

binned immune deficiency syndrome clinical trials,  $>5 \times 10^6$  cells with MLV integrations were injected into each child (21, 22). Assuming that 20% of integrations are near transcriptional start sites, there will be 1 million integrations distributed among the 18,214 RefSeq genes or an average of 55 integrations into the 5' region of the *LMO2* locus per treatment. Evaluation of the sites of integration of HIV-1-based vectors compared to those of MLV vectors will be necessary to fully understand the risk factors and advantages of different retroviral gene-therapy systems.

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#### Supporting Online Material

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Materials and Methods

SOM Text

Table S1

Fig. S1

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# Requirement of AMPA Receptor GluR2 Phosphorylation for Cerebellar Long-Term Depression

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Cerebellar long-term depression (LTD) is a model of synaptic memory that requires protein kinase C (PKC) activation and is expressed as a reduction in the number of postsynaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors. LTD was absent in cultured cerebellar Purkinje cells from mutant mice lacking the AMPA receptor GluR2 subunit and could be rescued by transient transfection with the wild-type GluR2 subunit. Transfection with a point mutant that eliminated PKC phosphorylation of Ser<sup>880</sup> in the carboxy-terminal PDZ ligand of GluR2 failed to restore LTD. In contrast, transfection with a point mutant that mimicked phosphorylation at Ser<sup>880</sup> occluded subsequent LTD. Thus, PKC phosphorylation of GluR2 Ser<sup>880</sup> is a critical event in the induction of cerebellar LTD.

Cerebellar LTD is a persistent depression of the parallel fiber–Purkinje cell synapse which occurs when parallel fiber and climbing fiber inputs to a Purkinje cell are repeatedly coactivated. Its induction is thought to require three initial signals: activation of the metabotropic glutamate receptor mGluR1, Ca<sup>2+</sup> influx through voltage-sensitive Ca<sup>2+</sup> channels, and activation of AMPA receptors. It is widely hypothesized to make up a portion of the memory trace for certain forms of motor learning (1, 2). As do most other forms of

LTD or LTP (long-term potentiation) described to date, cerebellar LTD induction requires activation of a protein kinase. Several lines of evidence, from both brain slices and cell-culture preparations, have indicated that this kinase is PKC (3–8).

The expression mechanism of cerebellar LTD has been well described. LTD may be detected with exogenous test pulses of glutamate (3, 9) or AMPA (10) in preparations that lack viable presynaptic terminals (11, 12), which indicates that it results from a functional down-regulation of postsynaptic AMPA receptors. Cerebellar LTD is not associated with changes in AMPA receptor desensitization, kinetics, agonist affinity, or unitary conductance (13) but appears to be mediated by a decrease in the number of synaptic AMPA receptors (14) via clathrin-mediated endocytosis (15). The processes that link PKC activation to AMPA

receptor internalization are unclear but have been hypothesized to involve the following: (i) phosphorylation of the GluR2 carboxy-terminus at Ser<sup>880</sup> within a PDZ domain–recognition site, (ii) consequent disruption of GluR2 binding to the PDZ domain–containing proteins GRIP 1 and 2, and (iii) promotion of binding to the PDZ domain–containing protein PICK1 (16–19).

To directly test this hypothesis, we first examined cerebellar LTD in whole-cell voltage-clamp recordings in a dissociated Purkinje cell culture system from wild-type mice and mice lacking the GluR2 subunit (GluR2 KO). In this system, parallel fiber and climbing fiber stimuli were replaced by exogenous iontophoretic glutamate pulses and step depolarizations, respectively (4, 10, 11). After LTD induction by pairing six 3-s-long depolarizations to 0 mV with six glutamate pulses, a persistent depression in the amplitude of glutamate currents was seen in wild-type Purkinje cells ( $51 \pm 8.1\%$  of baseline, measured at  $t = 35$  min;  $n = 6$ ) (Fig. 1). However, in Purkinje cells derived from the GluR2 KO mice, LTD was completely abolished ( $106 \pm 8.7\%$  of baseline;  $n = 7$ ). A similar result was seen when the number of glutamate-depolarization pairings was increased from 6 to 18 ( $101 \pm 10.3\%$  of baseline;  $n = 4$ ). The simplest explanation for these results is that LTD induction required the acute action of GluR2; it is also possible that the LTD deficit resulted from a secondary, developmental effect of the GluR2 deletion. Therefore, we used particle-mediated transfection to deliver expression constructs encoding wild-type GluR2 (GluR2 wt) and enhanced green fluorescent protein (EGFP) to cultured GluR2 KO Purkinje cells and made recordings 22 to 60 hours later. Transfection with GluR2 wt produced a near-complete rescue of LTD ( $65 \pm 8.8\%$  of baseline;  $n = 7$ ); however, an empty

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expression vector (plus EGFP) had no effect ( $106 \pm 7.7\%$  of baseline;  $n = 6$ ). Notably, transfection of wild-type Purkinje cells with GluR2 wt did not alter the amplitude or time course of LTD ( $57 \pm 9.3\%$  of baseline;  $n = 6$ ).

