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Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

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Various chronic antidepressant treatments increase adult hippocampal neurogenesis, but the functional importance of this phenomenon remains unclear. Here, using genetic and radiological methods, we show that disrupting antidepressant-induced neurogenesis blocks behavioral responses to antidepressants. Serotonin 1A receptor null mice were insensitive to the neurogenic and behavioral effects of fluoxetine, a serotonin selective reuptake inhibitor. X-irradiation of a restricted region of mouse brain containing the hippocampus prevented the neurogenic and behavioral effects of two classes of antidepressants. These findings suggest that the behavioral effects of chronic antidepressants may be mediated by the stimulation of neurogenesis in the hippocampus.

Depression and anxiety disorders are common public health problems, with 10 to 20% lifetime prevalence (*1*), yet the mechanisms underlying their pathophysiology are still poorly understood. Most antidepressant drugs (ADs) increase levels of the monoamines serotonin [5-hydroxytryptamine (5-HT)] and/or noradrenaline (NA); this suggests that biochemical imbalances within the 5-HT/NA systems may underlie the pathogenesis of these disorders—a theory also known as the monoaminergic hypothesis of depression. But although ADs produce a rapid increase in extracellular levels of 5-HT and NA, the onset of an appreciable clinical effect usually takes at least 3 to 4 weeks (*1*). This delay suggests that slow neurochemical and structural changes take place within the limbic target areas of monoaminergic projections.

Such changes may counteract neuropathological alterations that initiate or perpetuate anxiety and depressive disorders. Indeed, recent post mortem and brain imaging studies have revealed atrophy or loss of neurons in the prefrontal cortex and hippocampus of both depressed and anxious patients (*2–4*), and some of these alterations may be reversed by ADs (*5*). In addition, stress—an environmental factor capable of precipitating depressive episodes in humans—causes cell death, dendritic shrinkage, and decreased levels of neurotrophins within the hippocampus (*6–8*), as well as a reduction in hippocampal granule cell neurogenesis (*9*). Although it is unclear whether these events contribute to the pathogenesis of depression, the recent observation that adult hippocampal neurogenesis is decreased by stress and increased by chronic antidepressants (*9, 10*) suggests that this process may be involved in both the pathogenesis and treatment of mood disorders.

Adult neurogenesis—the production of new neurons within the brain of an adult organism—is primarily confined to two discrete areas: the subventricular zone (SVZ), and the subgranular zone (SGZ) of the dentate gyrus (*11*). In the hippocampus of both rodents and primates, adult-generated neuronal cells arise from progenitor cells in the SGZ and migrate into the granule cell layer, where they differentiate into granular neurons (*12*). Recently, these cells were shown to be capable of functional integration into the hippocampal circuitry, as evidenced by their responsiveness to stimulation of the perforant path and their ability to extend axonal projections to appropriate target areas (*13*). Although the function of newly generated cells in the adult hippocampus is still unclear, it has been suggested that young granule cells constitute a distinct population exhibiting a greater degree of plasticity than mature neurons (*12*). In the present study, we asked whether an increase in neurogenesis is required for antidepressant action.

Few behavioral paradigms have been able to reliably demonstrate changes in mouse behavior after chronic, but not acute, treatment with ADs (*14*). We adapted the novelty-suppressed feeding (NSF) test, previously used to assess chronic antidepressant efficacy in rats (*15*), to the 129/Sv mouse strain (*16*). We treated adult mice orally with fluoxetine, imipramine, desipramine, haloperidol, or vehicle for either 5 or 28 days before assessing latency to feed in the NSF test (*17*). Mice treated with either fluoxetine or imipramine for 5 days showed no effect on latency to feed relative to vehicle-treated mice, whereas all three antidepressants (but not haloperidol) produced significant decreases in latency to feed in mice treated for 28 days (Fig. 1A). The slow appearance of these changes resembles the delay in the onset of AD efficacy in humans.

Because ADs are known to have various effects on appetite, the feeding drive of each mouse was assessed by returning it to the familiar environment of the home cage immediately after the test and measuring the amount of food consumed over a period of 5 min. None of the drugs tested produced a significant change in food consumption after either subchronic or chronic treatment (Fig. 1B).

