all restored. Our results indicate that mGluR1 in PCs is essential for these three events and suggest that mGluR1 in PC is a key molecule needed for normal development and function of the cerebellum. A rescue experiment with tissue-specific promoter is a most productive approach to specify the brain region or cell type responsible for the phenotype observed in conventional knockout mice.

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9. We generated transgenic mice (L7-mGluR1) that expressed mGluR1α under the control of the PC-specific L7 promoter [J. Oberdick, R. J. Smeyne, J. R. Mann, S. Zackson, J. I. Morgan, *Science* **248**, 223 (1990); R. J. Smeyne *et al.*, *Science* **254**, 719 (1991); R. J. Smeyne *et al.*, *Mol. Cell. Neurosci.* **6**, 230 (1995)]. A 3.7-kb Sac II–Fsp I fragment of rat mGluR1α cDNA containing a 26 base pair (bp) 5′ untranslated region (UTR), a 3597-bp coding region, and a 36-bp 3′ UTR was introduced into exon 4 of the L7 gene cassette. We obtained eight independent L7-mGluR1 transgenic founder mice by microinjecting the transgene into the pronuclei of fertilized mGluR1 (+/−) eggs. The mGluR1-rescue mice were obtained by breeding mGluR1 (+/−) with transgenic mice. The cerebellum-restricted expression of the transgene was examined by Western blotting with polyclonal antibodies to rat mGluR1 (Upstate Biotechnology, Lake Placid, NY). One line expressed the L7-mGluR1α transgene in the cerebellum but not in the cerebral cortex.
10. Adult wild-type, mGluR1 (−/−), and mGluR1-rescue (Tg/+) mice were deeply anesthetized with pentobarbital (100 mg/kg of body weight) and were perfused transcardially with 3.5% paraformaldehyde, 0.05% glutaraldehyde, and 1% picric acid in 0.1 M sodium phosphate buffer (pH 7.3). The brains were cryoprotected with 25% (w/w) sucrose in 0.1 M phosphate buffer overnight at 4°C and cut on a freezing microtome or cryostat into 40-μm-thick parasagittal sections. The free-floating sections were incubated overnight at room temperature with antibodies to mGluR1α (1.0 μg/ml) [R. Shigemoto *et al.*, *Nature* **381**, 523 (1996)], 0.1% Triton X-100, and 0.25% carrageenan. These sections were then washed with phosphate buffered saline (PBS), incubated with biotinylated antibody to guinea pig immunoglobulin G, washed again, and reacted with avidin-biotin-peroxidase complex (ABC Kit, Vector, Burlingame, CA). Finally, the sections were reacted with 0.02% diaminobenzidine tetrahydrochloride and 0.002% hydrogen peroxide in 50 mM tris-HCl (pH 7.6).
11. Parasagittal cerebellar slices (250 μm thick) were prepared from wild-type, mGluR1 (−/−), and mGluR1-rescue mice, as described [I. Llano, A. Marty, C. M. Armstrong, A. Konnerth, *J. Physiol.* **434**, 183 (1991)]. Whole-cell recording was made from visually identified PCs with either an Olympus (BH-2, Tokyo, Japan) or Zeiss (Axioskop, Oberkochen, Germany) upright microscope [F. A. Edwards, A. Konnerth, B. Sakmann, T. Takahashi, *Pflügers Archiv. (Eur. J. Physiol.)* **414**, 600 (1989)]. Resistance of patch pipettes was 3 to 6 megohm when filled with an intracellular solution composed as follows: 60 mM CsCl, 30 mM Cs D-gluconate, 20 mM tetraethylammonium-Cl (TEA-Cl), 20 mM BAPTA [1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (a Ca^{2+} buffer)], 4 mM $MgCl_2$, 4 mM adenosine triphosphate (ATP), and 30 mM Hepes, pH 7.3 (adjusted with CsOH). The pipette access resistance was compensated. The standard bathing solution was composed as follows: 125 mM NaCl, 2.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgSO_4$, 1.25 mM NaH_2PO_4, 26 mM $NaHCO_3$, and 20 mM glucose, which was bubbled continuously with a mixture of 95% O_2 and 5% CO_2. Bicuculline (10 μM) was included to block spontaneous inhibitory postsynaptic currents. Membrane currents were recorded with an Axopatch-1D amplifier (Axon Instruments, Foster City, CA). Glass pipettes filled with standard extracellular solution were used to stimulate CFs in the granule cell layer. The PULSE software (version 8.2, HEKA, Lambrecht, Germany) was used for stimulation and data acquisition. The signals were filtered at 3 kHz and digitized at 20 kHz.
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13. To measure LTD, a potassium-based intracellular solution was used. The composition was as follows: 70 mM KCl, 60 mM K D-gluconate, 4 mM $MgCl_2$, 4 mM ATP, 0.4 mM guanosine triphosphate (GTP), and 30 mM Hepes, pH 7.3 (adjusted with KOH). EPSPs elicited by PF stimulation were recorded with an Axoclamp-2B amplifier (Axon Instruments). The membrane potential was kept constant at −70 to −80 mV by injecting hyperpolarizing currents (200 to 500 pA).
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15. Mice were placed under pentobarbital anaesthesia (40 to 50 mg/kg of body weight) before surgical operation. A platform for fixation of the head to a stereotaxic frame was built in aseptic conditions. After making an incision in the skin, four small screws around the central long bolt were mounted on the parietal cranium, and were sealed by dental cement. Cinematographic recordings were started 2 to 4 days after the surgery. During recordings, a mouse was mounted on the treadmill with its head fixed, but its body and limbs were not restrained. Locomotion was induced by moving the belts at moderate velocities (12, 14, and 16 cm/s). Movement of the mice was filmed with a video camera (SONY DXC-107A, Tokyo, Japan) equipped with a shutter operating at 60 fields per second. A field-by-field analysis (16.7-ms time resolution) of the videotapes revealed the temporal measurements.
16. Animals were housed at 21° ± 1°C with free access to food and water and tested at 12 to 15 weeks. Experiments were conducted in accordance with ethical guidelines of the Institute of Medical Science, University of Tokyo. In the open-field test, each mouse was placed in the middle of a 75-cm-diameter enclosure, and the walking route of the mouse was traced with a behavioral tracing analyzer (Muromachi Kikai, Tokyo). The total walking distance was recorded every 30 min over a 2-hour period.
17. The Rota-Rod Treadmill (Muromachi Kikai) consists of a gritted plastic rod (3 cm in diameter, 10 cm long) flanked by two large round plates (50 cm in diameter). The time the mouse remained on the rod was measured. A maximum of 120 s was allowed to test each animal.

