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Essential Role of BDNF in the Mesolimbic Dopamine Pathway in Social Defeat Stress

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Mice experiencing repeated aggression develop a long-lasting aversion to social contact, which can be normalized by chronic, but not acute, administration of antidepressant. Using viral-mediated, mesolimbic dopamine pathway-specific knockdown of brain-derived neurotrophic factor (BDNF), we showed that BDNF is required for the development of this experience-dependent social aversion. Gene profiling in the nucleus accumbens indicates that local knockdown of BDNF obliterates most of the effects of repeated aggression on gene expression within this circuit, with similar effects being produced by chronic treatment with antidepressant. These results establish an essential role for BDNF in mediating long-term neural and behavioral plasticity in response to aversive social experiences.

The mesolimbic dopamine pathway, composed of dopaminergic neurons in the midbrain ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc), allows an organism to identify emotionally salient stimuli in the environment, to learn about outcomes associated with those stimuli, and to express appropriate approach or avoidance responses (1, 2). Activation of this neural circuit has been characterized extensively in relation to drugs of abuse but has been less characterized in ethologically relevant contexts (3–5). The circuit is stimulated in humans and animals by psychosocial experiences such as affiliation and cooperation (6, 7), and it drives associative learning processes such as imprinting, pair bonding, and maternal attachment (8, 9). Aversive stimuli such as aggression and social subordination (10) also acutely activate the mesolimbic dopamine pathway (11–13) and have been linked to chronic alterations in dopaminergic function (14). These observations have led to the hypothesis that dopaminergic signaling to the NAc may be involved in the perception of social status and the appraisal of threats from the social environment (8). Imaging studies have linked the NAc to cognitive processes that lead to the attribution of salience to social stimuli (15). Alteration of this cognitive function could contribute to a

social withdrawal trait that is common to several human affective disorders, including depression, social phobia, and post-traumatic stress disorder (PTSD), in which dopaminergic abnormalities have been described (16–19). However, very little is known about the mechanisms through which the motivational value of socially relevant stimuli might be encoded by this pathway.

To characterize the neurobiological mechanisms through which psychosocial experience alters the activity of the mesolimbic dopamine pathway, we adopted a social defeat paradigm that profoundly alters the motivation for social interactions in rodents (20–22). Mice were subjected to daily bouts of social defeat, followed by continuous protected sensory contact with their aggressor [Fig. 1A; see fig. S1 in the supporting online material (SOM) for experimental details]. Mice were exposed to a different aggressor each day for 10 days and were then screened for social behavior. We measured social approach toward an unfamiliar mouse enclosed in a wire mesh cage by use of a video-tracking system (Fig. 1B). Undefeated control mice spent most of their time interacting socially when presented with an unfamiliar target mouse. Defeated mice displayed intense aversive responses and spent less time in close proximity to the target mouse (Fig. 1, B and C). This difference was observed exclusively in the presence of a social target and was not apparent in response to an inanimate novel object [the empty wire cage (Fig. 1B)]. No difference in total movement in the arena was observed (Fig. 1C). When tested again 4 weeks after the 10 days of repeated psychosocial stress, mice with a history of social defeat still displayed dramatic social avoidance (Fig. 1D). This aversive response was more robust when a former aggressor was used as a social target in the wire cage, but it also generalized to unfamiliar mice that were physically distinct from the

aggressors (fig. S2). To test whether this long-lasting change in social behavior is relevant to stress-linked human conditions characterized by social withdrawal, we studied the effect of antidepressants in our model. Chronic, but not acute, administration of fluoxetine or imipramine, two chemically distinct antidepressants used widely in humans, improved social interaction in defeated animals (Fig. 2A), an effect that could not be explained by changes in general locomotion (fig. S3). This effect was not produced by acute or chronic (fig. S4) treatment with chlordiazepoxide, a benzodiazepine used to treat anxiety but not depression in humans.

We next measured c-Fos expression in the VTA and NAc as a marker of neuronal activation after sensory exposure to social cues. We found robust c-Fos induction in VTA dopamine neurons and in their target neurons in the NAc when mice were exposed to a social partner through a perforated Plexiglas partition (fig. S5). As compared to naïve mice, defeated mice exhibited sensitized c-Fos responses when exposed to a social target 4 weeks after defeat (Fig. 1E).