Effects of fluoxetine. Various antidepressant treatments, including fluoxetine, increase neurogenesis in the dentate gyrus of the rat hippocampus, as evidenced by an in-

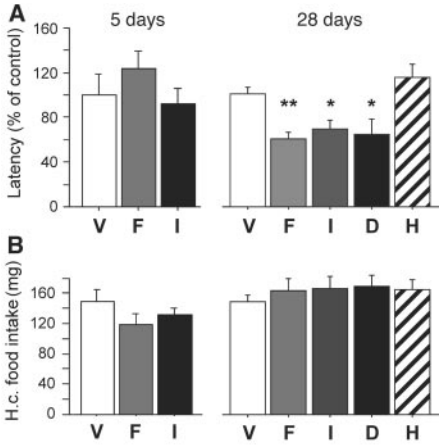

Fig. 1. The NSF paradigm. (**A**) Treatment with antidepressants, but not haloperidol, for 28 days resulted in a decreased latency to feed, whereas treatment for 5 days was ineffective (mean percentage of vehicle control latency ± SEM), as shown by unpaired *t* tests between vehicle (V) and fluoxetine (F), imipramine (I), desipramine (D), or haloperidol (H) (*$P < 0.05$, **$P < 0.01$; $n = 13$ to 15 mice per group). (**B**) None of the drugs tested produced a significant change in home cage (h.c.) food consumption (mean ± SEM).

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creased number of progenitor cells that incorporate the DNA synthesis marker 5-bromo-2′-deoxyuridine (BrdU) and differentiate into mature neurons (*10*). We thus treated adult mice with either vehicle or fluoxetine for 5, 11, or 28 days; all mice were injected with BrdU (4 × 75 mg/kg) on the final day of treatment and were killed 24 hours later. Fluoxetine caused a 60% increase in the number of BrdU-positive cells in the dentate gyrus of mice treated for 11 or 28 days, but it had no effect after 5 days (Fig. 2, A and B).

Several studies have shown that cells born in the SGZ of the adult rodent hippocampus express markers of adult neurons as they differentiate and mature (*12*). Mice were killed 4 weeks after injection of BrdU, and brain sections were colabeled with antibodies to BrdU and a neuronal marker [neuron-specific nuclear protein (NeuN)] or an astroglial marker [glial fibrillary acidic protein (GFAP)] (Fig. 2, C and D) to reveal the fate of BrdU-labeled cells after chronic treatment with either fluoxetine or vehicle. Analysis of the BrdU-positive cells showed that 70 ± 2% expressed NeuN, whereas only 15 ± 3% expressed GFAP. As previously reported, these proportions were not influenced by AD treatment (*10*).

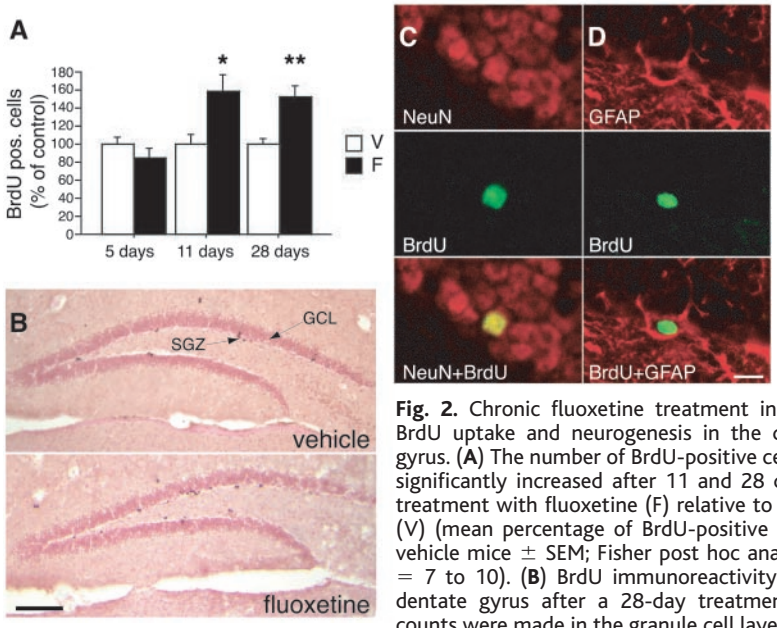

Fig. 2. Chronic fluoxetine treatment increases BrdU uptake and neurogenesis in the dentate gyrus. (**A**) The number of BrdU-positive cells was significantly increased after 11 and 28 days of treatment with fluoxetine (F) relative to vehicle (V) (mean percentage of BrdU-positive cells in vehicle mice ± SEM; Fisher post hoc analysis; n = 7 to 10). (**B**) BrdU immunoreactivity in the dentate gyrus after a 28-day treatment. Cell counts were made in the granule cell layer (GCL) and in the SGZ. Scale bar, 200 μm. (**C** and **D**) Confocal micrographs of cells double-labeled for BrdU (green) and NeuN or GFAP (red). Scale bar, 10 μm.