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Dissociating the Role of the Dorsolateral Prefrontal and Anterior Cingulate Cortex in Cognitive Control

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Theories of the regulation of cognition suggest a system with two necessary components: one to implement control and another to monitor performance and signal when adjustments in control are needed. Event-related functional magnetic resonance imaging and a task-switching version of the Stroop task were used to examine whether these components of cognitive control have distinct neural bases in the human brain. A double dissociation was found. During task preparation, the left dorsolateral prefrontal cortex (Brodmann's area 9) was more active for color naming than for word reading, consistent with a role in the implementation of control. In contrast, the anterior cingulate cortex (Brodmann's areas 24 and 32) was more active when responding to incongruent stimuli, consistent with a role in performance monitoring.

Cognitive control has long attracted the attention of philosophers and psychologists interested in how the human brain carries out the higher functions of awareness, memory, and language. The concept of control generally refers to a resource-limited system that guides voluntary, complex actions. Solving difficult, novel, or complex tasks, overcoming habitual responses, and correcting errors all require a high

degree of cognitive control. Cognitive control has frequently been operationalized as the provision of top-down support for task-relevant processes; for example, a representation of the attentional demands of the task can be used to bias processing in favor of task-relevant stimuli and responses and thereby establish the appropriate stimulus-response mapping (*1–3*). Other work suggests that a second component is required to provide ongoing feedback indicating whether control is being allocated effectively (*4, 5*).

Studies using functional neuroimaging techniques have related cognitive control to activity in the dorsolateral prefrontal cortex (DLPFC) [Brodmann's area (BA) 9 and BA 46] and the anterior cingulate cortex (ACC) (BA 24 and BA 32). For example, both the DLPFC and ACC activate when participants are required to hold increasingly long sequences of items in working memory or when two tasks are performed at once, compared to when they are performed one at a time (*6*). From these data, it is impossible to dissociate the respective roles of the DLPFC and ACC because, as the tasks become more difficult, there are increased demands both for strategic processes, such as top-down support, and for evaluating the output of the system.

