Neurotransmitter Switching in the Adult Brain Regulates Behavior

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Neurotransmitters have been thought to be fixed throughout life, but whether sensory stimuli alter behaviorally relevant transmitter expression in the mature brain is unknown. We found that populations of interneurons in the adult rat hypothalamus switched between dopamine and somatostatin expression in response to exposure to short- and long-day photoperiods. Changes in postsynaptic dopamine receptor expression matched changes in presynaptic dopamine, whereas somatostatin receptor expression remained constant. Pharmacological blockade or ablation of these dopaminergic neurons led to anxious and depressed behavior, phenocopying performance after exposure to the long-day photoperiod. Induction of newly dopaminergic neurons through exposure to the short-day photoperiod rescued the behavioral consequences of lesions. Natural stimulation of other sensory modalities may cause changes in transmitter expression that regulate different behaviors.

Signal transmission in neuronal circuits uses specific neurotransmitters that bind to cognate receptors on other neurons. Genetic programs establish initial expression patterns of neurotransmitters in different classes of neurons (*1*–*3*), and activity-dependent neurotransmitter respecification modifies them during development, either adding or switching transmitters (*4*–*9*). It is unknown, however, whether sensory stimuli promote transmitter switching in addition to other neuroplastic changes (*10*) in the adult brain. Alterations in photoperiod, circadian rhythm, and light exposure can each cause anxiogenic and depressive behavior in diurnal adult mammals (*11*, *12*). We hypothesized that nocturnal mammals would respond to light manipulation in the opposite manner (*13*) and that these changes in behavior would be mediated by transmitter switching. To test this hypothesis, we exposed adult rats to different photoperiods and determined whether transmitter specification and behavior were affected.

Photoperiod-Dependence of Dopamine Expression

The number of dopaminergic neurons in hypothalamic nuclei innervated by the retino-hypothalamic projection via the suprachiasmatic nucleus (SCN) (fig. S1) (*14*, *15*) changed with the light-dark (L-D) cycle to which animals were exposed. Animals were maintained in photoperiod chambers on long-day [19 hours light:5 hours dark (19L:5D)],

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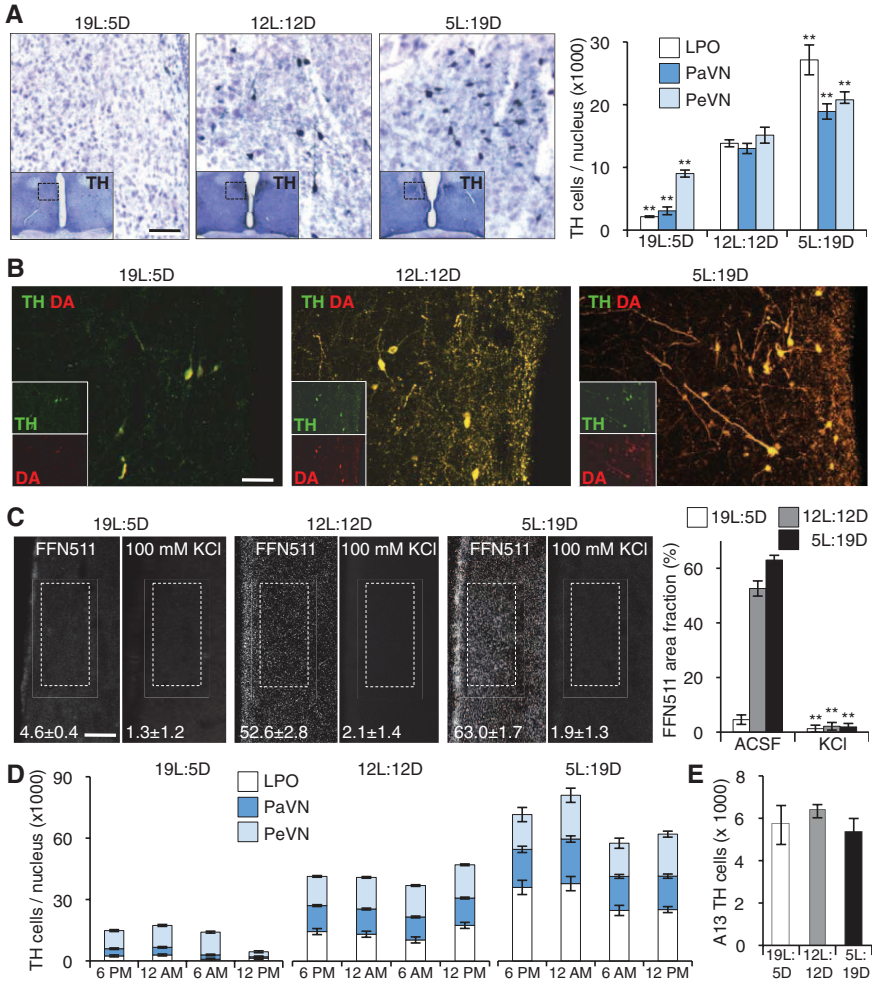