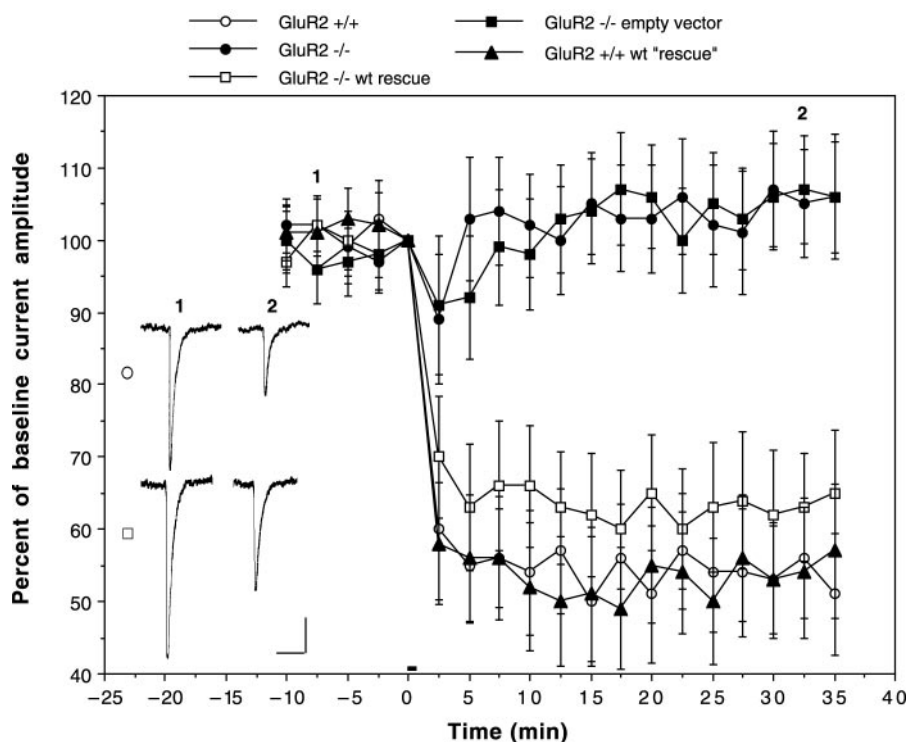
To determine whether PKC phosphorylation of Ser<sup>880</sup> within the carboxy-terminal PDZ ligand of GluR2 is required for cerebellar LTD, we sought a mutant form of GluR2 that could not be phosphorylated by PKC but that still showed normal binding to the PDZ domain-containing proteins GRIP 1 and 2

and PICK1. Because mutation of Ser<sup>880</sup> to alanine has previously been shown to disrupt binding of GluR2 to GRIP (20, 21), we instead created a mutation in which Lys<sup>882</sup> was replaced by alanine (GluR2 K882A). Mutation of this penultimate residue (-1 position) in the GluR2 carboxy-terminal tail should disrupt the PKC consensus site [S/T-X-K/R (22, 23)] but should not affect PDZ-mediated interactions (24). A phosphorylation site-specific antibody was first isolated that would recognize phosphorylation at Ser<sup>880</sup> in

the presence or absence of the K882A mutation [(25) Fig. 2A]. Heterologous cells were then transfected with GluR2 wt or GluR2 K882A and treated with the PKC activator phorbol-12-myristate-13-acetate (TPA, 1  $\mu$ M) or dimethyl sulfoxide (DMSO) as a control. Probing with the phosphorylation site-specific antibody confirmed phosphorylation of GluR2 wt in response to PKC activation, but we could not detect PKC phosphorylation of the GluR2 K882A mutant (Fig. 2B). To assess the effect of the K882A mutation on binding to GRIP and PICK, we performed coimmunoprecipitation experiments in heterologous cells. Both GluR2 wt and GluR2 K882A coimmunoprecipitated with GRIP1 and PICK1, which indicated that binding was not perturbed (Fig. 2C). In contrast, GluR2 S880E, a construct mimicking constitutive phosphorylation at Ser<sup>880</sup>, coimmunoprecipitated only with PICK1 (17, 18). GluR2 I883E, a construct containing a point mutation at the last carboxy-terminal residue designed to disrupt all PDZ-mediated interactions (21), coimmunoprecipitated with neither GRIP1 nor PICK1.

