity was similar to their influence on risk-taking behavior. The MFN effect (gain trial amplitude – loss trial

REPORTS

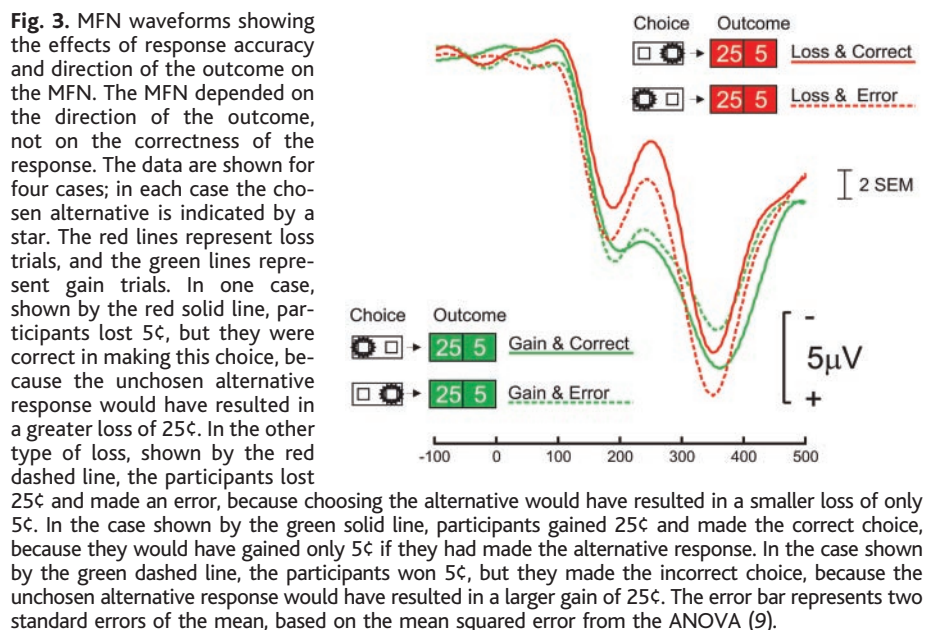
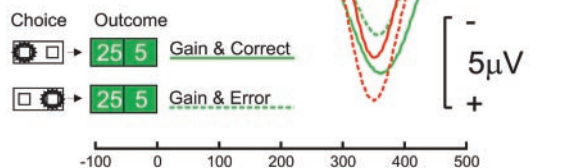


Fig. 3. MFN waveforms showing the effects of response accuracy and direction of the outcome on the MFN. The MFN depended on the direction of the outcome, not on the correctness of the response. The data are shown for four cases; in each case the chosen alternative is indicated by a star. The red lines represent loss trials, and the green lines represent gain trials. In one case, shown by the red solid line, participants lost 5¢, but they were correct in making this choice, because the unchosen alternative response would have resulted in a greater loss of 25¢. In the other type of loss, shown by the red dashed line, the participants lost



25¢ and made an error, because choosing the alternative would have resulted in a smaller loss of only 5¢. In the case shown by the green solid line, participants gained 25¢ and made the correct choice, because they would have gained only 5¢ if they had made the alternative response. In the case shown by the green dashed line, the participants won 5¢, but they made the incorrect choice, because the unchosen alternative response would have resulted in a larger gain of 25¢. The error bar represents two standard errors of the mean, based on the mean squared error from the ANOVA (9).

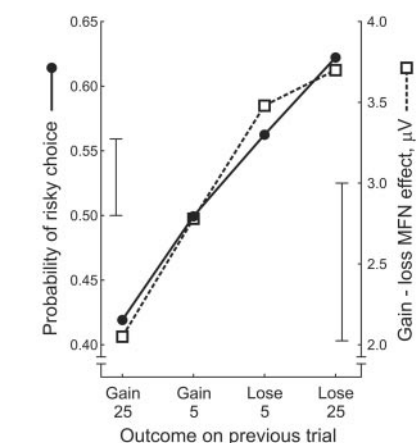


Fig. 4. The effect of the preceding outcome on the riskiness of behavior and on the MFN. The solid line (with solid circles) depicts the probability of a risky choice (choosing 25¢ rather than 5¢) on the current trial, when the previous trial had been (from left to right) a gain of 25¢, a gain of 5¢, a loss of 5¢, and a loss of 25¢. The dashed line (with open squares) depicts the MFN effect (gain trial amplitude – loss trial amplitude at the electrode Fz) on the current trial, after the same four outcomes. The error bars next to each axis represent two standard errors of the mean, based on the mean squared error from the ANOVA (9).

amplitude) was greater after loss trials than after gain trials ($P = 0.028$), and a linear relationship between the MFN effect and the value of the earlier outcome was evident (in the test of the linear trend, $P = 0.046$) (9). The MFN data thus suggest a correspondence between risk-taking behavior and the outcome processing reflected by the MFN (22).