Fig. 1. Photoperiods regulate numbers of dopaminergic neurons in hypothalamic nuclei. (**A**) Exposure to 19L:5D or 5L:19D photoperiods for 1 week changes the number of tyrosine hydroxylase immunoreactive (TH) neurons in the PaVN relative to control (12L:12L) (left). Number of TH neurons in the LPO, PaVN and PeVN for each condition (right). $n = 12$ animals for each photoperiod. (**B**) Dopamine is colocalized with TH in the PaVN after exposure to each of the photoperiods. $n = 5$ animals for each photoperiod. (**C**) FFN511 is taken up in the PeVN and released by KCl after exposure to each of the photoperiods (left). Fluorescence measured in boxed regions (right). $n = 6$ animals for each photoperiod. (**D**) Circadian fluctuations do not account for changes produced by different photoperiods. Numbers of TH neurons for all three nuclei at all four times from 19L:5D and 5L:19D are significantly different from those from 12L:12D. $n = 5$ animals for each photoperiod. (**E**) The number of TH neurons in the nearby A13 nucleus is not significantly different after exposure to each of the photoperiods. $n = 5$ animals for each photoperiod. $^{**}P < 0.01$. Scale bars, (A) 120 μm; (B) 100 μm; (C) 80 μm.

short-day (5L:19D), or balanced-day (12L:12D; control) cycles for 1 week, and sections through the lateral preoptic area (LPO), paraventricular nucleus (PaVN), and periventricular nucleus (PeVN) were immunostained for tyrosine hydroxylase (TH), an enzyme in the dopamine synthetic pathway (*16*). The number of TH-immunoreactive (TH-IR) neurons decreased with long-day exposure and increased with short-day exposure in relation to control (Fig. 1A and fig. S2). TH and dopamine were colocalized in all three conditions (Fig. 1B). To assess the functional status of TH-IR neurons, we examined uptake and release of fluorescent false neurotransmitter 511 (FFN511) (*17*), which is taken up by vesicular monoamine transporter 2 (VMAT2). FFN511 generated fluorescent signals in hypothalamic slices from brains of animals exposed to each of the three photoperiods. Fluorescence decreased upon KCl depolarization (Fig. 1C).

Neurotransmitter respecification could be induced through changes in photoperiod or alteration of the circadian rhythm. To address the circadian contribution to changes in numbers of TH-IR neurons, we quantified their numbers at 6-hour intervals in animals exposed to each of the different photoperiods for 1 week (Fig. 1D). Although there is variation at some time points during each photoperiod (table S1), values for all three nuclei at all four times from 19L:5D and 5L:19D were significantly different from those from 12L:12D photoperiod exposure (table S2). The effects of different photoperiods are thus unlikely to have arisen from measurements collected at nonequivalent phases of the circadian rhythm. Week-long exposure to each of the different photoperiods failed to produce changes in numbers of TH-IR neurons in an adjacent nucleus, A13 (Fig. 1E and fig. S2B), which does not receive retinal input via the SCN (*18*).

Transmitter Switching Between Dopamine and Somatostatin

Neurons in the PaVN and PeVN also express somatostatin (SST) (*19*, *20*). The number of SST neurons showed an inverse relationship to the number of TH neurons with exposure to the three different photoperiods (Fig. 2A). This result could arise from changes in the numbers of neurons of each type or from transmitter switching within neurons. To determine whether these reciprocal changes result from adult neurogenesis (*21*, *22*), we injected animals with BrdU on days 2 to 4 of the week of exposure. No significant BrdU labeling was detected in the LPO, PaVN, or PeVN (fig. S3A). To ascertain whether apoptosis causes decreased numbers of TH-IR neurons and SST-IR neurons after exposure to long- and short-day photoperiods, respectively, we subjected sections from animals after 1 week of exposure to each of the photoperiods to terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labeling (TUNEL) assay. No significant differences in sporadic cell death were observed (fig. S3B). Photoperiod-dependent changes in the numbers of TH-IR neurons were reversible. When animals were exposed to 2 weeks of consecutive but opposite, short-, or long-day, photoperiods, TH expression did not differ from controls exposed to the 12L:12D photoperiod for 2 weeks (fig. S3C).

Are individual neurons reciprocally shifting transmitter expression between dopamine and SST? Double immunofluorescence revealed that different photoperiods changed the balance of dopamine and SST coexpression in neurons in the PaVN and PeVN. Long-day exposure reduced TH-IR and increased SST-IR, whereas short-day exposure increased TH-IR and decreased SST-IR (Fig. 2B). The 43% increase and 96% decrease in TH-IR/SST-IR coexpression after short- and long-day exposure, in contrast to the balanced photoperiod, suggest that TH-IR and SST-IR neurons are recruited from a reserve pool of cells (*23*) that are switching transmitters. Changes in TH and SST expression in cell bodies were also observed at high magnification in PaVN axons and en passant terminals in the periventricular region (Fig. 2C) and in PeVN cell bodies (fig. S4). The number of intracellular SST-IR storage vesicles depended on photoperiod light-cycle duration