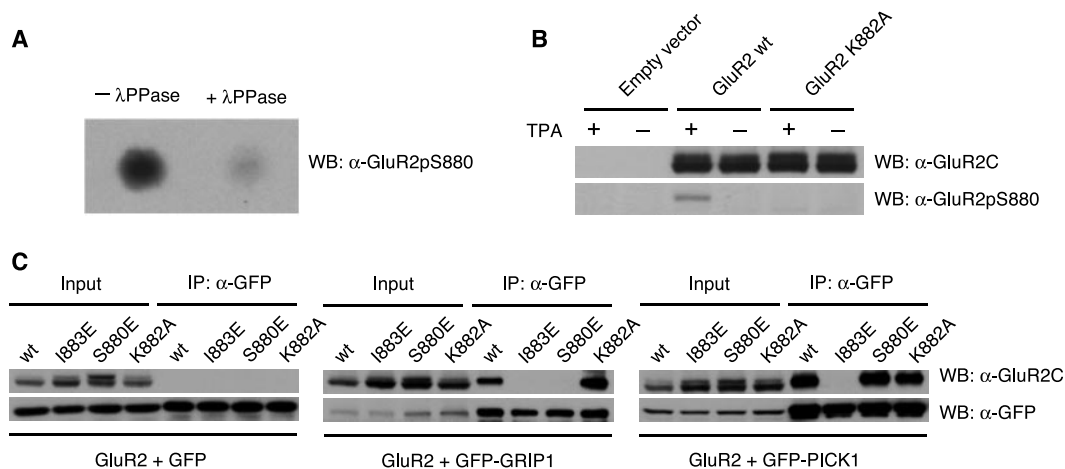
The above results demonstrate that GluR2 K882A is an appropriate mutant to test the hypothesis that phosphorylation of GluR2 Ser<sup>880</sup> is required for cerebellar LTD. We therefore transfected GluR2 KO Purkinje cells with this construct, and we examined LTD expression. Transfection of GluR2 K882A failed to rescue LTD (Fig. 3A;  $105 \pm 6.9$  of baseline;  $n = 11$ ). Transfection with a constitutive phosphorylation mimic, GluR2 S880E, also failed to rescue LTD expression ( $104 \pm 8.6\%$  of baseline;  $n = 6$ ), which implies that the dynamic phosphorylation of Ser<sup>880</sup> is required for induction of LTD.

Deletion of the GluR2 subunit or transfection of the neurons may alter the initial signals required to activate PKC during LTD induction. To address this possibility, we used bis-Fura-2 microfluorimetric imaging of Purkinje cell dendrites to measure the Ca<sup>2+</sup> transient evoked by



**Fig. 1.** Cerebellar LTD is abolished in Purkinje cells derived from GluR2 KO mice and is restored by acute transfection with GluR2 wt. After we acquired baseline responses to glutamate, LTD was induced by glutamate in conjunction with depolarization at  $t = 0$  min (horizontal bar). Error bars indicate the SEM in this and all other graphs. Representative raw current traces were acquired at the times indicated on the graph. Scale bars = 50 pA, 1 s. GluR2<sup>+/+</sup>,  $n = 6$ ; GluR2<sup>-/-</sup>,  $n = 7$ ; GluR2<sup>-/-</sup> wt rescue,  $n = 7$ ; GluR2<sup>-/-</sup> empty vector,  $n = 6$ ; GluR2<sup>+/+</sup> wt "rescue",  $n = 6$ .

**Fig. 2.** Biochemical characterization of GluR2 K882A. (A) Spot blot of BSA-conjugated GluR2 carboxy-terminal peptide used for antibody purification after treatment with lambda phosphatase (+ $\lambda$ -PPase) or control (- $\lambda$ -PPase), showing phosphospecificity of the antibody. (B) Phorbol-12-myristate-13-acetate (TPA, 1  $\mu$ M) treatment of transfected HEK 293T cells, showing Ser<sup>880</sup> phosphorylation of GluR2 wt, but not GluR2 K882A. (C) Coimmunoprecipitation in transfected HEK 293T cells of GluR2 wt and GluR2 point mutants with green fluorescent protein (GFP) alone (left), GFP-GRIP1 (middle), and GFP-PICK1 (right), with results as described in text.