The neurotrophic factor BDNF (brain-derived neurotrophic factor) is a key regulator of the mesolimbic dopamine pathway. BDNF potentiates dopamine release in the NAc through activation of TrkB receptors on dopaminergic nerve terminals (23), and it potentially regulates NAc function directly via activation of TrkB receptors on NAc neurons (24–26). We hypothesized that BDNF function within the mesolimbic dopamine pathway may be a critical mediator of changes in social motivation. We found that 10 days of social defeat increased BDNF protein levels in the NAc, an effect that was apparent both 24 hours and 4 weeks after the stress (Fig. 1F).

A major source of BDNF protein in the NAc is thought to be the VTA (26), because BDNF mRNA is expressed at high levels by dopaminergic neurons (27, 28) but is barely detectable in NAc neurons (29). We thus induced a local deletion of the gene encoding BDNF that was restricted to VTA neurons in adult mice. We used a line of mice in which 1 kb of the single coding exon of the BDNF gene is flanked by loxP sites (floxed BDNF mice) (Fig. 3A). We injected adult mice with an adenoassociated virus (AAV) vector expressing green fluorescent protein (GFP)-tagged Cre recombinase (CreGFP) or with GFP as a control directly into the VTA (30). Animals were subjected to the social defeat paradigm 20 days after the infusion, when AAV-CreGFP-induced recombination is maximal (see methods in the SOM). Local deletion of the BDNF gene exerted an antidepressant-like effect by opposing the development of social avoidance behavior in defeated mice (Fig. 2B). Defeated mice injected with AAV-GFP showed the expected social avoidance behavior. Control mice injected with AAV-CreGFP were indistinguishable from AAV-

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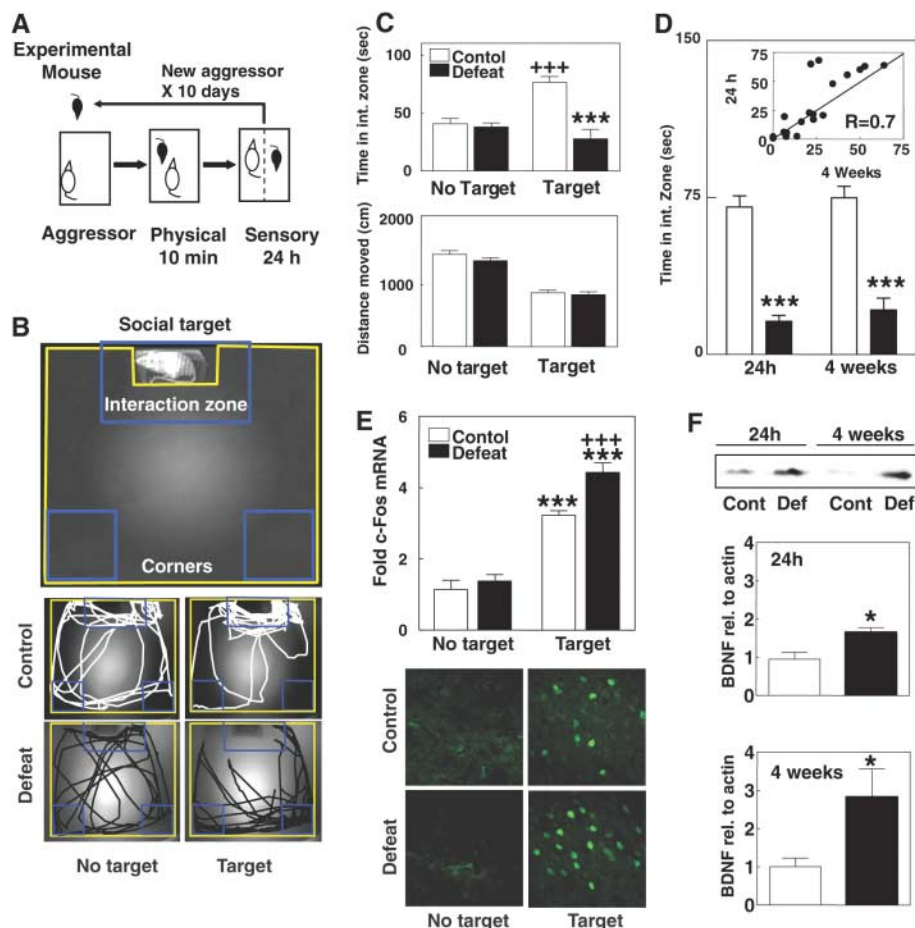