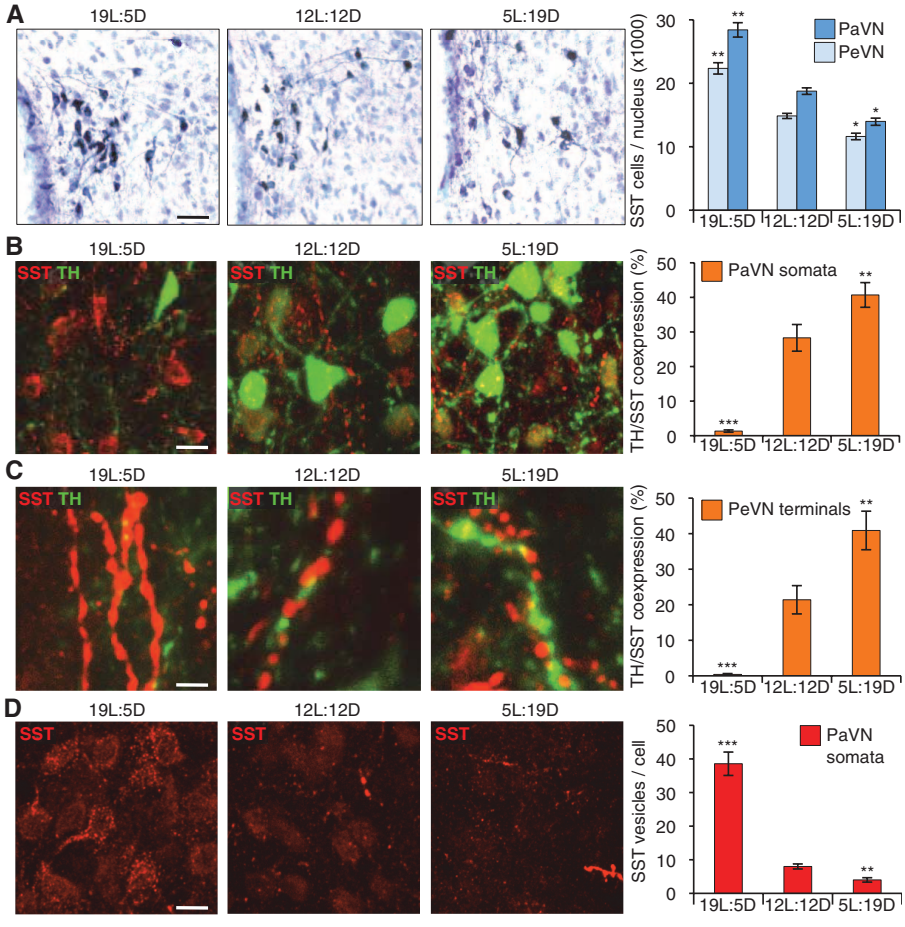

Fig. 2. Photoperiods drive neurotransmitter switching between dopamine and somatostatin. (**A**) Exposure to 19L:5D or 5L:19D photoperiods changes the number of SST-IR neurons in the PaVN relative to control (12L:12D) (left). Number of SST neurons in the PaVN and PeVN for each photoperiod (right). $n = 6$ animals for each photoperiod. (**B** and **C**) SST and TH immunofluorescence in the (B) PaVN and (C) PeVN change after exposure to each of the photoperiods (left). TH/SST coexpression (right). $n = 7$ animals for each photoperiod. (**D**) The number of SST vesicles/neuron cell body in the PaVN follows photoperiod light cycle duration (left). $n = 9$ cells for each photoperiod. Scale bars, (A) 100 μm; (B) 20 μm; (C) 3 μm; (D) 20 μm. $^{*}P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$.