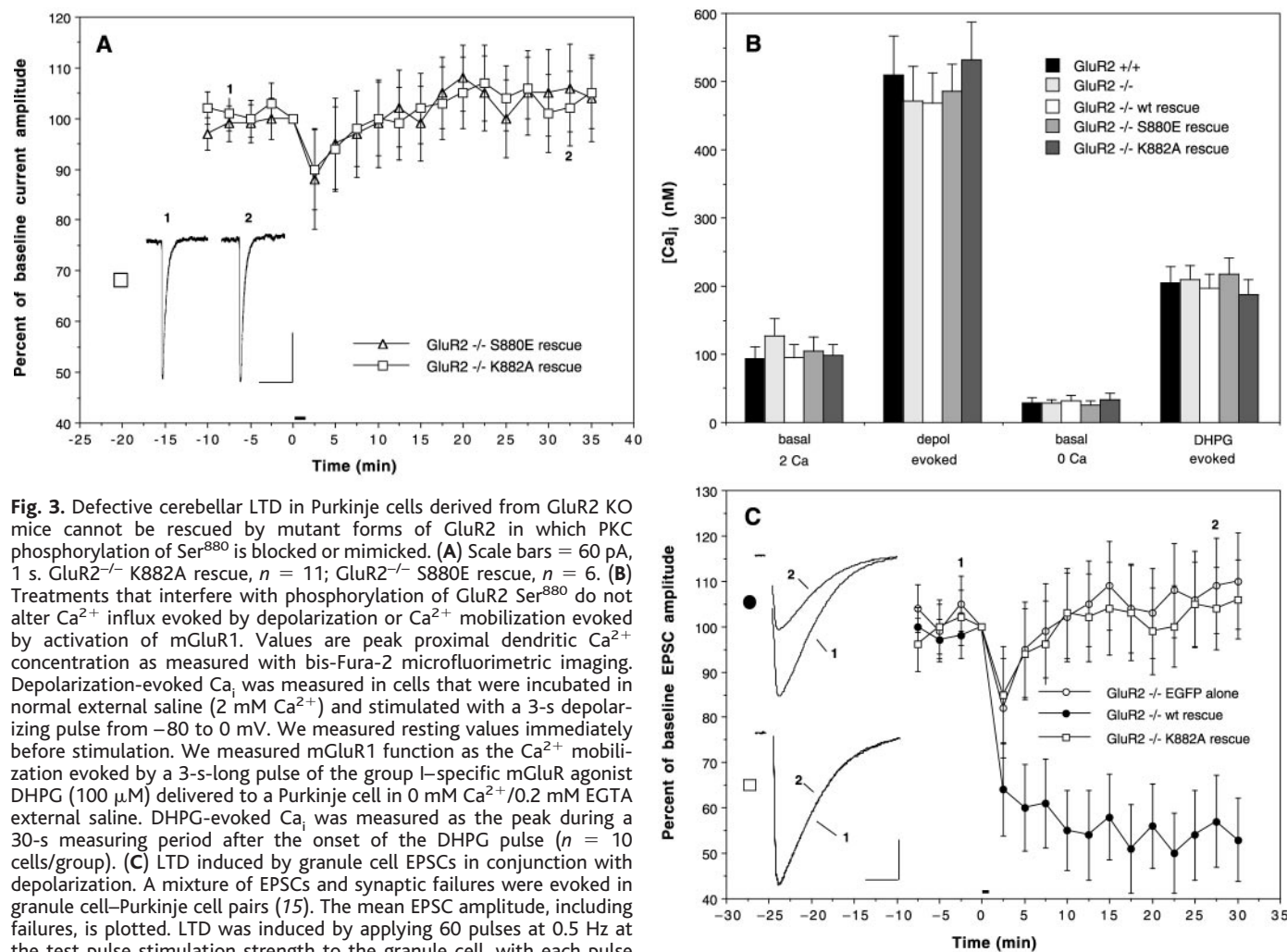


a depolarizing step (an index of voltage-gated  $Ca^{2+}$  channel function) and the  $Ca^{2+}$  transient evoked by application of an mGluR1 agonist (DHPG, 100  $\mu$ M) in  $Ca^{2+}$ -free external saline (an index of mGluR1 function). Neither of these measures was significantly altered in GluR2 KO as compared with wild-type Purkinje cells, nor were they altered by transfection of GluR2 wt, GluR2 K882A, or GluR2 S880E into the GluR2 KO background (Fig. 3B). Other basal properties of Purkinje cells were likewise unaltered by these treatments (Table 1).