Fig. 1. Persistent social aversion after repeated aggression in mice. **(A)** Social defeat paradigm. **(B)** Videotracking data from control and defeated mice in the absence and presence of a social target. **(C)** (Top) A social target increased the time spent in the interaction zone by control mice ($n = 18$ mice), an effect suppressed after social defeat ($n = 36$ mice), which had no effect on total locomotion (bottom). [Analysis of variance (ANOVA): Target \times defeat interaction $F(2,150) = 7.26$, $P < 0.001$. Least-square difference (LSD) post-hoc test: $+++P < 0.001$ versus control "no target," $***P < 0.001$ versus "target."] **(D)** Stable social avoidance in defeated mice tested 24 hours and 4 weeks after 10 days of defeat stress ($n = 13$ or 14 mice). [Effect of social defeat $F(1,60) = 115.5$, $P < 0.0001$; no significant effect of test days, $F(1,60) = 0.94$, $P = 0.33$; significant correlation at 24 hours and 4 weeks, Pearson $R = 0.696$, $P < 0.001$.] **(E)** Sensitized *c-Fos* induction in the NAC of mice 4 weeks after repeated social defeat upon exposure to a social target. [ANOVA: Target \times defeat interaction $F(1,21) = 4.62$, $P < 0.05$. LSD post-hoc test: $+++P < 0.001$ versus control "target" $***P < 0.001$ versus "no target," $n = 6$ or 7 mice.] **(F)** Increased BDNF protein levels in the NAC 24 hours and 4 weeks after 10 days of defeat stress [$t(8) = -3.22$, $*P < 0.05$, $n = 5$ mice]. Cont., control; def., defeat.

GFP-injected or uninjected controls (Fig. 2B). This indicates that the effect of BDNF deletion on social behavior is experience-dependent and requires repeated exposure to an aggressor. Therefore, in defeated mice, BDNF from VTA neurons is required for a social target to progressively acquire salience as a threatening stimulus. This associative process implicates a form of activity-dependent neuronal plasticity in the VTA-NAC pathway, which is mediated by BDNF. Indeed, *c-Fos* co-immunolabeling with tyrosine hydroxylase and GFP indicated that a significant proportion of the neurons infected by the AAV-CreGFP vector in the VTA were activated as a consequence of exposure to social cues (Fig. 3E).

Several lines of evidence confirm the efficiency of Cre-induced recombination in VTA dopaminergic neurons in our assay. Adult Rosa26 mice, in which recombination induces the *lacZ* gene, were injected with AAV-CreGFP or AAV-GFP in the VTA. Both vectors induced robust GFP expression in the VTA, but β -galactosidase (β -Gal) expression (evidence of recombination) was seen only in the AAV-CreGFP-injected mice (fig. S6). This β -Gal expression was seen solely within Cre-expressing cells, which were largely dopaminergic (a conclusion based on colabeling with tyrosine hydroxylase). Roughly 75% of all dopaminergic neurons were infected under our conditions (Fig. 3D). Floxed BDNF mice injected