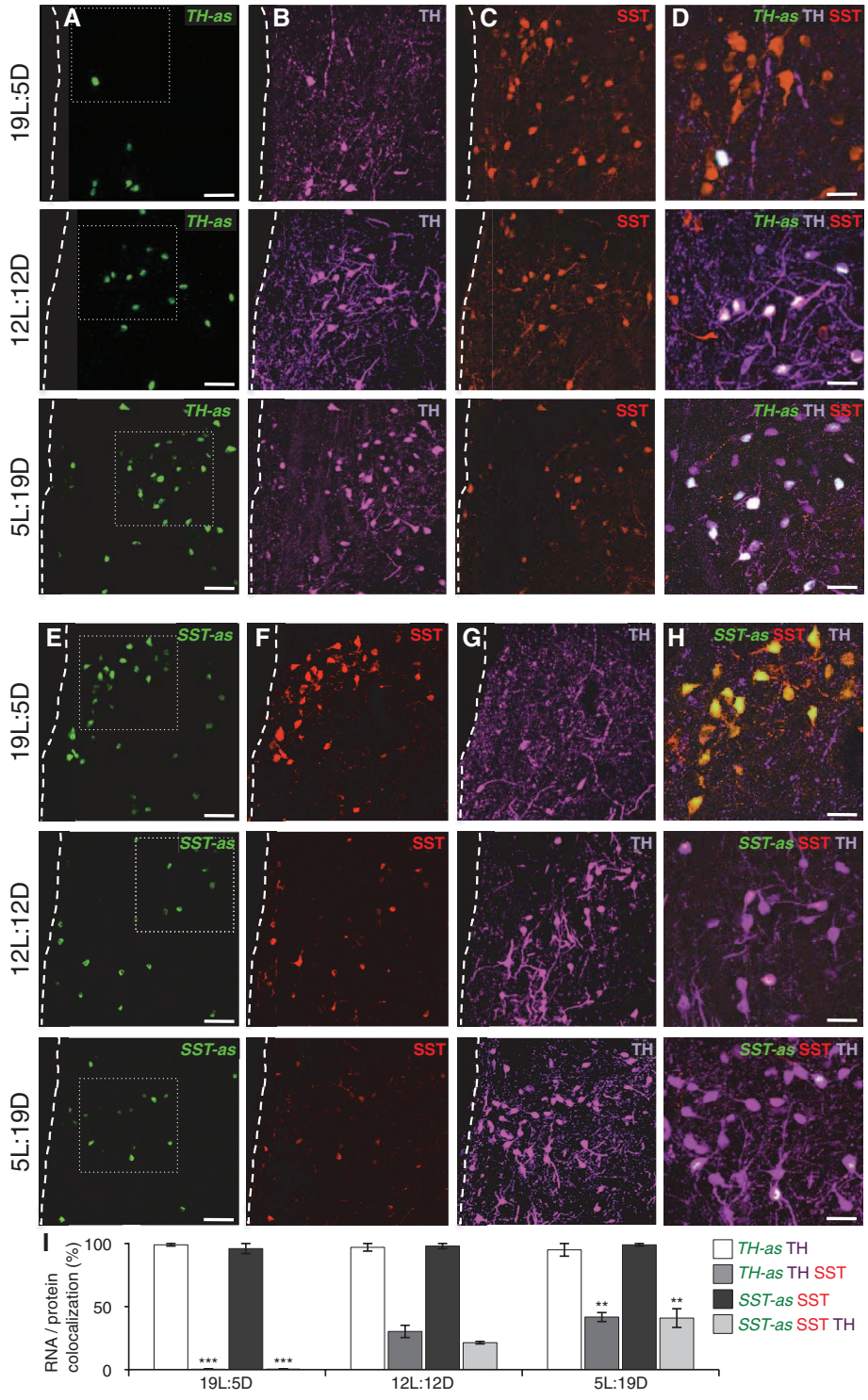

Fig. 3. Photoperiod-dependent changes in TH and SST parallel changes in TH and SST transcripts in the PaVN. Triple labeling of TH-antisense (*TH-as*) or *SST-as*, TH, and SST in single sections from animals exposed to each photoperiod. (**A** to **C**) Short-day photoperiods drive increases in numbers of *TH-as* and TH cells and a decrease in the number of SST cells. (**D**) Higher-magnification three-channel merged images of boxed regions at left. (**E** to **G**) Short-day photoperiods drive decreases in numbers of *SST-as* and SST cells and an increase in the number of TH cells. (**H**) Higher-magnification three-channel merged images of boxed regions at left. (**I**) More than 200 cells/PaVN were analyzed for each probe, and cells that were positive for one probe or the other were scored for colocalization with protein. Scale bars, (A) to (C) and (E) to (G) 100 μm; (D) and (H) 50 μm. n = 8 animals for (A) to (D) and (E) to (H); quantification (I) for all 16 animals.

(Fig. 2D). Decreased and increased numbers of TH-IR neuronal cell bodies resulting from exposure to long- and short-day photoperiods (Fig. 1A) were matched by corresponding increases and decreases in numbers of SST-IR neuronal cell bodies (Fig. 2A and fig. S5). Newly expressing TH-IR neurons induced through short-day photoperiod exposure coexpressed additional dopaminergic markers (*3*), VMAT2 (fig. S6), and the dopamine transporter, DAT (fig. S7).

To test the transcriptional dependence of transmitter respecification, we performed single-molecule fluorescence in situ hybridization with probes for TH and SST. Photoperiod-dependent changes in the number of labeled neurons identified regulation at the transcriptional level (Fig. 3, A to I), which is consistent with increased SST transcripts in PeVN neurons after exposure to stressors (*24*). Simultaneous immunostaining showed that changes in numbers of TH (Fig. 3, B and G) and SST (Fig. 3, C and F) neurons paralleled changes in mRNA expression (Fig. 3, D, H, and I). These results demonstrate that transmitter respecification is not achieved by translation from preexisting transcripts and involves de novo induction of TH or SST mRNA. Not all neurons underwent this transmitter switch; after exposure to the long-day photoperiod, 25% of the number of 12L:12D TH-IR PaVN neurons (Fig. 1A) expressed TH immunoreactivity without detectable SST immunoreactivity (Fig. 2B). SST was not expressed in the LPO after exposure to any of the three photoperiods, and a transmitter switch partner for dopaminergic neurons in this nucleus remains to be determined.

Changes in Postsynaptic Receptor Populations

Are presynaptic changes in transmitter identity matched by changes in postsynaptic receptor populations? SST interneurons of the parvocellular PaVN and the anterior PeVN make synapses on corticotropin-releasing factor (CRF) neurons distributed along the third ventricle, as do dopaminergic interneurons (*25*, *26*). To determine whether dopamine D2 receptor (D2R) and SSTR were coexpressed on periventricular CRF cells innervated by TH-IR neurons, we stained sections with antibodies for CRF, SST2/4R, and D2R (Fig. 4A) (*27*, *28*). After exposure to the control 12L:12D photoperiod, the two classes of receptors appeared colocalized on CRF cells along the ependymal layer in the PeVN, which is consistent with presynaptic transmitter coexpression (Figs. 2 and 3). After the long-day photoperiod, colocalization of D2R and SST2/4R was rare because D2R expression was down-regulated in parallel with the decrease in number of dopaminergic neurons. In contrast, after short-day photoperiod exposure, colocalization of these receptors was abundant as the number of dopaminergic neurons expanded (Fig. 4, A to C, and fig. S5).