Another possible complication in these experiments relates to the activation of extrasynaptic receptors in a system relying on exogenous glutamate pulses rather than synaptically released glutamate. Therefore, additional experiments were conducted to examine LTD induction with evoked monosynaptic EPSCs in granule cell–Purkinje cell pairs (Fig. 3C). In granule cell–Purkinje cell pairs derived from GluR2 KO mice, Purkinje cell transfection with GluR2 wt rescued LTD (53  $\pm$  9.2% of baseline at  $t = 30$  min;  $n = 4$ ),

whereas transfection of EGFP alone failed (110  $\pm$  10.6% of baseline;  $n = 6$ ). Moreover, Purkinje cell transfection with GluR2 K882A failed to rescue LTD (106  $\pm$  8.8% of baseline;  $n = 7$ ), which confirmed the results obtained with the combination of glutamate and depolarization.

AMPA receptors that lack the GluR2 subunit are highly permeable to  $Ca^{2+}$ ; those that contain GluR2 are relatively  $Ca^{2+}$ -impermeable (26, 27). In accordance with this observation, measures of the permeability ratio

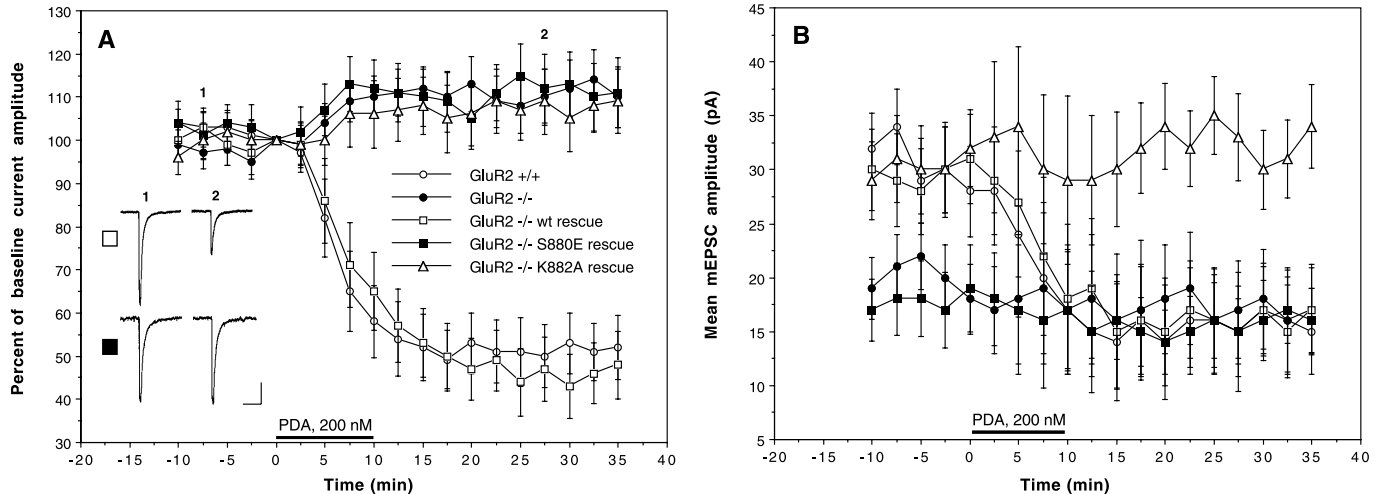


**Fig. 3.** Defective cerebellar LTD in Purkinje cells derived from GluR2 KO mice cannot be rescued by mutant forms of GluR2 in which PKC phosphorylation of Ser<sup>880</sup> is blocked or mimicked. (A) Scale bars = 60 pA, 1 s. GluR2<sup>-/-</sup> K882A rescue,  $n = 11$ ; GluR2<sup>-/-</sup> S880E rescue,  $n = 6$ . (B) Treatments that interfere with phosphorylation of GluR2 Ser<sup>880</sup> do not alter  $Ca^{2+}$  influx evoked by depolarization or  $Ca^{2+}$  mobilization evoked by activation of mGluR1. Values are peak proximal dendritic  $Ca^{2+}$  concentration as measured with bis-Fura-2 microfluorimetric imaging. Depolarization-evoked  $Ca_i$  was measured in cells that were incubated in normal external saline (2 mM  $Ca^{2+}$ ) and stimulated with a 3-s depolarizing pulse from  $-80$  to 0 mV. We measured resting values immediately before stimulation. We measured mGluR1 function as the  $Ca^{2+}$  mobilization evoked by a 3-s-long pulse of the group I-specific mGluR agonist DHPG (100  $\mu$ M) delivered to a Purkinje cell in 0 mM  $Ca^{2+}$ /0.2 mM EGTA external saline. DHPG-evoked  $Ca_i$  was measured as the peak during a 30-s measuring period after the onset of the DHPG pulse ( $n = 10$  cells/group). (C) LTD induced by granule cell EPSCs in conjunction with depolarization. A mixture of EPSCs and synaptic failures were evoked in granule cell–Purkinje cell pairs (15). The mean EPSC amplitude, including failures, is plotted. LTD was induced by applying 60 pulses at 0.5 Hz at the test pulse stimulation strength to the granule cell, with each pulse paired with a 100-ms-long depolarization of the Purkinje neuron to 0 mV (horizontal bar). Current traces are the average of 12 consecutive responses. Scale bars = 5 ms, 7 pA. GluR2<sup>-/-</sup> EGFP alone,  $n = 4$ ; GluR2<sup>-/-</sup> wt rescue,  $n = 6$ ; GluR2<sup>-/-</sup> K882A rescue,  $n = 7$ .