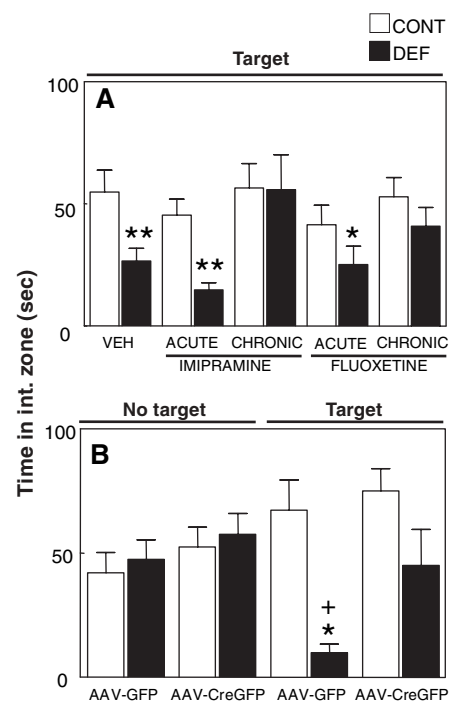


Fig. 2. Chronic treatments with antidepressant or VTA-specific deletion of BDNF oppose the development of social aversion after defeat stress. (Int. zone, interaction zone; veh., vehicle.) **(A)** Administration of imipramine [20 mg per kg of body weight (mg/kg)] or fluoxetine (20 mg/kg) daily for 28 days (chronic), but not a single injection (acute), reduced social avoidance caused by defeat stress. [ANOVA, significant effect of social defeat $F(1,196) = 7.51$, $P < 0.01$. Significant effect of antidepressants $F(4,196) = 5.01$, $P < 0.001$. LSD post-hoc test: $*P < 0.05$ and $**P < 0.01$ versus control, $n = 9$ to 18 mice.] **(B)** Social avoidance caused by defeat stress in floxed-BDNF mice injected with AAV-GFP in the VTA was reduced in mice injected with AAV-CreGFP [ANOVA: significant effect of virus, $F(1,86) = 5.17$, $P < 0.05$; significant target \times defeat interaction, $F(1,86) = 12.27$, $P < 0.001$. LSD post-hoc test: $+P < 0.05$ versus AAV-GFP "no target," $*P < 0.05$ versus AAV-Cre "target," $n = 10$ to 13 mice.]

with AAV-CreGFP showed a selective loss of BDNF expression within the VTA as determined by double-labeling in situ hybridization (Fig. 3B). Analysis of VTA tissue by real-time polymerase chain reaction (PCR) showed that AAV-CreGFP induces recombination of the BDNF gene (Fig. 3A) and that this causes an almost complete loss of BDNF mRNA expression (Fig. 3C). In contrast, the loss of BDNF had no effect on the expression of tyrosine hydroxylase. This finding, together with the observation that CreGFP had no effect on the total number of dopaminergic neurons (Fig. 3D), indicates no loss of these neurons in the VTA after BDNF suppression. This is in contrast to previous reports, which found loss of substantia nigra dopamine neurons upon