We hypothesized that levels of CRF in the cerebrospinal fluid (CSF) would decrease as a result of increased inhibition resulting from exposure to the short-day photoperiod that leads to

coexpression of D2R with SST2/4R, if receptor activation is more substantial than the level of presynaptic SST. We envisaged that levels would increase with reduced D2R expression after the long-day photoperiod. Assays of CRF in the CSF and corticosterone in the plasma confirmed this to be the case (Fig. 4D). The number of CRF-immunoreactive neurons was also reduced after exposure to the short-day photoperiod (Fig. 4, A to C), reflecting low levels of CRF in the absence of apoptosis and consistent with reduced induction of CRF synthesis due to increased inhibition by both D2R and SST2/4R (*29*, *30*). SST2/4R but not D2R expression was observed on CRF neurons in the PaVN.

Photoperiod-Dependence of Behaviors

To investigate behavioral consequences of these changes in transmitter status, we tested rats on the elevated plus maze (EPM) (*31*) and in the forced swim test (FST) (*32*, *33*). Relative to controls, short-day exposure caused rats to spend more time exploring the open arm of the maze (movies S1 and S2) and spend a longer time swimming before becoming immobile (movies S3 and S4). Locomotor behavior and swimming ability appeared normal. Long-day exposure produced the opposite effects (Fig. 5A). The results of EPM testing during the middle of the light or dark phases after 24-hour-cycle photoperiods were not different. EPM testing at the conclusion of treatment with the same 19L:5D, 12D:12L, or 5L:19D ratios of total light/dark exposure distributed across much shorter (72 min) cycles yielded indistinguishable results (fig. S8).

To determine whether the behavioral changes observed are specifically related to changes in the number of TH-IR neurons, we made stereotaxic injections of 6-hydroxydopamine (6-OHDA) adjacent to the PaVN (fig. S9, A and B) so as to focally ablate TH-IR neurons in animals maintained on a 12L:12D cycle. Artificial CSF (ACSF) was injected as a sham control. After ablation, we observed a 95% reduction in time spent exploring the open arm of the EPM and a 57% increase in duration of the immobility time in the FST (Fig. 5B). Infusion of animals on a 12L:12D cycle with dopamine receptor antagonists SCH23390 and sulpiride, which selectively block D1 and D2 dopamine receptors (*34*), affected these behaviors similarly to 19L:5D exposure (Fig. 5C). Neither 6-OHDA nor receptor antagonists affected locomotor activity or swimming performance. Post-test histology of 6-OHDA–injected animals revealed that the number of TH-IR neurons was decreased by more than 50% in all three of these hypothalamic dopaminergic nuclei (Fig. 5D). The total number of cells in the PaVN was reduced (fig. S9C), indicating loss of neurons after 6-OHDA treatment. However, counts of TH-IR neurons in A13 after 6-OHDA treatment were not affected, demonstrating that dopaminergic nuclei located as close as 200 μm were spared by focal toxin delivery (Fig. 5D). Sham operation and injection of ACSF had no effect on the number of TH-IR neurons.

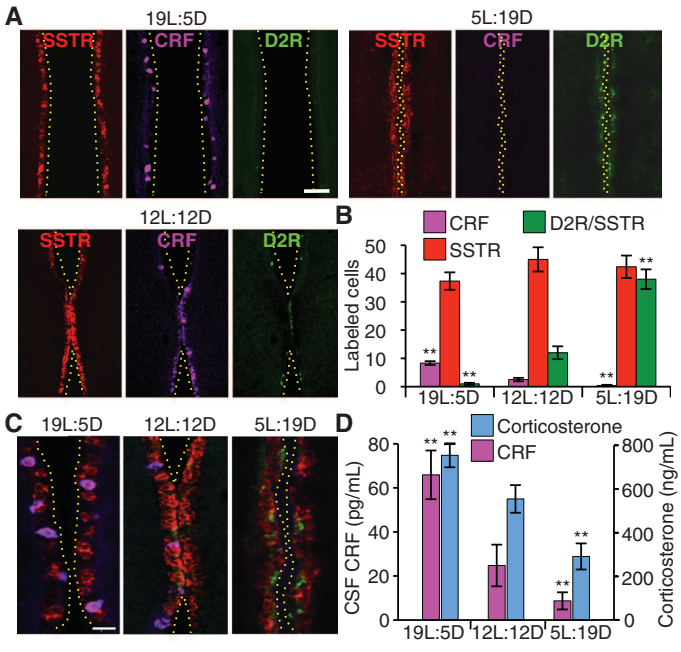

Fig. 4. Dopamine and somatostatin receptor colocalization on CRF neurons. (**A**) Triple labeling of SST2/4R, CRF, and D2R in single sections after exposure to each photoperiod. (**B** and **C**) D2R and SST2/4R colocalization on CRF cells. Labeled cells were scored along the walls of the third ventricle (dotted lines), and the number was averaged for 10 30-μm sections of the rostral hypothalamus. For (B), $n = 6$ animals. (**D**) CRF levels in the CSF and corticosterone levels in the plasma after exposure to each photoperiod. $n = 6$ animals. $^{**}P < 0.01$. Scale bars, (A) 120 μm; (C) 40 μm.