In sum, the MFN responded to the motivational impact of the outcome event, not to the response- or error-feedback information.

Moreover, its response to the preceding outcome mirrored the pattern of risk taking in behavior.

These findings have a number of theoretical implications. Normative theories of judgment and decision making posit that the context in which a choice occurs—such as the sequence of recent gains and losses or the aspirations of a decision maker—should not affect the choice. A great deal of evidence, however, suggests that individuals deviate from normative behavior, making decisions that depend on the status quo or other nonnormative reference points (21). A critical issue for psychological theories of choice behavior is how cognitive and affective processing drive behavior in nonnormative ways.

Our data suggest that a rapid assessment of the motivational impact of an event participates in the evaluation of outcomes and that this processing is particularly sensitive to losses. In decision-making behavior, such processing could affect nonnormative decision making by mediating the role that outcome events play in choices. Studies of higher level decisions have shown that “losses loom larger than gains,” meaning that the aversion to a loss of a certain magnitude is greater than the attraction to a gain of the same magnitude (21). Consistent with this finding, studies of emotion have shown that affective responses are faster and stronger to proximate negative events than to positive ones (3, 23). In particular, the processing represented by the MFN could contribute to the experience that Kahneman refers to as “instant utility,” which is the momentary mental state resulting from the continuous evaluation of events along a good-bad dimension (24). Such a computation can contribute

to decision making by influencing the emotional state that individuals anticipate will occur upon making a choice (25), or it may affect the emotional state that drives behavior at the moment of the choice itself (26).

As for the neural circuitry that produces the MFN, our results suggest that the ACC is likely to contribute to the MFN. Certainly the medial-frontal scalp distribution of the MFN is consistent with an ACC origin, and the dipole localization modeling further supports an ACC locus. Moreover, the loss-related processing that gives rise to the MFN and the relation between the MFN and risky behavior are both consistent with evidence for a close functional relationship between the affective and behavioral control functions of the ACC (27, 28), and in particular with evidence for a sensitivity of ACC activity to reductions in reward or to penalties (6, 7).

The ACC is also the putative source of the ERN (15–18), and an important unresolved issue is how the ERN and MFN are related functionally and neuroanatomically. The MFN resembles the ERN in its scalp localization and likely neural generator, and the latency of the MFN is similar to the latency of ERN-like potentials that occur after error-feedback stimuli (29). Just as we propose an evaluative function for the MFN, some investigators have suggested that the ERN might reflect appraisal of the motivational or affective impact of the error rather than a computation related to detecting the error or response conflict (27, 28, 30). Support for this view includes evidence that ERN-like activity occurs in response to events associated with a negative affect (31) and evidence localizing error-related ACC activity to the rostral, affective subdivision of the ACC (as opposed to the more caudal, cognitive subdivision) (17, 18). It is plausible that the ERN and the MFN reflect a common source of underlying ACC activity, serving the same computational function in processing errors as it does in processing monetary losses (32, 33). Nevertheless, our data suggest that the ACC activity is not involved in evaluating performance per se, but is instead involved in assessing the motivational impact of the outcome events. Our results thus suggest that the primary computational function that is activated in studies of the ERN is not the detection of an error or of response conflict, but is instead the appraisal of the penalty or loss of resources associated with the error response (34, 35).

References and Notes

1. J. A. Bargh, M. J. Ferguson, *Psychol. Bull.* **126**, 925 (2000).
2. A. Bechara, H. Damasio, D. Tranel, A. R. Damasio, *Science* **275**, 1293 (1997).
3. J. T. Cacioppo, W. L. Gardner, *Annu. Rev. Psychol.* **50**, 191 (1999).
4. H. C. Breiter, I. Aharon, D. Kahneman, A. Dale, P. Shizgal, *Neuron* **30**, 619 (2001).