A number of neuroimaging studies have reported relative dissociations for these regions. DLPFC activity in the absence of ACC activity has been found for tasks that require maintenance and manipulation of information in working memory (*7*). For example, the DLPFC is active when a simple cue has to be maintained over a delay (*8*). ACC activity has been more consistently observed than DLPFC activity when tasks require divided attention, novel or open-ended responses, or the overcoming of a prepotent response (*9*). For example, the traditional Stroop task involves naming the ink color of colored words. Sometimes the word and ink color are congruent ("RED" printed in red ink), and sometimes they are incongruent ("RED" printed in blue ink). Because participants automatically read the word, they are slower to name the color in the incongruent condition, which is also when greater ACC activation is observed (*10*).

These relative dissociations led us to hypothesize that the DLPFC may be involved in representing and maintaining the attentional demands of the task. In contrast, the ACC may be involved in evaluative processes, such as monitoring the occurrence of errors or the presence of response conflict, which occurs when two incompatible responses are both compelling. Monitoring such occurrences is necessary to provide feedback as to when strategic processes must be more strongly engaged to adapt ongoing behavior. However, because these studies report single dissociations, this interpretation is tenuous; that is, both the DLPFC and ACC may be engaged for many of these tasks, but either because of the demands of the subtractive condition or a lack of power, activity in only one region crosses a statistical threshold. As a result, uncertainty remains about how these two frontal regions contribute to cognitive control processes.

To test for a hypothesized double dissociation between the functions of the DLPFC and ACC, we used a modified version of the Stroop paradigm (Fig. 1), in which subjects were given an instruction before each trial indicating whether to read the word (a more automatic response) or name the color (requiring greater control). Following a delay, the stimulus was presented. Thus, the task temporally separated instruction-related strategic processes, including those responsible for representing and maintaining the attentional demands of the task (color naming versus word reading) from response-related, including evaluative, processes.

Twelve participants completed the switching Stroop task (*11*) during a functional magnetic resonance imaging scanning session (*12*). Instruction-related activity was examined for the first five scans of each trial. As illustrated in Fig. 1, activity was observed within the DLPFC in response to instructions to name the color but not read the word. This pattern was only observed within the DLPFC and is consistent with the increased requirement for top-down control in the color-naming task and the role of the DLPFC in representing and maintaining task demands needed for such control. No instruction-related activity was observed in the ACC. We hypothesized that if the DLPFC implements a top-down control function, more activity in this region should lead to less conflict (i.e., smaller reaction time interference effects) when responding to incongruent colored words. Consistent with this prediction, individuals who showed the most activation in the left DLPFC after the color-naming instruction showed the smallest Stroop interference effect (correlation coefficient $r = -0.63$, $P = 0.02$, one-tailed).

Response-related activity was examined for the last four scans of each trial. As illustrated in Fig. 1, within the right ACC, greater activity was observed for incongruent, compared to congruent, color-naming trials, consistent with a role in conflict monitoring (*13*). Although the DLPFC was active during the response, it was no more active during incongruent than during congruent color-naming trials. If the ACC monitors conflict, then high conflict (i.e., larger reaction time interference effects) should be associated with more ACC activation. Consistent with this prediction, individuals who showed the largest Stroop interference effect tended to have more ACC activation, although this effect was not sig-