Role of Newly Dopaminergic Neurons in Stress Behaviors

We next determined whether photoperiod-dependent hypothalamic transmitter respecification reported here was likely to account for the observed changes in stress responses. We first ablated TH-IR neurons in these nuclei by means of local stereotaxic injection of 6-OHDA and then exposed animals to the long-day photoperiod, so as to further reduce their number, or to the short-day photoperiod, so as to recruit more neurons to become TH-IR (fig. S10). The behavioral results of focal ablation of TH-IR neurons were partially reversed by exposure to the short-day photoperiod, demonstrating behavioral rescue (Fig. 5E). Post-test histology demonstrated photoperiod-dependent reduction and induction of TH-IR neurons (Fig. 5F). The appearance of newly dopaminergic neurons is unlikely to have resulted from recruitment from a preexisting dopaminergic pool of neurons with undetectable levels of neurotransmitter because the inducible reserve pool was not ablated by 6-OHDA before exposure to the short-day photoperiod. FFN511 uptake and release in hypothalamic slices confirmed the functionality of newly dopaminergic neurons (fig. S11).

Because behavioral recovery could be achieved by a parallel mechanism not involving recruitment of newly TH-IR neurons in these nuclei, we determined whether it could be reversed by acute, local infusion of dopamine receptor antagonists. TH-IR neurons were again ablated with 6-OHDA, and animals were exposed to the short-day photoperiod for 1 week to recruit newly TH-IR neurons. ACSF or SCH23390 and sulpiride were stereotactically and acutely introduced through a cannula into the region in between the LPO and PaVN. Behavioral testing showed decreased time in the open arm of the EPM and increased immobility time in the FST in response to infusion with antagonists as compared with infusion with ACSF (Fig. 5E).

Discussion

Our results demonstrate transmitter switching between dopamine and somatostatin in neurons in the adult rat brain, induced by exposure to short- and long-day photoperiods that mimic seasonal changes at high latitudes. The shifts in SST/dopamine expression are regulated at the transcriptional level, are matched by parallel changes in postsynaptic D2R/SST2/4R expression, and have pronounced effects on behavior. SST-IR/TH-IR local interneurons synapse on CRF-releasing cells, providing a mechanism by which the brain of nocturnal rats generates a stress response to a long-day photoperiod, contributing to depression (*35*, *36*) and serving as functional integrators at the interface of sensory and neuroendocrine responses (*36*–*38*).

SST/dopamine interchange illustrates neuroplasticity in self-balancing networks (*39*) that tunes neural function and behavior to a dynamic environment. The molecular mechanism remains to be discovered, but AST-1 and Etv1 transcription factors bind to a specific dopamine motif in *Caenorhabditis elegans* and mouse to drive the expression of genes that encode components necessary for synthesis, packaging, and reuptake of dopamine (*3*, *40*). Activity-dependent transmitter switching may serve functions similar to homeostatic synaptic scaling (*41*), changes in ion channel expression (*42*), and neuropeptide remodeling of sensory networks (*43*) and is an additional form of brain plasticity to add to modifications of synaptic strength, synapse number, and electrical excitability. Sensory stimulation driving transmitter switching in specific microcircuits affected in neurological or psychiatric disorders could contribute to noninvasive restoration of normal function in the mature nervous system.

