Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression

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Enhanced glutamatergic transmission in the nucleus accumbens (NAc), a region critical for reward and motivation, has been implicated in the pathophysiology of depression; however, the afferent source of this increased glutamate tone is not known. The NAc receives glutamatergic inputs from the medial prefrontal cortex (mPFC), ventral hippocampus (vHIP) and basolateral amygdala (AMY). Here, we demonstrate that glutamatergic vHIP afferents to NAc regulate susceptibility to chronic social defeat stress (CSDS). We observe reduced activity in vHIP in mice resilient to CSDS. Furthermore, attenuation of vHIP-NAc transmission by optogenetic induction of long-term depression is pro-resilient, whereas acute enhancement of this input is pro-susceptible. This effect is specific to vHIP afferents to the NAc, as optogenetic stimulation of either mPFC or AMY afferents to the NAc is pro-resilient. These data indicate that vHIP afferents to NAc uniquely regulate susceptibility to CSDS, highlighting an important, novel circuit-specific mechanism in depression.
Alterations in nucleus accumbens (NAc), a region critical for reward and motivation, are implicated in the pathophysiology of depression. Glutamatergic transmission in medial NAc is increased in mice exhibiting depression-like behaviour after chronic stress. However, the role of presynaptic changes in driving stress-induced postsynaptic adaptations in NAc medium spiny neurons (MSNs) is not well understood. The NAc integrates corticostriatal afferents with dopaminergic modulation from the ventral tegmental area. Integration occurs at the cellular level, with individual NAc MSNs receiving convergent glutamatergic projections from ventral hippocampus (vHIP), medial prefrontal cortex (mPFC) and basolateral amygdala (AMY), in addition to other regions such as the thalamus. Complex competitive interactions between inputs gate postsynaptic MSN responses to afferent activation to direct the finely tuned integration of executive control from mPFC, conditioned associations and emotion from AMY and contextual, spatial and emotion-related inputs from vHIP to orchestrate adaptive motivated behaviour.

mPFC activity is reduced in depression-like states in rodents, and optogenetic activation of mPFC, a manipulation that, among other actions, increases glutamate release in NAc, is antidepressant. These findings are paradoxical in view of observed increases in mini EPSC frequency and AMPA current in NAc MSNs of stress-susceptible mice, which point to stress-induced facilitation of both pre- and postsynaptic mechanisms of glutamate transmission. This raises the question of whether chronic stress may produce pathway-specific alterations, with distinct glutamatergic inputs exerting opposing effects on depression-like behaviour. To examine this possibility, we investigated regulation of vHIP-NAc, mPFC-NAc and AMY-NAc projections by chronic social defeat stress (CSDS), a validated mouse model of depression. Examining immediate early gene (IEG) expression as an indicator of neuronal activity and electrophysiological correlates of presynaptic neurotransmitter release, we report afferent-specific CSDS-induced adaptations in vHIP and mPFC. Using optogenetic manipulations to bidirectionally control afferent-specific synaptic function, we demonstrate a unique role for vHIP-NAc in driving depression-like behavioural phenotypes.

Results

CSDS oppositely regulates activity of vHIP and mPFC. We examined mRNA expression of two IEGs, Arc and Egr1, in mPFC, vHIP and AMY of susceptible and resilient mice versus stress-naive controls to assess basal activation of these brain regions 48 h after CSDS. Mice were determined to be susceptible or resilient based on their social interaction ratio (time in interaction zone with social target/time with target absent) in a social interaction test 24 h after CSDS (susceptible ratio <1; resilient ratio >1; Supplementary Fig. 1). This designation has been highly validated in previous studies and shown to correlate with other depression-related, but not anxiety-related, behavioural abnormalities. Both Arc and Egr1 transcript levels were reduced in vHIP of resilient mice versus controls, whereas Arc, but not Egr1, was decreased in mPFC of susceptible mice and neither transcript was altered in AMY (Fig. 1a–f). To identify vHIP, mPFC and AMY neurons projecting to NAc, we injected the retrograding AAV2/5-CaMKIIa-ChR2-EYFP virus into NAc before CSDS. Double-immunofluorescence labelling revealed increased EGR1-positive EYFP-labelled vHIP neurons in susceptible mice (Fig. 1g). No significant effects were observed in NAc-projecting mPFC and AMY neurons (Fig. 1i,k). ARC protein levels are too low under these conditions to perform the equivalent analysis. Reduced IEG expression in these regions of resilient versus susceptible mice suggests that decreased vHIP activity might be pro-resilient, whereas decreased mPFC activity is pro-susceptible.