5. W. Schultz, P. Dayan, P. R. Montague, *Science* **275**, 1593 (1997).

6. B. Knutson, A. Westdorp, E. Kaiser, D. Hommer, *Neuroimage* **12**, 20 (2000).

7. G. Bush et al., *Proc. Natl. Acad. Sci. U.S.A.* **99**, 507 (2002).

8. The expected value is the sum of the values of potential outcomes weighted by their respective probabilities.

9. Supplementary details of experimental procedures and analyses are available on Science Online at www.sciencemag.org/cgi/content/full/295/5563/2279/DC1.

10. To increase the motivational properties of the monetary incentives, cash (dollar bills and coins) in the amount of the cumulative total was kept on the table at which the participant was seated and was incremented after each block of trials. When trial blocks resulted in a net loss, that total was not subtracted from the take-home amount delivered at the end of the experimental session. These procedures—the presence of the cash and the steadily increasing cumulative award—were used to increase the participant's motivation to attend to the gains and losses.

11. ERP activity was quantified as the mean amplitude in the 200- to 300-ms epoch after the onset of the stimulus, relative to a 100-ms prestimulus baseline. Analyses used repeated-measures analysis of variance (ANOVA), with Greenhouse-Geisser correction applied for violations of the ANOVA assumption of sphericity (9).

12. M. Scherg, in *Advances in Audiology*; vol. 6, *Auditory Evoked Magnetic Fields and Electrical Potentials*, F. Grandori, M. Hoke, G. L. Romani, Eds. (Karger, Basel, Switzerland, 1990), pp. 40–69.

13. M. Falkenstein, J. Hohnsbein, J. Hoormann, L. Blanke, *Electroencephalogr. Clin. Neurophysiol.* **78**, 447 (1991).

14. W. J. Gehring, B. Goss, M. G. H. Coles, D. E. Meyer, E. Donchin, *Psychol. Sci.* **4**, 385 (1993).

15. S. Dehaene, M. I. Posner, D. M. Tucker, *Psychol. Sci.* **5**, 303 (1994).

16. C. S. Carter et al., *Science* **280**, 747 (1998).

17. K. A. Kiehl, P. F. Liddle, J. B. Hopfinger, *Psychophysiology* **37**, 216 (2000).

18. V. Menon, N. E. Adelman, C. D. White, G. H. Glover, A. L. Reiss, *Hum. Brain Mapp.* **12**, 131 (2001).

19. The distinction between risky and cautious behavior in this task is different from the traditional distinction between "risk-seeking" and "risk-averse" behavior, and technically, the type of risk-aversion represented here is an aversion to mean-preserving spread, that is, an aversion to the variance in possible outcomes, holding expected values constant (20).

20. J. F. Yates, E. R. Stone, in *Risk-Taking Behavior*, J. F. Yates, Ed. (Wiley, New York, 1992), pp. 1–25.

21. D. Kahneman, A. Tversky, *Econometrica* **47**, 263 (1979).

22. This correspondence between behavior and outcome processing characterized the data of most of the participants. All 12 subjects showed both greater riskiness after losses than after gains, and 10 of those 12 showed greater MFN effects in the condition for which there was greater riskiness.

23. S. E. Taylor, *Psychol. Bull.* **110**, 67 (1991).

24. D. Kahneman, in *Well Being: The Foundations of Hedonic Psychology*, D. Kahneman, E. Diener, N. Schwarz, Eds. (Russell Sage Foundation, New York, 1999), pp. 3–25.

25. B. A. Mellers, *Psychol. Bull.* **126**, 910 (2000).

26. G. F. Loewenstein, E. U. Weber, C. K. Hsee, N. Welch, *Psychol. Bull.* **127**, 267 (2000).

27. G. Bush, P. Luu, M. I. Posner, *Trends. Cognit. Sci.* **4**, 215 (2000).

28. T. Paus, *Nature Rev. Neurosci.* **2**, 427 (2001).

29. W. H. R. Miltner, C. H. Braun, M. G. H. Coles, *J. Cognit. Neurosci.* **9**, 788 (1997).

30. W. J. Gehring, D. E. Fencsik, *J. Neurosci.* **21**, 9430 (2001).

31. D. M. Tucker, A. Hartry-Speiser, A. L. McDougal, P. Luu, D. deGrandpre, *Biol. Psychol.* **50**, 103 (1999).

32. Recently it was reported that the ERN may be part of an oscillatory potential in the theta frequency band

(4 to 7 Hz) (33). It was apparent that this might be true of the MFN as well, because the MFN was followed by activity that appeared oscillatory when a bandpass filter for the theta frequency was applied.