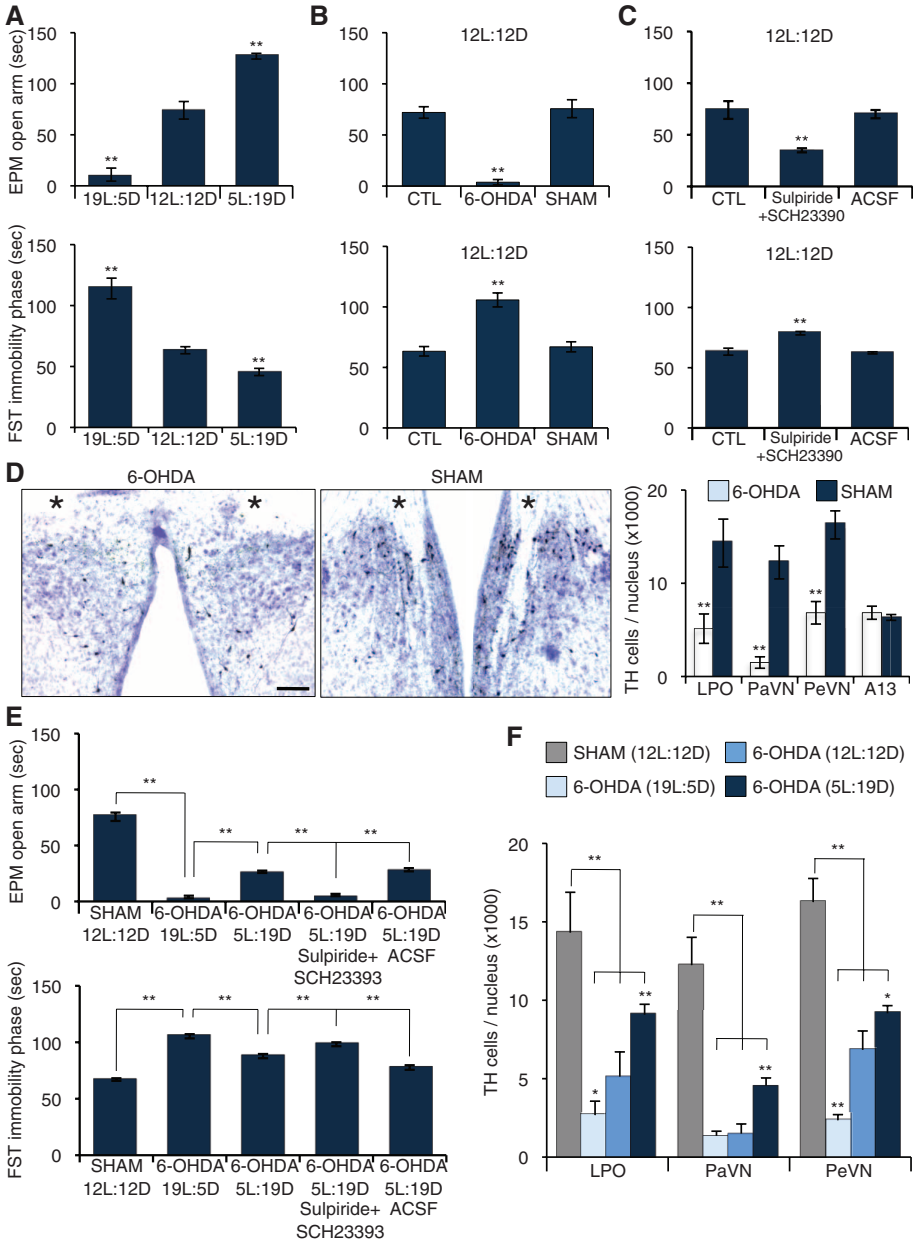

Fig. 5. Behavioral changes after lesions of dopaminergic neurons are rescued through photoperiod induction of newly dopaminergic neurons. (**A**) Baseline behavior on EPM and FST after exposure to 19L:5D, 12L:12D, or 5L:19D photoperiods for 1 week. (**B**) Effect of 6-OHDA ablation of DA neurons versus sham operation on behavior of animals exposed to 12L:12D for 1 week. (**C**) Behavior of 12L:12D animals without and with acute infusion of D1 and D2 receptor antagonists, SCH23390 and sulpiride. (**D**) Histology of tissue and stereology of TH-IR neurons after 6-OHDA, accompanying behavioral tests. Asterisks indicate injection sites. Scale bar, 150 μm. For (A) and (C), $n = 5$ animals; for (B) and (D) $n = 10$ animals. $^{**}P < 0.01$ compared with 12L:12D control [(A) to (C)] and to sham (D). (**E**) Effect on behavior of 19L:5D or 5L:19D exposure for 1 week after 6-OHDA ablation of DA neurons in animals exposed to 12L:12D. The rescue achieved with 5L:19D exposure is selectively abolished by infusion of D1 and D2 receptor antagonists, SCH23390 and sulpiride. (**F**) Number of TH neurons after 6-OHDA ablation of LPO, PaVN, and PeVN in animals exposed to 12L:12D followed by 19L:5D, 12L:12D, or 5L:19D for 1 week. For (E) and (F), $n = 5$ and 4 animals, respectively. $^{*}P < 0.05$. $^{**}P < 0.01$ for (E) comparisons between adjacent groups and (F) comparisons with 6-OHDA [sham (12L:12D)].

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27. Dopamine D2R and somatostatin SST1-5R are homologous and can assemble as heteromers (*28*), and SST-IR and TH-IR terminals colocalize with SST1-5R in the PeVN of the rat hypothalamus (*26*). Such arrangements could facilitate continuity of circuit function during transmitter switching.
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Supplementary Materials

www.sciencemag.org/cgi/content/full/340/6131/449/DC1
Materials and Methods
Figs. S1 to S11
Tables S1 and S2
Movies S1 to S4

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NEUROSCIENCE

Plasticity in the Neurotransmitter Repertoire

A switch in the type of neurotransmitter released in the brain underlies changes in mammalian behavior associated with day-night cycles.

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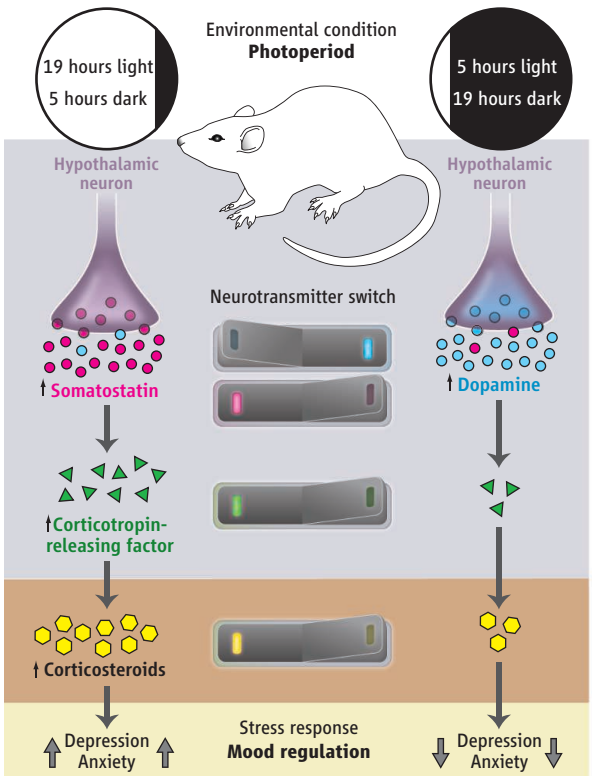
In the earliest days of neuroscience, it was thought that a neuron made and released only a single chemical, known as a neurotransmitter, to send a signal across a synapse to an adjacent neuron (*1*). At the same time, it was deeply mysterious why so many signaling molecules were used in nervous systems. Subsequently, it became clear that many, if not most, neurons (including those in mammals) make and release two or more neurotransmitters including small-molecules and neuropeptides (*2*–*4*). As the list of these potential cotransmitters and their receptors has increased, we are faced with understanding the functional relevance of this embarrassment of riches for neural circuits and behavior. Neurotransmitters and neuromodulators (substances often released with small-molecule neurotransmitters) can elicit a variety of different actions on their neuron targets, including directly opening ion channels or acting through signal transduction pathways to alter neuronal excitability or synaptic transmission. Thus, characterizing the mixture of cotransmitters released by a neuron is important for understanding how neuronal circuits operate. The mechanisms that change the profile of neurotransmitter release provide opportunities for plastic changes in circuit function, and consequently in organism behavior. On page 449 of this issue, Dulcis *et al*. (*5*) report changes in the neurotransmitter profile of neurons that underlie photoperiod-triggered changes in animal behavior. The findings argue that neurotransmitter switching is a new mechanism for neuroplasticity (*6*) in adult nervous systems.