Among the 14 known 5-HT receptor subtypes, the 5-HT_{1A} receptor has been prominently implicated in the modulation of mood and anxiety-related behaviors (*18, 19*). We compared the effects of serotonin- and norepinephrine-enhancing ADs in wild-type (WT) mice and in mice lacking this receptor [5-HT_{1A} receptor knockout (KO) mice]. WT and KO mice were treated with fluoxetine, imipramine, desipramine, or vehicle for a period of 28 days before being tested in the NSF paradigm. KO mice displayed a higher latency than their littermate controls to begin feeding (Fig. 3A), in agreement with their increased levels of anxiety-like behaviors (*19*). In addition, KO mice were insensitive to the effects of chronic fluoxetine but were still responsive to both imipramine and desipramine (Fig. 3A).

To determine whether activation of 5-HT_{1A} receptors is sufficient to alter NSF behavior, we administered a 5-HT_{1A}–selective agonist (8-OH-DPAT) for 28 days before performing the test. 8-OH-DPAT significantly decreased latency to feed in WT mice but was ineffective in KO mice (Fig. 3B), indicating that its effects were mediated by 5-HT_{1A} receptors.

WT and KO mice were injected with BrdU after a 27-day treatment with fluoxetine, imipramine, or vehicle. One group was killed 24 hours later to assess the effect of ADs on cell proliferation. Fluoxetine caused a doubling of BrdU-labeled cells in WT mice but had no effect in KO mice (Fig. 3C). Further paralleling the behavioral data (Fig. 3A), chronic treatment with imipramine induced a significant increase in BrdU-labeled cells in both WT and KO mice (Fig. 3C). A second group of mice was killed 28 days after BrdU injection to determine whether chronic AD treatment affects newborn cell survival. Similar to the pattern of responsiveness in the proliferation experiment, fluoxetine had an effect in WT but not KO mice, whereas imipramine was effective in both genotypes (fig. S1).

These results indicate that 5-HT_{1A} receptors are required for fluoxetine-induced but not imipramine-induced neurogenesis. To test whether activation of this receptor is sufficient to enhance cell proliferation, we treated WT and KO mice chronically with 8-OH-DPAT or vehicle before BrdU injection. In WT mice, 8-OH-DPAT caused an increase in cell proliferation similar to that seen after AD treatment (Fig. 3D). This effect was not observed in KO mice, indicating that the action of 8-OH-DPAT was specific to 5-HT_{1A} receptors.

Effects of hippocampal irradiation. To test whether hippocampal neurogenesis participates in the mechanism of action of ADs, we sought to disrupt this process. Long-term