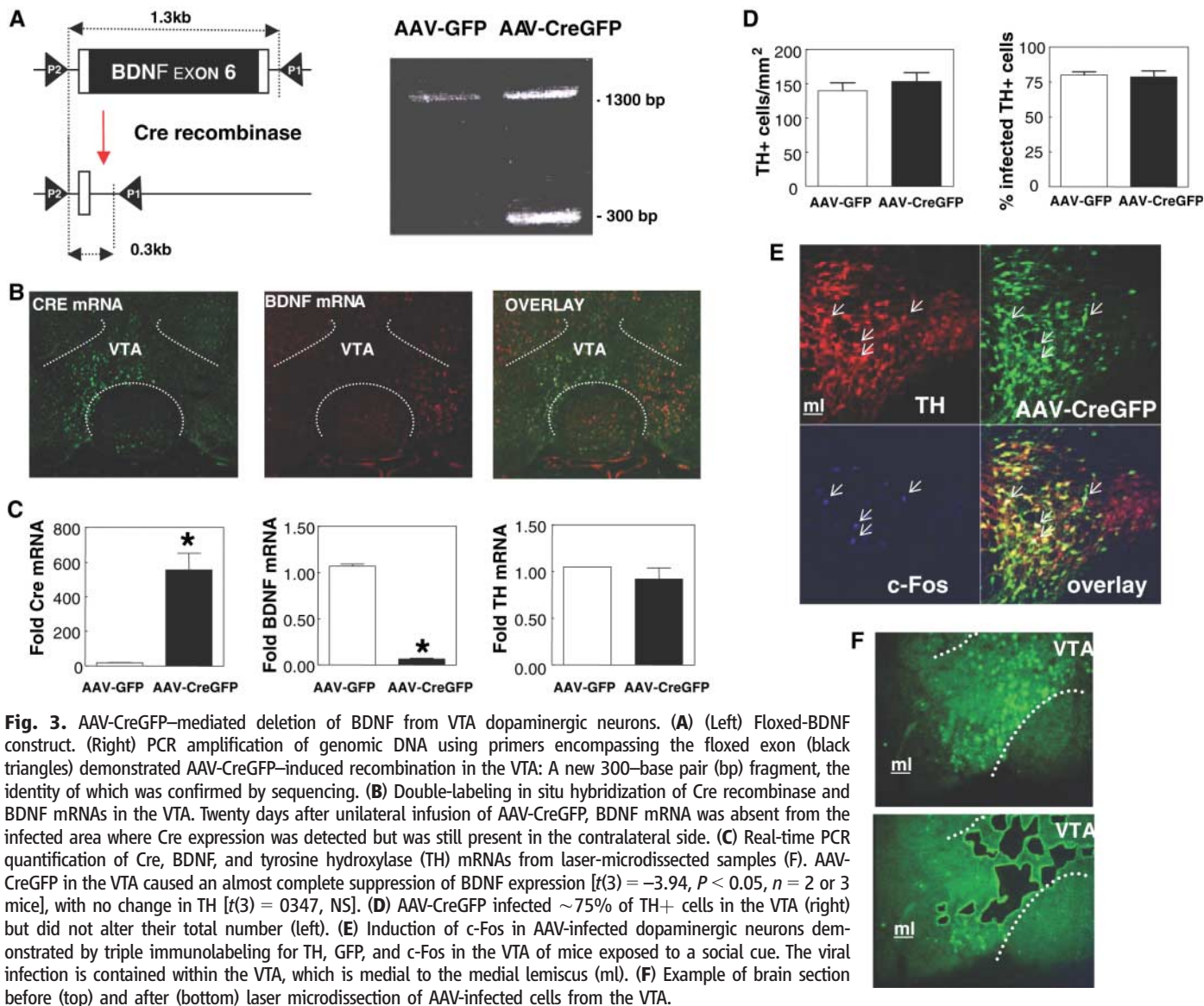


Fig. 3. AAV-CreGFP-mediated deletion of BDNF from VTA dopaminergic neurons. **(A)** (Left) Floxed-BDNF construct. (Right) PCR amplification of genomic DNA using primers encompassing the floxed exon (black triangles) demonstrated AAV-CreGFP-induced recombination in the VTA: A new 300-base pair (bp) fragment, the identity of which was confirmed by sequencing. **(B)** Double-labeling in situ hybridization of Cre recombinase and BDNF mRNAs in the VTA. Twenty days after unilateral infusion of AAV-CreGFP, BDNF mRNA was absent from the infected area where Cre expression was detected but was still present in the contralateral side. **(C)** Real-time PCR quantification of Cre, BDNF, and tyrosine hydroxylase (TH) mRNAs from laser-microdissected samples (F). AAV-CreGFP in the VTA caused an almost complete suppression of BDNF expression [$t(3) = -3.94, P < 0.05, n = 2$ or 3 mice], with no change in TH [$t(3) = 0.347, NS$]. **(D)** AAV-CreGFP infected ~75% of TH+ cells in the VTA (right) but did not alter their total number (left). **(E)** Induction of c-Fos in AAV-infected dopaminergic neurons demonstrated by triple immunolabeling for TH, GFP, and c-Fos in the VTA of mice exposed to a social cue. The viral infection is contained within the VTA, which is medial to the medial lemniscus (ml). **(F)** Example of brain section before (top) and after (bottom) laser microdissection of AAV-infected cells from the VTA.

suppression of BDNF using early postnatal Cre expression (28) or the infusion of antisense oligonucleotides (31). The lack of dopaminergic neuronal loss seen in our study could reflect the different methodologies used or the lower sensitivity of VTA dopamine neurons to neurotoxic insults (32).