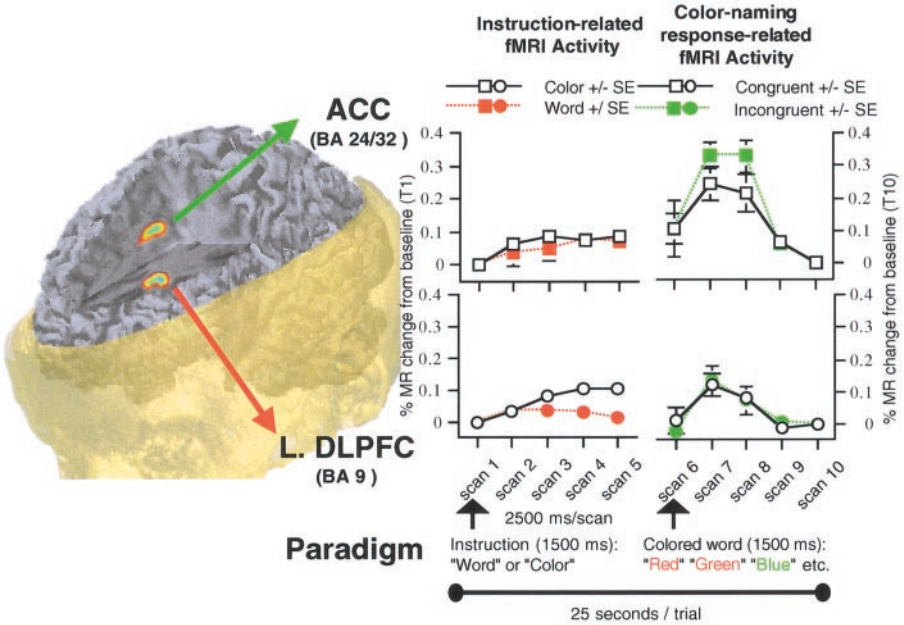

Fig. 1. Functional magnetic resonance imaging (fMRI) activity across the course of a trial in the left DLPFC (L. DLPFC) (BA 9; Talairach coordinates $x = -41$, $y = 18$, $z = 28$; maximum $F = 7.14$; 36 pixels) and ACC (BA 24 and BA 32; Talairach coordinates $x = 4$, $y = 1$, $z = 43$; maximum $F = 7.98$; 10 voxels). At the beginning of each 25-s trial, subjects were given an instruction to either read the word or name the color of the following stimulus. A colored word was presented 12.5 s after the beginning of each trial. Significant differences between conditions were detected in the left DLPFC across scans 1 to 5 (lower left quadrant) and in the ACC across scans 7 to 10 (upper right quadrant).

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nificant for the number of subjects tested (r = 0.38, P = 0.12, one-tailed).

These findings suggest a dissociation between the left DLPFC and the ACC. The left DLPFC was selectively engaged during the preparatory period, more for color naming than for word reading. This is consistent with a role in the implementation of control, by representing and actively maintaining the attentional demands of the task. In contrast, the ACC was selectively activated during the response period, more for incongruent than for congruent color-naming trials. This is consistent with a role in conflict monitoring. Thus, these regions appear to have distinct, complementary roles in a neural network serving cognitive control.

The association between the left DLPFC and strategic control processes is consistent with findings from neuropsychological, neurophysiological, and lesion studies, as well as from computational analyses of the function of the prefrontal cortex. For example, patients with injuries to this region have shown a great deal of difficulty on the Stroop task, as well as with other tasks that require the representation and maintenance of the attentional demands of the task (*14*). Sustained neural activity during a delayed response task in a homologous region of the primate frontal cortex has been interpreted as strategic processing related to control, and lesions to this region result in an inability to use complex information stored in working memory (*15*). Computational modeling of the Stroop and related paradigms suggested that the DLPFC may be responsible for maintaining and representing context information, including the attentional demands of the task (*16*).

ACC activation during responses to incongruent colored words on the Stroop task has been found in previous studies using blocked paradigms and is frequently interpreted as evidence that the ACC is involved in implementing control [e.g., (*10, 17*)]. The current dissociation is not consistent with the interpretation that the ACC is implementing control by representing and maintaining the attentional demands of the task. Another possibility is that the ACC performs a more transient form of control, preferentially engaged by attentionally demanding (e.g., incongruent) stimuli. However, a number of considerations weigh against this interpretation of the observed ACC activity. Regions implementing control should be negatively correlated with the amount of conflict (i.e., more control, less conflict). This pattern was observed in the DLPFC, but the correlation between ACC activity and conflict was in a positive direction. This finding is consistent with significant, positive correlations found in two previous studies of ACC activity and conflict (*18*). This previous work has also shown that ACC activity increases when top-down control is low, whether control is reduced from trial to trial or across a number of trials (*18*). Further, computational modeling work suggests that many behavioral effects related to Stroop interference can be explained by representing and maintaining the attentional demands of the task, without the need for stimulus-dependent transient control (*12*). Therefore, it seems unlikely that the ACC activity observed in the current study reflects a transient form of top-down control, although if it does, the mechanism of this control must be quite different from attentional activity associated with the DLPFC.

One parsimonious interpretation of these results is that control and evaluative processes are linked in a negative feedback loop as part of a network to maintain optimal performance. The controversial role of the ACC in control highlights the problem of parsing the components of such a network; if evaluative components signal when more control is required, activity in regions serving these two functions will be correlated. In the past, the limited temporal resolution of functional neuroimaging relative to the underlying neural events made it difficult to discern whether increases in ACC activity were coincident with or produced increases in DLPFC activity. In a previous study that took advantage of the faster time scale of the event-related potential, increased error-related negativity magnitude (thought to index ACC activity) was followed by reduced error commission and an increased latency for the next correct response (*19*), suggesting that control is increased in response to the ACC signal. In recent modeling work (*15*), it was demonstrated that a simple feedback loop, incorporating a conflict-monitoring mechanism that regulates the strength of task-demand representations, can account for a variety of strategic adjustments in control that have been observed in simple response choice and selective attentional tasks, including the Stroop [e.g., (*20*)].