33. P. Luu, D. M. Tucker, *Clin. Neurophysiol.* **112**, 1295 (2001).

34. This hypothesis is further strengthened by findings that dissociate error detection and correction from the ERN (30, 35).

35. W. J. Gehring, R. T. Knight, *Nature Neurosci.* **3**, 516 (2000).

36. We thank L. Alattar, B. Freed, and K. Sajja for numerous contributions to this project. We are grateful to K. Berridge, D. Horn, R. Gonzalez, M. Jones, D. Meyer, J. Riis, E. Veinott, T. Wager, and F. Yates for helpful discussions and comments on earlier drafts.

5 October 2001; accepted 22 February 2002

Control of Synaptic Strength by Glial TNF α

Eric C. Beattie,¹ David Stellwagen,¹ Wade Morishita,¹ Jacqueline C. Bresnahan,² Byeong Keun Ha,² Mark Von Zastrow,³ Michael S. Beattie,^{2*} Robert C. Malenka^{1*}

Activity-dependent modulation of synaptic efficacy in the brain contributes to neural circuit development and experience-dependent plasticity. Although glia are affected by activity and ensheath the synapses, their influence on synaptic strength has largely been ignored. Here, we show that a protein produced by glia, tumor necrosis factor α (TNF α), enhances synaptic efficacy by increasing surface expression of AMPA receptors. Preventing the actions of endogenous TNF α has the opposite effects. Thus, the continual presence of TNF α is required for preservation of synaptic strength at excitatory synapses. Through its effects on AMPA receptor trafficking, TNF α may play roles in synaptic plasticity and modulating responses to neural injury.

Glia, long considered to be primarily supportive of neurons, are now thought to be more active participants in neural circuit function (1, 2). Recently, it has been shown that astrocytes are required for normal synaptogenesis and synaptic stability due to the release of diffusible, extracellular signal(s) (3–5), one of which appears to be cholesterol (6). Whether glia are required for the rapid continual maintenance of synaptic strength is unknown. Here we present evidence that in both cultured hippocampal neurons and hippocampal slices, glial cells constitutively release the cytokine TNF α , which markedly influences synaptic strength at excitatory synapses via rapid effects on the trafficking of AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (AMPA receptors). That TNF α might influence surface expression of AMPARs and synaptic strength was suggested by observations that TNF α enhanced brainstem neuron responses to excitatory afferent inputs (7) and potentiated the cell death induced by injection of the excitotoxin kainate into the spinal cord, an effect that was blocked by an

AMPA antagonist (8). Furthermore, several reports have suggested that TNF α may influence synaptic function (9–11).

To determine if TNF α increases AMPAR surface expression, we exposed cultured hippocampal neurons to TNF α (0.6 to 60 nM for 15 min) (12). This caused a twofold increase in the levels of surface AMPARs in the plasma membrane (Fig. 1, A and B). Because the media contained antagonists of all subtypes of glutamate receptors (12), this action of TNF α was not due to an indirect effect of TNF α on astrocyte-mediated glutamate release (13), which might affect AMPAR trafficking (14, 15). To determine whether the effect of TNF α on AMPAR surface expression was due to an increase in the delivery of new surface AMPARs, we visualized only those AMPARs that appeared in the plasma membrane during the TNF α treatment (16) (Fig. 1C). TNF α treatment (6 nM for 10 min) caused a marked increase in the delivery of new AMPARs to the plasma membrane compared to untreated cells (Fig. 1, C and D).

To address whether the TNF α -induced increase in AMPAR surface expression happens at synapses and thereby modifies synaptic strength, we compared the percentage of synapses, identified by synaptophysin staining, that contained detectable levels of AMPARs in untreated and TNF α -treated cells (17). TNF α caused a significant increase in this measure (Fig. 1, E and F). We also examined whether TNF α af-

¹Nancy Pritzker Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA 94304, USA. ²Department of Neuroscience, The Ohio State University Medical Center, Columbus, OH 43210, USA. ³Departments of Psychiatry and Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94143, USA.

*To whom correspondence should be addressed. E-mail: beattie.2@osu.edu (M.S.B.); malenka@stanford.edu (R.C.M.)