**Table 1.** Effects of GluR2 manipulations on some basal properties of granule cell–Purkinje cell synapses in culture.  $R_{input}$  is Purkinje cell input resistance;  $P_{Ca}/P_{Na}$  is the ratio of Ca permeability to Na permeability.

Measure	GluR2 <sup>+/+</sup>	GluR2 <sup>-/-</sup>	GluR2 <sup>-/-</sup> wt rescue	GluR2 <sup>-/-</sup> empty vector	GluR2 <sup>+/+</sup> wt "rescue"	GluR2 <sup>-/-</sup> S880E rescue	GluR2 <sup>-/-</sup> K882A rescue
$R_{input}$ (M $\Omega$ )	196 $\pm$ 35	207 $\pm$ 24	190 $\pm$ 22	212 $\pm$ 31	188 $\pm$ 30	199 $\pm$ 28	202 $\pm$ 25
mEPSC amplitude (pA)	28 $\pm$ 5	21 $\pm$ 4	29 $\pm$ 4	21 $\pm$ 4	29 $\pm$ 5	18 $\pm$ 4	29 $\pm$ 5
mEPSC 10 to 90% rise time (ms)	1.7 $\pm$ 0.5	1.9 $\pm$ 0.3	1.6 $\pm$ 0.3	1.8 $\pm$ 0.4	1.8 $\pm$ 0.5	1.7 $\pm$ 0.4	1.9 $\pm$ 0.5
mEPSC 50% decay time (ms)	6.9 $\pm$ 0.9	6.2 $\pm$ 1.0	7.0 $\pm$ 0.8	6.3 $\pm$ 0.9	6.6 $\pm$ 1.1	7.1 $\pm$ 1.0	6.6 $\pm$ 1.1
AMPA-R unitary conductance (pS)	23.8 $\pm$ 2.8	22.6 $\pm$ 2.0	24.5 $\pm$ 2.6	22.0 $\pm$ 2.9	24.7 $\pm$ 2.6	25.0 $\pm$ 2.8	24.4 $\pm$ 2.1
$P_{Ca}/P_{Na}$	0.28 $\pm$ 0.08	3.85 $\pm$ 0.59	0.20 $\pm$ 0.05	3.99 $\pm$ 0.62	0.19 $\pm$ 0.06	0.21 $\pm$ 0.07	0.16 $\pm$ 0.06

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**Fig. 4.** An LTD-like phenomenon induced by PKC-activating phorbol ester in Purkinje cells derived from GluR2 KO mice. **(A)** An LTD-like effect was induced by bath application of phorbol-12,13-diacetate (200 nM) at  $t = 0$  to 10 min as indicated by the horizontal bar. Scale bars = 40 pA, 1 s. GluR2<sup>+/+</sup>,  $n = 6$ ; GluR2<sup>-/-</sup>,  $n = 6$ ; GluR2<sup>-/-</sup> wt rescue,  $n = 7$ ; GluR2<sup>-/-</sup> S880E,  $n = 6$ ; GluR2<sup>-/-</sup> K882A,  $n = 6$ . **(B)**

mEPSCs were measured in the same Purkinje cells shown in **(A)** and are expressed as mean raw amplitudes (rather than a normalized scale). Some recordings could not be analyzed for mEPSCs because of higher noise levels and were omitted. GluR2<sup>+/+</sup>,  $n = 5$ ; GluR2<sup>-/-</sup>,  $n = 6$ ; GluR2<sup>-/-</sup> wt rescue,  $n = 5$ ; GluR2<sup>-/-</sup> S880E,  $n = 5$ ; GluR2<sup>-/-</sup> K882A,  $n = 5$ .