To assess afferent-specific glutamatergic synaptic transmission in NAc, mice were injected with (non-retrograding) AAV5-CaMKIIa-ChR2–EYFP virus in vHIP, mPFC or AMY (Supplementary Fig. 2). The CaMKIIa promoter targets viral infection to glutamatergic neurons within the injected brain regions (see Methods), and we confirmed that optically induced currents are blocked completely by glutamate receptor antagonists (Supplementary Fig. 2c). Six weeks later, when robust transgene expression was seen in nerve terminals in NAc, mice were exposed to CSDS. Using whole-cell patch-clamp in brain slices, optogenetically stimulated paired-pulse responses were recorded in medial NAc from control, susceptible and resilient mice beginning 48 h after CSDS. The resulting ratio of excitatory postsynaptic current (EPSC) amplitudes to paired stimulations is indicative of vesicle release probabilities and suggestive of changes in glutamate release. Paired-pulse ratios (PPRs) of vHIP afferent-stimulated responses in NAc were increased in resilient relative to susceptible mice, suggesting a potential decreased probability of glutamate release (Fig. 1m). In contrast, PPRs of mPFC afferent-stimulated responses were decreased in resilient animals relative to susceptible mice (Fig. 1o). PPRs of AMY afferent-stimulated responses were not regulated by CSDS (Fig. 1q). These findings suggest that glutamate release at vHIP-NAc synapses may be decreased in resilient mice, whereas mPFC-NAc synaptic glutamate release is increased in resilient mice.

LTD attenuation of vHIP-NAc synaptic transmission is pro-resilient. To determine whether decreasing glutamatergic synaptic transmission at vHIP-NAc synapses could promote resilience in previously defeated mice, we injected AAV5-CaMKIIa–ChR2–EYFP or AAV5–CaMKIIa–EYFP into vHIP and 6 weeks later exposed mice to CSDS. Optic fibres targeting medial NAc were then surgically implanted, and optogenetic low frequency stimulation (LFS; 473 nm, 10 min, 1 Hz, 4 ms pulse width) of ChR2-infected terminals in NAc was used to induce long-term depression (LTD) of MSN EPSCs. One week after surgery, we delivered LFS to reduce vHIP-NAc synaptic transmission 45 min before social interaction testing (Fig. 2a); LTD-like responses were electrophysiologically validated by optogenetic terminal stimulation of inputs in brain slices and in vivo (Fig. 2b–d; Supplementary Fig. 3a–c) as previously described, vHIP ChR2-infected mice spent more time interacting with a target mouse in comparison with EYFP-infected controls (Fig. 2e) and similar to what is normally observed in resilient mice indicating a pro-resilient effect. The same manipulations did not affect social interaction in mice injected with AAV5–CaMKIIa–ChR2–EYFP in mPFC or AMY (Fig. 2f,g), vHIP, mPFC or AMY injected stress-naive controls were unaffected by optical stimulations (Supplementary Fig. 3).

Enhancement of vHIP-NAc synaptic transmission is pro-susceptible. To examine whether conversely increasing glutamate synaptic transmission in NAc could increase stress susceptibility, vHIP terminals in medial NAc were acutely stimulated to increase glutamate release at vHIP-NAc synapses during social interaction testing following CSDS (Fig. 3a; fidelity of acutely evoked EPSCs was validated in brain slices Fig. 3b–d; and in vivo, Supplementary Fig. 4a–c). Mice receiving acute optical stimulation (4 Hz, 5 ms) during social interaction testing spent less time interacting with a target animal and increased time in corner zones compared with non-stimulated controls (Fig. 3e,h). To assess whether increasing glutamate release selectively at NAc postsynaptic sites.
mPFC-NAc synapses could increase resilience to stress, similar to the effect of global mPFC stimulation\textsuperscript{16}, we acutely stimulated mPFC terminals in medial NAc. Mice receiving acute stimulation of mPFC terminals in NAc spent more time interacting with a target mouse and less time in the corner zones (Fig. 3f,i). Acutely stimulated mice that were injected intra-AMY with AAV5-CAMKIIa–ChR2–EYFP spent more time interacting with a target mouse and less time in the corner zones (Fig. 3f,i). Effects of acute stimulation of each of the three afferents increased locomotor activity in the open field test (Supplementary Fig. 4j–l). Effects of acute stimulation on social-avoidance behaviour require previous stress exposure: manipulations in stress-naive-mice did not alter social interaction. Of note, AMY stimulation decreased exploration of the empty interaction zone, but time spent interacting with a target mouse was not affected (Supplementary Fig. 6).