Neurotransmitter switch. During long days, there is a shift in the neurotransmitters released by hypothalamic neurons in the adult rat brain from dopamine to somatostatin, whereas the opposite shift is seen during short days. Increased dopamine signaling during short days results in decreased release of CRF from target neurons, and consequently less CRF and corticosteroids in the plasma. These conditions are associated with a decrease in stress behaviors in nocturnal rodents. The converse is seen with decreased dopamine signaling during long-day conditions. In humans and in other diurnal animals, short days are more stressful and are associated with depression.

Early studies using cultured developing neurons showed that individual neurons can switch their transmitter phenotype (*7*, *8*). For example, peripheral sympathetic neurons that normally release norepinephrine as their neurotransmitter can undergo a developmental switch to acetylcholine. A role for this switch was shown for sympathetic neurons innervating rat sweat glands. These neurons release acetylcholine when innervating sweat glands, whereas they secrete norepinephrine when innervating other organs, including the heart (*9*). Subsequent work has studied the molecular pathways underlying these developmental switches (*10*, *11*) and has demonstrated activity-dependent transmitter plasticity in adult rodent brains (*12*). This type of regulation became even more intriguing when it was found that the production of new neurotransmitters by neurons can induce new behaviors such as pigmentation changes in amphibian larvae (*6*, *13*).

The work by Dulcis *et al*. is remarkable in that it ties these well-characterized phenomena to plasticity in the mammalian response to the light-dark cycle. Specifically, the exposure of adult rats to light was altered by keeping the animals in photoperiod chambers for a week on either long-day (19 hours of light and 5 hours of dark) or short-day (5 hours of light and 19 hours of dark) cycles. The number of dopamine-releasing neurons in several hypothalamic nuclei (clusters of neurons) increased with short-day cycles and decreased with long-day cycles, whereas the inverse was seen with somatostatin. Dopamine is a neurotransmitter whose functions in the brain include modulating cognition, motivation, mood, memory, and learning; somatostatin is a peptide neuromodulator that is widely expressed in the nervous system and may be involved in the regulation of stress responses. The number of dopamine receptors on target neurons in the brain increased and decreased homeostatically, likely to ensure that the changes in the cotransmission of dopamine and somatostatin would result in functional outcomes. Strikingly, the animals' behavior was also modified with short-day cycles, as seen in two assays thought to indicate mood, anxiety, and depression. Changes in light-dark cycle have profound effects on human mood and behavior as well, contributing to a variety of disorders such as seasonal affective disorder. Thus, there is now a potential mechanistic link among mood, photoperiod, and neurotransmitter plasticity that mirrors associations observed in humans among seasonal affective disorder, photoperiod, and dopamine signaling (*14*).

Supporting this link are measurements of corticotropin-releasing factor (CRF) secretion by adult rat hypothalamic neurons in response to different photoperiods. Dulcis *et al*. noted that the change in the ratio of dopa-

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minergic signaling to somatostatin signaling correlated with changes in the amount of CRF and corticosteroid in the plasma (see the figure). CRF is released by neurons in the mammalian brain that are targets of dopamine and somatostatin. This triggers a cascade of events that raises the concentration of circulating corticosteroids. These steroids have a wide range of physiological effects and have been implicated in stress and depression (*15*). The findings suggest that the transmitter switch potentially couples photoperiod and mood regulation. The ability of neurons to switch their neurotransmitter repertoire has been known for 40 years; the study of Dulcis *et al*. demonstrates the use of this mechanism to control adult behavior in response to sensory variation.

Although the work by Dulcis *et al*. was carried out in nocturnal rodents for which long-day photoperiods are stressful, it is possible to imagine broader implications of this work for human behavior in which short-day photoperiods are stressful. Admittedly, the mechanistic details in humans may be different. Nonetheless, given the ubiquitous ability of neurons to release multiple neurotransmitters and the demonstrated capacity for plasticity, it is critical to consider the potential role of transmitter plasticity in understanding the human brain in health and disease.

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