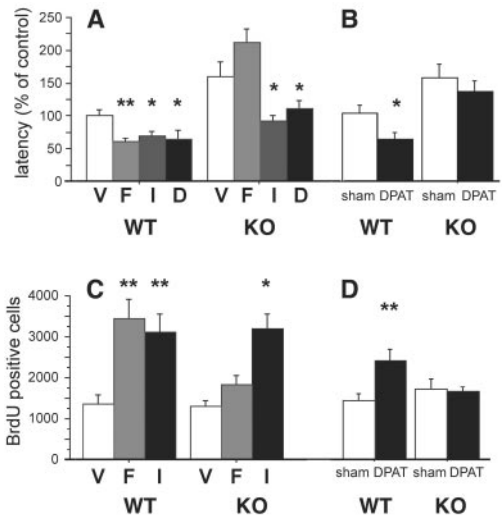

Fig. 3. Requirement of 5-HT_{1A} receptors for fluoxetine's effects on anxiety-related behaviors and hippocampal neurogenesis. (**A** and **B**) Novelty-suppressed feeding. (A) Fluoxetine, imipramine, and desipramine (F, I, and D) decreased latency to feed, relative to vehicle (V), in WT mice. Only imipramine and desipramine were effective in KO mice. Analysis of variance (ANOVA) revealed significant effects of AD treatment ($F_{3,77}$ = 5.8, P = 0.0012), genotype ($F_{1,77}$ = 33.3, P < 0.0001), and an interaction between the two [$F_{3,77}$ = 6.2, P = 0.0008 (n = 10 to 15)]. Differences between vehicle and treatment were calculated by Fisher post hoc test. (B) A 28-day 8-OH-DPAT (DPAT) regimen decreased latency to feed in WT but not KO mice (planned Fisher post hoc test, n = 11 to 20). (**C** and **D**) BrdU uptake 24 hours after injection. (C) After a 4-week treatment with ADs or vehicle, imipramine increased the number of BrdU-positive cells in both genotypes, but fluoxetine was effective only in WT mice. ANOVA found significant effects of AD treatment ($F_{2,30}$ = 9.4, P = 0.0006) and interaction between treatment and genotype ($F_{2,30}$ = 3.2, P = 0.05). Differences between vehicle and either fluoxetine or imipramine were assessed by Fisher post hoc test (n = 6 or 7). (D) WT but not KO mice showed DPAT-induced increases in BrdU-labeled cells. ANOVA revealed an effect of DPAT treatment ($F_{1,28}$ = 4.3, P = 0.046) and an interaction between treatment and genotype ($F_{1,28}$ = 5.8, P = 0.02). Differences between sham and DPAT-treated mice were assessed by Fisher post hoc analysis (n = 7 to 9). Values are means ± SEM (*P < 0.05, **P < 0.01).

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reductions in cell proliferation within the dentate gyrus have previously been reported after low-dose x-irradiation of the heads of rats (*20*). To determine whether focal irradiation can produce similar effects in mice, we delivered fractionated, low doses of x-rays to the hippocampus while sparing the body and most of the brain (Fig. 4, A and B) (*21*). Irradiation resulted in ~85% reduction in BrdU-positive cells in the SGZ. This effect persisted at the time of behavioral testing (Fig. 4C) and lasted for at least 8 weeks after delivery of the final x-ray dose.

The number of BrdU-positive cells in the SVZ was unaltered by irradiation (Fig. 4C), indicating that exposure to x-rays was confined to the hippocampus and the overlying and underlying structures. As shown earlier (*10*), chronic treatment with fluoxetine had no effect in the SVZ (Fig. 4C).

Previous studies in the rodent have shown that whole-brain irradiation results in a selective ablation of precursor cells by inducing apoptosis (*22*). We thus subjected a group of mice to one 15-Gy dose of x-rays (the same cumulative dose given in the behavioral experiments) and killed them 10 hours later for TUNEL (terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labeling) analysis. Although few TUNEL-positive nuclei were found in controls, irradiation caused a marked increase in the number of apoptotic nuclei, predominantly confined to the SGZ (Fig. 4, D and E).

We subjected adult mice to x-rays as described above, and concurrently began treatment with fluoxetine, imipramine, or vehicle, before assessing their performance in the NSF test (Figs. 4B and 5A). AD treatment caused a significant reduction in latency to feed in sham mice, but this effect was absent in irradiated mice. Irradiation did not affect latency to feed in vehicle-treated mice (Fig. 5A), and no change in home cage food consumption resulted from either drug or x-ray treatment (*23*). Therefore, the lack of effect of ADs in the irradiated mice cannot be explained by an alteration in the feeding drive of these mice, or by a change in their baseline behavior in the NSF test.

To determine whether the effect of irradiation on antidepressant response specifically involved the brain region containing the hippocampus, rather than being due to a nonspecific response of the brain to radiological injury, we designed a sliding lead shield that allows the irradiation of different brain areas. We irradiated another neurogenic region just rostral to the hippocampus (containing the SVZ), as well as the nonneurogenic cerebellar region (CRB) caudal to the hippocampus [see (*21*)]. Mice were treated as shown in Fig. 4B. There was a significant main effect of drug treatment on latency across all groups (Fig. 5B) and no effect of x-ray, indicating that neither SVZ nor CRB irradiation attenuates the response to ADs. Again, no change in food intake as a result of irradiation or drug treatment was detected in the food consumption test.