To gain further insight into the molecular events underlying the similar regulation of social defeat by BDNF gene deletion and antidepressant treatment, we carried out DNA microarray studies of gene expression in the NAc. In one experiment, mice received intra-VTA injections of AAV-CreGFP or AAV-GFP; half were then subjected to 10 days of social defeat stress; and 24 hours later, all mice were analyzed for NAc gene expression. In a parallel experiment, control or defeated mice received fluoxetine or vehicle for 4 weeks after chronic defeat stress. In mice injected with AAV-GFP and analyzed 24 hours after the end of the stress procedure, social

defeat up-regulated 309 genes in the NAc, as compared to nondefeated mice, whereas 17 genes were down-regulated (Fig. 4A and tables S1 and S2). A similar pattern of gene expression, with 127 genes up-regulated and 9 genes down-regulated, was still observed 4 weeks after the cessation of social defeat in mice receiving vehicle injections (Fig. 4A and tables S1 and S2). After a discrete period of psychosocial stress, NAc neurons thus showed an activated pattern of gene expression, which persisted, like the change in social behavior, for up to 4 weeks. This heightened transcriptional activity may participate in encoding the motivational changes induced by aggression.

After local deletion of BDNF in the VTA, the effect of social defeat on most of these genes in the NAc was lost or reversed (Fig. 4A and tables S1 and S2). Chronic fluoxetine treatment also reversed most of the gene expression changes that persisted in the NAc after 4 weeks (Fig.

4A). Figure S7 provides examples of genes showing this pattern of expression in the NAc. Analysis of the regulated genes revealed specific molecular pathways induced prominently by defeat stress and reversed by BDNF deletion or fluoxetine treatment (fig. S8 and table S3). The largest subset of these regulated genes function in BDNF signaling cascades [such as phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (table S3 and figs. S8 and S9)] (33). The identification of PI3K in the NAc as an interface between the effects of social defeat and fluoxetine is particularly interesting because of its reported influence on dopamine release (23) and motivational processes (34, 35). These microarray data thereby suggest that chronic treatment with antidepressant restores social approach behaviors partly by interfering with the activity of neurotrophic cascades that mediate experience-induced neuroadaptations in the mesolimbic dopamine pathway. Al-



B

	BDNF KO	FLUOXETINE		BDNF KO	FLUOXETINE
DOPAMINERGIC SYSTEM			SIGNAL TRANSDUCTION		
Dopa decarboxylase	+		cAMP pathway		
Dopamine receptor 2	+		cAMP responsive element binding protein 1 (CREB1)		+
Dopamine receptor D1A	+		cAMP responsive element modulator	+	
GROWTH FACTORS AND GROWTH FACTOR SIGNALING			Cbp/p300-interacting transactivator	+	
Fibroblast growth factor (acidic) intracellular binding protein	+		Phosphodiesterase 4B	+	
Fibroblast growth factor receptor 1	+		Phosphodiesterase 8B	+	+
Fibroblast growth factor receptor 3		+	CREB binding protein	+	
Glycogen synthase kinase 3 beta	+		Cyclic AMP-regulated phosphoprotein, 21	+	
Insulin-like growth factor 2 receptor	+		Map Kinase pathway		
Insulin-like growth factor binding protein 1	+		Mitogen-activated protein kinase kinase 5	+	
Thymoma viral proto-oncogene 1 (AKT1)		+	Mitogen-activated protein kinase kinase 7	+	
Thymoma viral proto-oncogene 2 (AKT2)		+	Mitogen-activated protein kinase kinase 10	+	
Thymoma viral proto-oncogene 3 (AKT3)	+		Mitogen-activated protein kinase kinase 3	+	
MAD3 homolog (TGF signaling)	+	+	Mitogen-activated protein kinase kinase 1 interacting protein 1	+	
Nerve growth factor, beta	+		Mitogen-activated protein kinase kinase kinase 4		+
Mitochondrial tumor suppressor 1	+	+	Mitogen-activated protein kinase kinase kinase 5	+	
CELL ADHESION AND MOTILITY			phosphoinositides		
Integrin alpha 6	+		Phosphatidylinositol 4-kinase type 2 beta	+	
Integrin beta 4	+		Phosphatidylinositol binding clathrin assembly protein	+	
Integrin beta1	+	+	Phosphatidylinositol transfer protein, cytoplasmic 1	+	
Non-catalytic region of tyrosine kinase adaptor protein 2	+	+	Phosphatidylinositol-3-phosphate/phosphatidylinositol 5-kinase, type III		+
Dedicator of cytokinesis 9	+	+	Phosphatidylinositol-4-phosphate 5-kinase, type 1 beta		+
Chemokine (C-C motif) receptor 4	+		Phosphatidylinositol 3-kinase, C2 domain containing, alpha polypeptide		+
ADAM10	+		Phosphatidylinositol 3-kinase, catalytic, beta polypeptide	+	
ADAM11		+	CONTROL OF GENE TRANSCRIPTION		
ADAMTS-like 3	+		Mef2A	+	+
Kinesin family member 1A		+	Pbx/knotted 1 homeobox	+	+
Kinesin family member 1B	+		Nuclear receptor interacting protein 2	+	+
AP2 associated kinase 1	+	+	Deoxynucleotidyltransferase, terminal	+	+
Beta-2 microglobulin	+	+	BTB (POZ) domain containing 14A	+	+
Unc-5 homolog C (axon guidance)	+	+	MISCELLANEOUS		
CYTOSKELETON			DIX domain containing 1	+	+
Microtubule-actin crosslinking factor 1	+		Sarcolemma associated protein	+	+
Actin-related protein 3-beta	+	+	Sec63	+	+
Procollagen-proline alpha 1 polypeptide	+	+	Dihydroipoamide S-acetyltransferase	+	+
			Poly (ADP-ribose) polymerase family, member 6	+	+
			Low density lipoprotein-related protein 1B	+	+