$P_{Ca}/P_{Na}$  for responses to exogenous AMPA yielded values of  $0.28 \pm 0.08$  and  $3.85 \pm 0.59$  for wild-type and GluR2 KO Purkinje cells, respectively (Table 1). In GluR2 KO Purkinje cells, transfection with GluR2 wt, GluR2 K882A, or GluR2 S880E all reconstituted AMPA receptors with low  $Ca^{2+}$  permeability ( $0.20 \pm 0.05$ ,  $0.16 \pm 0.06$ , and  $0.21 \pm 0.07$ , respectively). This suggests that the failure of GluR2 K882A and GluR2 S880E to rescue LTD cannot result simply from a lack of expression and the inability to become incorporated into functional multimers at the dendritic plasma membrane.

Although cerebellar LTD is typically induced by pairing stimulation, an LTD-like process that has many of the properties of cerebellar LTD can be induced by bath application of PKC-activating phorbol ester (3, 4, 13, 14). This chemical LTD has the advantage that it bypasses the requirements for mGluR1 signaling and voltage-gated  $Ca^{2+}$  channel function. We tested whether GluR2 phosphorylation is also required for this form of chemical LTD. A 10-min-long application of phorbol-12,13-diacetate (PDA, 200 nM) induced an LTD-like phenomenon in wild-type Purkinje cells (Fig. 4A;  $52 \pm 7.5\%$  of baseline at  $t = 35$  min;  $n = 6$ ) but failed to induce LTD in Purkinje cells from a GluR2 KO mouse ( $110 \pm 7.0\%$ ;  $n = 6$ ). The LTD-like effect produced by PDA was also rescued in GluR2 KO Purkinje cells by transfection with GluR2 wt ( $48 \pm 7.8\%$ ;  $n = 7$ ) but not by GluR2 K882A ( $109 \pm 7.5\%$ ;  $n = 6$ ) or GluR2 S880E ( $111 \pm 8.0\%$ ;  $n = 5$ ).

Failure of LTD induction can result from either blockade of LTD induction or occlusion by prior stimulation that induced maximal LTD. Miniature excitatory postsynaptic

currents (mEPSCs) were thus recorded as a measure of the level of synaptic AMPA receptors before and after induction of chemical LTD with PDA (Fig. 4B). The mean basal amplitude of mEPSCs was reduced in GluR2 KO as compared with wild-type Purkinje cells ( $19 \pm 2.9$  versus  $32 \pm 3.2$  pA at  $t = -10$  min,  $n = 5$ ). Subsequent PDA treatment failed to produce a depression in the mEPSC amplitudes in GluR2 KO Purkinje cells ( $17 \pm 4.2$  pA at  $t = 35$  min), whereas the mEPSC amplitude decreased in wild-type Purkinje cells ( $15 \pm 4.0$  pA;  $n = 6$ ). Transfection of GluR2 KO Purkinje cells with GluR2 wt rescued both the basal amplitude and the LTD-like effect on mEPSC amplitude ( $30 \pm 3.8$  and  $17 \pm 3.9$  pA at  $t = -10$  and 35 min, respectively;  $n = 5$ ). Transfection with GluR2 K882A resulted in high basal mEPSC amplitude but no significant effect of PDA treatment ( $29 \pm 3.6$  and  $34 \pm 3.9$  pA at  $t = -10$  and 35 min, respectively,  $n = 5$ ). In contrast, transfection with GluR2 S880E resulted in low basal mEPSC amplitude and no effect of PDA ( $17 \pm 2.9$  and  $16 \pm 3.0$  pA at  $t = -10$  and 35 min, respectively;  $n = 5$ ). These data suggest a model in which phosphorylation of GluR2 Ser<sup>880</sup> results in a depression of synaptic AMPA receptor function: when Ser<sup>880</sup> is rendered unphosphorylatable (GluR2 K882A), basal synaptic strength is high and cerebellar LTD is blocked; when Ser<sup>880</sup> is rendered constitutively phosphorylated (GluR2 S880E), basal synaptic strength is low and LTD is occluded.

We conclude that the phosphorylation state of GluR2 Ser<sup>880</sup> regulates the responsiveness of synaptic AMPA receptors in cerebellar Purkinje cells. In contrast to a previous report proposing a role for Ser<sup>880</sup> phosphorylation in exocy-

totic transport of AMPA receptors in hippocampal neurons (28), our finding that GluR2 K882A was delivered to synapses but failed to restore LTD in GluR2 KO Purkinje cells implicates Ser<sup>880</sup> phosphorylation as an upstream regulator of receptor endocytosis in response to LTD-inducing stimuli. Although PKC appears to be the kinase engaging this mechanism, it is possible that other kinases can phosphorylate this site, as has recently been suggested for hippocampal LTD induction (29). In addition, the phosphorylation state of GluR2 Ser<sup>880</sup> is also regulated by phosphatases, and coordinated phosphatase inhibition may be necessary for maximal phosphorylation. Indeed, it has recently been shown that PKC activation of myosin/moesin phosphatase inhibitor protein, CPI-17, is necessary for LTD induction (30). A signaling cascade involving nitric oxide, cyclic guanosine monophosphate (cGMP), and cGMP-dependent protein kinase and resulting inhibition of protein phosphatase 2A has also been implicated in LTD (31).