We assessed whether hippocampal irradiation also blocks the effects of fluoxetine in a second behavioral test, the chronic unpredict-

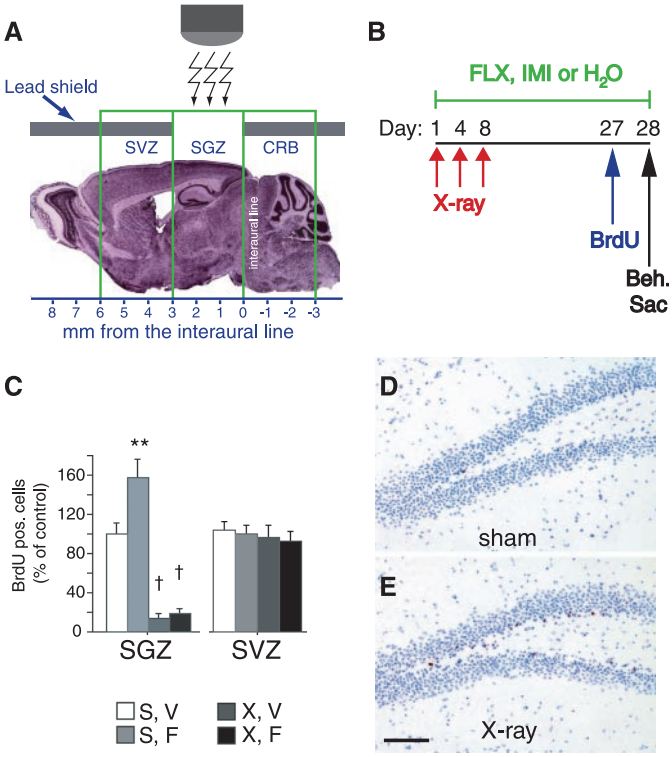

Fig. 4. X-ray treatment: ablation of cell proliferation in the SGZ. (**A**) A sliding shield protected the mouse's body while exposing the SGZ, the SVZ, or the cerebellum (CRB) to x-rays. (**B**) Experimental design: 5 Gy were delivered on days 1, 4, and 8, and mice were concurrently treated with fluoxetine, imipramine, or vehicle before the NSF test on day 28. BrdU was injected on day 27 to assess cell proliferation. (**C**) Irradiation drastically reduced cell proliferation in the SGZ but had no effect in the SVZ (S, sham; X, x-ray; V, vehicle; F, fluoxetine). Differences between sham/vehicle and other groups were assessed by Fisher post hoc analysis (n = 7 to 9; $^{**}P < 0.01$, $\dagger P <$ 0.001). (**D** and **E**) X-ray causes apoptosis selectively in the SGZ. Ten hours after x-ray, a large increase in the number of apoptotic nuclei was observed in the SGZ. Scale bar, 100 μm.