Fig. 4. VTA-specific deletion of BDNF and chronic administration of fluoxetine reverse the effects of social defeat stress on gene expression in the NAC. Gene expression in the NAC was evaluated using gene profiling (see SOM for a detailed experimental protocol and complete gene lists). **(A)** Hierarchical clusters of genes significantly up-regulated in the NAC of AAV-GFP-injected mice after 10 days of social defeat stress and how they are regulated by defeat across other experimental conditions. The results show that virtually all of these genes that were up-regulated 24 hours after defeat stress show

the opposite regulation upon local deletion of BDNF from the VTA. Similarly, a large subset of the stress-regulated genes remain up-regulated after 4 weeks of treatment with vehicle, and most of these persistent changes are reversed by chronic treatment with fluoxetine. The intensity and direction of gene regulation are represented with a heat map (red, up-regulated; green, down-regulated). **(B)** Examples of genes significantly up-regulated ($+P < 0.05$) after intra-VTA BDNF knockdown or fluoxetine treatment in control mice. See tables S1 and S2 for detailed gene lists.

though this is in contrast to the reported effects of stress and antidepressants on BDNF signaling in the hippocampus (10), several manipulations that sensitize the dopaminergic system (36), such as social defeat, have been shown to increase dendritic branching in the NAc (37).

The demonstration that social stimuli become persistently aversive after repeated experiences of aggression in mice is one major finding of the present study. This behavioral phenomenon shares some similarities with persistent conditioned submissive responses that have been described previously in other rodent species (22).

Here, we took advantage of this observation to develop a murine model relevant to human psychiatric conditions such as depression, social phobia, and PTSD, in which social withdrawal is a common symptom. The observation that chronic but not acute treatments with antidepressant partly restore social approach behavior

in defeated mice further validates this model. Social cues stimulate the VTA-NAc pathway in mice, and this neural response becomes sensitized in defeated mice with social aversion. The second major finding of this study is the demonstration that intact BDNF function in the VTA is required for the development of this persistent social aversion. Our gene profiling study suggests that this process is mediated in large part by BDNF-regulated molecular pathways in the NAc and is counteracted by antidepressant drugs. The present results confirm our previous report that blockade of BDNF activity in the VTA-NAc pathway exerts an antidepressant-like activity in rodent models of stress (38). This profile is opposite to the antidepressant-like activity of BDNF reported in hippocampal studies (39) and suggests new directions for antidepressant drug discovery.

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Supporting Online Material

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Materials and Methods

Figs. S1 to S9

Tables S1 to S3

References

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