Taken together, these data suggest that cognitive control is a dynamic process implemented in the brain by a distributed network that involves closely interacting, but nevertheless anatomically dissociable, components. Within this system, the DLPFC provides top-down support of task-appropriate behaviors, whereas other components, such as the ACC, are likely to be involved in evaluative processes indicating when control needs to be more strongly engaged. We look forward to future studies that further detail these complementary functions and the role that the DLPFC and ACC play in the regulation of cognition and behavior.

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11. Informed consent was obtained from right-handed participants recruited from the community (seven males and five females, with an age range of 18 to 30 years). Ninety-six trials were obtained for each subject (see Fig. 1 for paradigm). Each trial began with a 1500-ms instruction: "word," indicating that the stimulus should be read aloud, or "color," indicating that the color of the stimulus should be named (50% of trials for each instruction). After an 11-s delay, a colored word stimulus was presented for 1500 ms, to which subjects verbally responded. Half of the trials were congruent (the word was printed in the same color), and half were incongruent (the word was printed in a different color). Four colors were used: green, blue, red, and purple. There were 24 trials in each combination of instruction and congruency, equally represented and randomized within each block. Verbal responses were recorded and subsequently coded for accuracy and reaction time. For equipment-related reasons, one subject could not be scored for reaction time. There were <3% errors in all conditions, and there was no overall difference in accuracy between color-naming and word-reading trials [$F(1, 11) = 0.10$, not significant]. Trimmed reaction time (150 ms < RT < 1500 ms) was examined for correct trials only for 11 subjects. Mean RT was 821 ms (SD = 100) in the congruent and 937 ms (SD = 91) in the incongruent color-naming condition, leading to an overall Stroop effect of 116 ms [the RT difference between incongruent and congruent color naming was $F(1, 10) = 8.18$, $P < 0.01$]. In the word-reading condition, the mean RT was 810 ms (SD = 121) in the congruent and 904 ms (SD = 140) in the incongruent word-reading condition.
12. A 1.5-T scanner (General Electric Company) with a standard head coil acquired all images. Three functional longitudinal relaxation time (T1)–weighted scouts (in the axial, coronal, and sagittal planes) were used to localize common anatomical landmarks for all subjects (the anterior commissure and the posterior commissure). Transverse relaxation time (T2*)–weighted two-shot spiral scans (3.75-mm^3 voxels, repetition time = 1.25 s, echo time = 35 ms, flip angle = 60°) allowed full image acquisition every 2.5 s (10 images every 25-s trial, as illustrated in Fig. 1) [D. Noll, J. D. Cohen, C. H. Meyer, W. Schneider, *J. Magn. Reson. Imaging* **5**, 49 (1995)]. Incremental (scan to scan) and total movement were corrected using automated image registration (AIR) [R. P. Woods, S. T. Grafton, C. J. Holmes, S. R. Cherry, J. C. Mazziotta, *J. Comput. Assisted Tomogr.* **22**, 139 (1998)]. Structural images were cross-registered to a reference brain by minimizing signal intensity differences with 12-parameter AIR, after which images were set to a standard mean intensity, smoothed (8-mm full width at half maximum kernel), and pooled across subjects to improve the signal-to-noise ratio. Spatial F maps were generated using analysis of variance (two instructions by five scans for instruction-related activity and two congruencies by four scans for response-related activity) with subject as a random factor. Scan 6 was not included because of potential noise associated with verbal responding. Within specified anatomical areas (BA 9 and 46 and BA 24 and32), regions were identified by thresholding spatial F maps with the requirement of eight adjacent pixels, $P < 0.005$, to control for type 1 error. Individuals' activations were based on an aver-

aged change from the baseline of all pixels in the regions identified in the group analysis. These data were pooled for planned contrasts and evaluated for correlations with behavioral data.

13. Other regions with a similar response pattern (incongruent > congruent) include two in the right precentral (BA 6; Talairach coordinates $x = 51, y = -3, z = 43$; 10 voxels and $x = 59, y = -10, z = 13$; 11 voxels), the medial extrastriate (BA 31; $x = 2, y = -65, z = 16$; 8 voxels), and the thalamus ($x = -2, y = -16, z = 14$; 21 voxels).
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