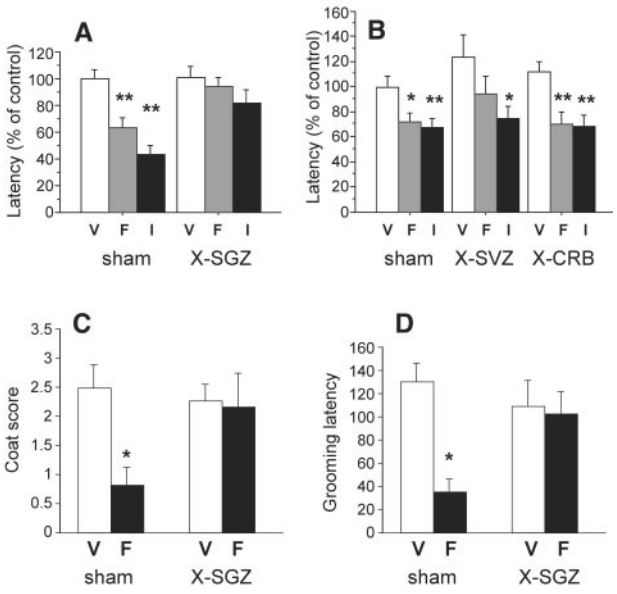

Fig. 5. X-ray of hippocampus suppresses behavioral responses to antidepressants. (**A** and **B**) Novelty-suppressed feeding. (A) A 28-day regimen of fluoxetine (F) or imipramine (I) reduced latency in sham but not hippocampal-irradiated mice (X-SGZ), as indicated by significant effects of AD treatment ($F_{2,176}$ = 9.3, P = 0.0001), irradiation ($F_{1,176}$ = 9.4, P = 0.0025), and an interaction between the two [$F_{2,176}$ = 3.9, P = 0.02 (ANOVA, n = 25 to 35)]. Differences between vehicle (V) and fluoxetine or imipramine were found by Fisher post hoc test. (B) Irradiation of brain regions rostral (X-SVZ) or caudal (X-CRB) to the hippocampus did not prevent the effects of AD treatment, as shown by a significant main effect of AD treatment [$F_{2,122}$ = 12.2, $P < 0.0001$ (ANOVA, n = 13 to 15)]; differences between vehicle and fluoxetine or imipramine were assessed by Fisher planned comparison. (**C** and **D**) Effects of CUS procedure. (C) Fluoxetine improved the state of the coat in sham but not X-SGZ mice, as shown by a significant interaction between x-ray and fluoxetine treatment [$F_{1,24}$ = 4.6, P = 0.044 (ANOVA)]. Significant differences between the fluoxetine-treated sham group and all the others were assessed by Fisher post hoc test (n = 6 to 8). (D) In the grooming test, fluoxetine decreased latency in sham but not irradiated mice. ANOVA revealed a significant main effect of fluoxetine ($F_{1,24}$ = 6.4, P = 0.02) and an interaction between fluoxetine and x-ray treatments [$F_{1,24}$ = 4.5, P = 0.043 (n = 6 to 8 mice per group)]. Fisher post hoc analyses showed significant differences between the fluoxetine-treated sham group and all the others. Values are means ± SEM ($^{*}P < 0.05$, $^{**}P < 0.01$).

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able stress (CUS) paradigm. This paradigm results in a deterioration of the state of the coat and an impaired grooming response that can be reversed by chronic, but not acute, AD treatment (*24*). Sham and irradiated mice were subjected to CUS, during which fluoxetine was administered to half of the mice in each group. At the end of the stress period, the state of each mouse's fur was assessed and assigned a score based on observations from several body regions (*21*). Fluoxetine treatment was continued for one more week, after which we measured latency to begin grooming after application of a sucrose solution to the snout. Fluoxetine significantly improved the state of the fur in sham mice, and this effect was absent in irradiated mice (Fig. 5C). Likewise, grooming latency was decreased by fluoxetine in sham mice but not in irradiated mice (Fig. 5D).

We next subjected an independent group of mice to hippocampal irradiation as described above. Four weeks later, no discernible changes in brain structure or integrity were found, as assessed by Nissl staining and stereological cell counts conducted within the superior and inferior blades of the dentate gyrus (fig. S2).

To determine whether irradiation alters the function of mature hippocampal neurons, we assessed synaptic transmission and plasticity in the CA1 region of hippocampal slices. The input-output relationships between the Schaffer collateral pathway and CA1 neurons, as well as theta burst–induced long-term potentiation (LTP), were not altered in irradiated mice (fig. S3).

The brain area targeted by irradiation includes not only the hippocampus, but also structures that are known to be involved in fear and anxiety responses, such as the hypothalamus and the amygdala. To assess the possibility that the behavioral effects observed after irradiation result from damage to these structures, rather than from a blockade of neurogenesis in the hippocampus, we conducted two control experiments. First, we showed that the neuroendocrine response to stress, as assessed by serum corticosterone before and after open-field stress, was unchanged in irradiated mice (fig. S3C). We next examined the effects of the irradiation procedure on amygdala function by means of a cued fear conditioning paradigm (*25*). Sham and irradiated mice showed no significant difference in percentage of time spent freezing either before or during the conditioned stimulus (fig. S3D).