Several factors may account for the low basal mEPSC amplitude we observed in GluR2 KO Purkinje cells. First, immunohistochemical analysis on cerebellar slices from GluR2 KO mice with an antibody that recognizes the carboxy-terminal regions of GluR2, GluR3, and GluR4c demonstrated no significant up-regulation of GluR3 and GluR4c (fig. S1) (32). With GluR2 as the dominant subunit in heteromeric receptor complexes composed of GluR2/GluR3 or GluR2/GluR4c, elimination of GluR2 expression in the knock-out mouse could result in a significant reduction in surface AMPA receptor expression. Second, expression of the GluR2 subunit itself or GluR2 binding to interacting proteins such as NSF (*N*-ethylmaleim-

ide-sensitive factor) (33–35) or AP2 (36) may be required for export of functional heteromeric receptor complexes and/or stabilization of these complexes at the cell surface.

Our results suggest that phosphorylation of GluR2 Ser<sup>880</sup> is necessary for LTD induction. In Purkinje cells transfected with GluR2 K882A, which presumably contain at least some GluR2 K882A/GluR3 and/or GluR2 K882A/GluR4c heteromeric receptor complexes, the presence of a PKC consensus site on subunits other than GluR2 appears to be insufficient to enable LTD. It is unknown whether the corresponding serines on GluR3 and GluR4c are indeed phosphorylated by PKC or if upstream sequence differences and differential protein binding render these subunits incapable of supporting LTD.

Previous attempts to test the involvement of cerebellar LTD in motor learning paradigms have relied on drugs or genetic manipulations that act early in the LTD induction signaling cascade, either at receptors or second messengers (1). These studies have been limited owing to the nonspecific nature of the manipulations (e.g., disruption of mGluR1 or PKC function). A GluR2 K882A knock-in mouse could provide the first strong test of the hypothesis that cerebellar LTD is required for certain forms of motor learning.

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#### Supporting Online Material

www.sciencemag.org/cgi/content/full/300/5626/1751/DC1

Materials and Methods

Fig. S1

References

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## The Neural Basis of Economic Decision-Making in the Ultimatum Game

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The nascent field of neuroeconomics seeks to ground economic decision-making in the biological substrate of the brain. We used functional magnetic resonance imaging of Ultimatum Game players to investigate neural substrates of cognitive and emotional processes involved in economic decision-making. In this game, two players split a sum of money; one player proposes a division and the other can accept or reject this. We scanned players as they responded to fair and unfair proposals. Unfair offers elicited activity in brain areas related to both emotion (anterior insula) and cognition (dorsolateral prefrontal cortex). Further, significantly heightened activity in anterior insula for rejected unfair offers suggests an important role for emotions in decision-making.

Standard economic models of human decision-making (such as utility theory) have typically minimized or ignored the influence of emotions on people's decision-making behavior, idealizing the decision-maker as a perfectly rational cognitive machine. However, in recent years this assumption has been challenged by behavioral economists, who have identified additional psychological and emotional factors that influence decision-making (1, 2), and recently researchers have begun using neuroimaging to examine behavior in economic games (3). This study applies functional neuroimaging techniques to investigate the relative contributions of cognitive and emotional processes to human social decision-making.

The limitations of the standard economic model are effectively illustrated by empirical findings from a simple game known as the

Ultimatum Game. In the Ultimatum Game, two players are given the opportunity to split a sum of money. One player is deemed the proposer and the other, the responder. The proposer makes an offer as to how this money should be split between the two. The second player (the responder) can either accept or reject this offer. If it is accepted, the money is split as proposed, but if the responder rejects the offer, then neither player receives anything. In either event, the game is over.

The standard economic solution to the Ultimatum Game is for the proposer to offer the smallest sum of money possible to the responder and for the responder to accept this offer, on the reasonable grounds that any monetary amount is preferable to none. However, considerable behavioral research in industrialized cultures indicates that, irrespective of the monetary sum, modal offers are typically around 50% of the total amount. Low offers (around 20% of the total) have about a 50% chance of being rejected (4–8). This latter, quite robust, experimental finding is particularly intriguing, demonstrating that circumstances exist in which people are motivated to actively turn down monetary reward.

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