Discussion. Our data indicate that, in mice, latency to feed in a novel environment is decreased specifically by chronic, but not acute, treatment with antidepressants that act through either serotonergic or noradrenergic mechanisms (Fig. 1A). A similar decrease in latency to feed was obtained by chronic activation of 5-HT_{1A} receptors with the direct agonist 8-OH-DPAT (Fig. 3B). This observation is consistent with the clinical use of the partial 5-HT_{1A} agonist buspirone for the treatment of generalized anxiety disorder and in combination with serotonin selective reuptake inhibitors (SSRIs) for the treatment of depression (*26*). Interestingly, 5-HT_{1A} receptor KO mice responded to the tricyclic antidepressants (TCAs) imipramine and desipramine, but not to the SSRI fluoxetine, in the NSF test; this finding suggests that activation of 5-HT_{1A} receptors is a critical component in the mechanism of action of SSRIs but not TCAs (Fig. 3A). These results indicate that serotonin- and norepinephrine-enhancing ADs act via independent molecular pathways. Indeed, there is both preclinical and clinical evidence supporting this interpretation (*27, 28*).

The fact that deletion of the 5-HT_{1A} receptor resulted in a blockade of both the behavioral and neurogenic effects of fluoxetine suggests that these two phenomena may be causally related. Further support for this hypothesis comes from the fact that disrupting hippocampal neurogenesis with x-irradiation blocked the effects of chronic AD treatment. It is unlikely that the lack of AD effect was due to nonspecific disruption of limbic circuits caused by irradiation, as evidenced by normal behavioral and neurochemical responses to fearful or stressful stimuli, as well as normal synaptic plasticity in the LTP paradigm (fig. S3).

Although our data show a strong correspondence between behavior and neurogenesis, we found two noteworthy instances of dissociation: (i) 5-HT_{1A} KO mice show higher levels of anxiety-related behaviors in the NSF test, as well as in a number of other conflict tests (Fig. 3A) (*29*), but have WT levels of basal neurogenesis; and (ii) a 28-day ablation of neurogenesis in vehicle-treated mice does not produce any behavioral deficit in either the NSF or CUS test (Fig. 5). Concerning the first point, we have previously shown that the anxious-like phenotype of the 5-HT_{1A} KO mice results from the lack of expression of this receptor during the early postnatal period (*19*); therefore, it is likely that the mechanisms underlying this phenotype are developmentally determined and independent of adult hippocampal neurogenesis. Regarding the second point, it is possible that a longer period of ablation is necessary to reveal behavioral deficits in the NSF and CUS paradigms and thereby uncover a potential role of basal hippocampal neurogenesis. Alternatively, the functional properties of neurons that are generated in response to antidepressants may be different from those of cells generated in baseline conditions. In either case, the lack of effect of irradiation on basal behavioral responses in the NSF and CUS suggests that our focal x-ray procedure does not elicit a nonspecific behavioral impairment. The specificity of the effects of hippocampal irradiation is also supported by the fact that the irradiation of other brain regions does not alter the behavioral response to ADs in the NSF test (Fig. 5B). These results strengthen our hypothesis that neurogenesis contributes to the effects of antidepressants, but we cannot exclude the possibility that other consequences of hippocampal irradiation contribute to the lack of effect of antidepressants.

The hippocampus has long been associated with learning and memory processes, but there is increasing evidence that this structure is also involved in the modulation of emotional responses (*30–33*). Lesions of the ventral hippocampus or local administration of pharmacological agents result in altered behavior in a number of rodent models of anxiety (*32, 34–38*). Recently, a double dissociation was found regarding the roles of the dorsal and ventral hippocampus in spatial learning versus hyponeophagia, an anxiety test that is similar to the NSF test used in the present study. Specifically, whereas dorsal hippocampal lesions had an effect on spatial learning but not on hyponeophagia, ventral lesions decreased hyponeophagia but had no effect on learning (*39*). Thus, a functional differentiation of the hippocampus may exist along its dorsoventral axis.

In further support of the hippocampus's involvement in mood regulation are recent reports that manipulations of transcription or neurotrophic factors in this structure can produce an antidepressant-like effect (*40*). Moreover, there is evidence in both the rodent and human literatures that chronic stress and depression result in hippocampal atrophy, and that these effects can be reversed by certain antidepressants (*5, 6, 41*). Our results suggest that strategies aimed at stimulating hippocampal neurogenesis could provide novel avenues for the treatment of anxiety and depressive disorders.

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16. The NSF is a conflict test that elicits competing motivations: the drive to eat and the fear of venturing into the center of a brightly lit arena. Latency to begin eating has been used as an index of anxiety-like behavior because classical anxiolytic drugs decrease it.

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17. Fluoxetine is an SSRI. Imipramine is a TCA that blocks the reuptake of both 5-HT and NA. Desipramine is a TCA that selectively blocks NA reuptake. Haloperidol is a neuroleptic devoid of antidepressant activity.
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Supporting Online Material

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REPORTS

An All-Optical Quantum Gate in a Semiconductor Quantum Dot

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We report coherent optical control of a biexciton (two electron-hole pairs), confined in a single quantum dot, that shows coherent oscillations similar to the excited-state Rabi flopping in an isolated atom. The pulse control of the biexciton dynamics, combined with previously demonstrated control of the single-exciton Rabi rotation, serves as the physical basis for a two-bit conditional quantum logic gate. The truth table of the gate shows the features of an all-optical quantum gate with interacting yet distinguishable excitons as qubits. Evaluation of the fidelity yields a value of 0.7 for the gate operation. Such experimental capability is essential to a scheme for scalable quantum computation by means of the optical control of spin qubits in dots.

The rapid evolution of quantum dot (QD) studies has opened up the possibility of building devices that reveal both classical and quantum features. In particular, biexciton transitions in QDs have been proposed as the physical realization of universal quantum logic gates (*1*–*3*). In a single QD, quantum confinement greatly enhances the higher order Coulomb interaction, leading to the formation of a bound state of two orthogonally polarized excitons. The excitation of one exciton affects the resonant energy of the other, which corresponds to the characteristic conditional quantum dynamics that are needed for quantum computing.

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Fig. 1, A and B, shows the mapping from the single-particle picture of the two exciton transitions in a single QD to the excitation-level diagram. This simplest two-bit system involves the crystal ground state ($|00\rangle$), two distinguishable excitonic states with orthogonal polarizations ($|01\rangle$ and $|10\rangle$), and the biexciton state ($|11\rangle$), where the value 0 (or 1) represents the absence (or presence) of an exciton. In a controlled rotation (CROT) gate, the target bit (the second bit) is rotated through π (i.e., from state 0 to 1 or vice versa) if and only if the control bit (the first bit) is 1. The unitary transformation matrix of the CROT shown in Fig. 1C operates on the input wave function defined in the computational basis and yields the output wave function. The CROT gate is equivalent to the standard controlled-NOT (CNOT) gate, despite the slight difference in the minus-sign placement in their matrix representations (*4*). Unitary rotations like the CROT are much easier to realize than the CNOT operations (*4*, *5*).

We demonstrated Rabi oscillations between the exciton and biexciton states that are similar to the excited-state Rabi oscillations observed in atomic systems. This work builds on earlier demonstrations of the ground-state-to-exciton Rabi oscillations in QDs (*6*–*9*). The result is important in that the π pulse in this experiment plays a critical role in quantum information processing. It transforms a factorizable state into an entangled state: $|00\rangle + |10\rangle \rightarrow |00\rangle + |11\rangle$. It can also be used as the operational pulse for the CROT. When we combine this result with the exciton Rabi oscillations, the truth table of a CROT gate can be mapped out in this two-bit system. The performance of the gate is

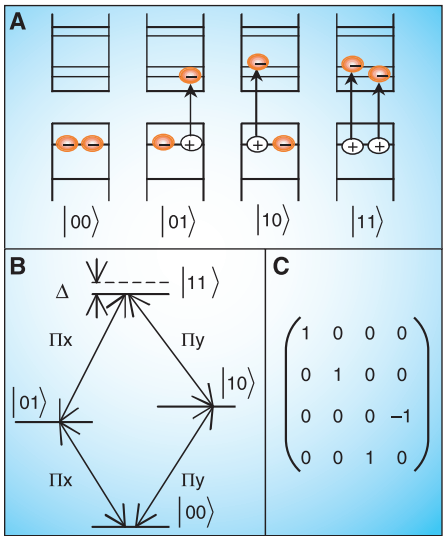

Fig. 1. (**A**) Two exciton transitions in a single QD. (**B**) Excitation-level diagram, where $|00\rangle$, $|01\rangle$ and $|10\rangle$, and $|11\rangle$ denote the ground state, the excitons, and the biexciton, respectively. The optical selection rules for various transitions are labeled. Π_x and Π_y indicate orthogonally and linearly polarized lights. Δ represents the binding energy. (**C**) The transformation matrix for a CROT gate.

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