Discussion
NAc MSNs receive dense glutamatergic projections from vHIP, mPFC and AMY, among other regions. Here, we present data suggesting that vHIP-NAc synaptic transmission is selectively increased in mice susceptible to CSDS, and demonstrate that in vivo optogenetic manipulations of vHIP-NAc synaptic

Figure 1 | Opposing effects of CSDS on vHIP and mPFC IEG expression and synaptic function. mRNA expression of two immediate early genes in vHIP of control (CON), susceptible (SUS) and resilient (RES) mice. (a) Arc (F\textsubscript{2,40} = 6.485, \(P < 0.01\), post hoc **\(P < 0.01\), \(n = 13,15,15\)) and (b) Egr1 (F\textsubscript{2,36} = 5.415, \(P < 0.01\), post hoc **\(P < 0.01\), \(n = 12,14,13\)) were decreased in vHIP of RES mice 48 h post-defeat. In contrast, (c) Arc expression was decreased in mPFC of SUS mice (F\textsubscript{2,37} = 3.433, \(P < 0.05\), post hoc CON versus SUS *\(P < 0.05\), n = 12,14,14). (d) Egr1 expression was not significantly different (n = 11,13,12). Neither Arc (e) nor Egr1 (f) expression was regulated by defeat in AMY (n = 14,15,15). A greater percentage of EYFP retrogradely labelled NAc-projecting neurons were EGR1 positive in vHIP (g) of SUS mice compared to controls (F\textsubscript{2,16} = 3.618, \(P < 0.05\), post hoc *\(P < 0.05\), \(n = 7,5,7\)). EGR1 levels in mPFC (i) and AMY (k) in NAc-projecting neurons were not significantly regulated by defeat. Representative images show Hoechst nuclear stain (blue) in EYFP labelled EGR1 (red) staining in NAc-projecting neurons in vHIP (h), mPFC (j) and AMY (l) labelled by retrograde AAV2/5-CaMKIIa–EYFP injected into NAc (scale bar 10 μm). In RES relative to SUS mice, paired-pulse ratios (P\textsubscript{2}/P\textsubscript{1}; 100 ms interpulse interval) of optically evoked EPSCs in NAc shell MSNs were increased from (m) vHIP (F\textsubscript{2,50} = 4.023, \(P < 0.05\), post hoc *\(P < 0.05\), \(n = 14,20,19\) cells from n = 67,6 mice) and decreased from (n) mPFC (F\textsubscript{2,45} = 5.459, \(P < 0.01\), post hoc **\(P < 0.01\), \(n = 9,18,12\) cells from n = 5,4,7 mice). Paired-pulse ratios from AMY (o) were not regulated by defeat (n = 10,8,8 cells from n = 4,3,4 mice). Representative EPSCs evoked by optical stimulation of vHIP (n), mPFC (p) and AMY (r) ChR2-expressing terminals. Vertical scale bar (n) 80 pA, (p,r) 40 pA, horizontal scale bar 40 ms. Blue squares indicate light pulse delivery. One-way-ANOVAS with Bonferroni post hoc tests. Grubb’s test was used to detect and remove statistical outliers in panels a–f. Error bars represent s.e.m.
transmission bidirectionally regulate depression-like behaviours. In contrast, our findings suggest that mPFC-NAc synaptic transmission is decreased in susceptible animals, and show that increasing either mPFC or AMY synaptic transmission by acute stimulation in vivo promotes resilience.

The mechanism of these distinct pathway-specific adaptations is unclear. Opposing effects of vHIP versus mPFC and AMY synaptic transmission could reflect the relative strengths of the examined inputs; vHIP projections to NAc shell are denser than synaptic transmission that could reflect the relative strengths of the inputs25,26. Previous work has demonstrated that blockade of AMPA receptors in NAc increases resilience to stress. 

Figure 2 | LTD at vHIP-NAc induces resilience to CSDS. (a) Schematic of experimental time-course. Representative traces validating that 1 Hz stimulation of ChR2-expressing vHIP (b) (scale bar 200 pA, 1 s), mPFC (c) (scale bar 50 pA, 1 s) and AMY (d) (scale bar 200 pA, 1 s) terminals reliably evoke EPSCs with temporal fidelity in NAc MSNs (upper panels). 10 min, 1 Hz stimulation (low frequency stimulation; LFS) induces LTD of evoked EPSCs measured 45 min after LFS (b–d, lower panels; scale bars 80 pA, 50 ms) 45 min post-LFS (grey traces) compared to pre-LFS baselines (black traces). Blue squares indicate light pulse delivery. (e) In vivo, LFS of vHIP-NAc synapses in defeated mice increased time spent in the interaction zone in the presence of a target (f1,16 = 5.274 interaction effect, P < 0.05, post hoc *P < 0.05, n = 9,11) but did not alter time spent in corners (h). Stimulation of mPFC-NAc (f, n = 6, 16) or AMY-NAc synapses (g, n = 9,11) had no effect on time spent in interaction or corner zones (i, j). Two-way repeated measures ANOVA with Bonferroni post hoc tests. ‘EYFP’ and ‘ChR2’ denote AAV5-CaMKIIa–EYFP and AAV5-CaMKIIa–ChR2–EYFP, respectively. ‘No target’ and ‘Target’ indicate absence or presence of a target mouse during testing. Error bars represent s.e.m.
LTD. While human structural imaging studies have reported decreased hippocampal volume in depressed patients, functional imaging studies report indicators of increased hippocampal glutamate associated with familial risk of depression, increased hippocampal activation during negative information processing and an association between decreased hippocampal metabolism and antidepressant responses. The mechanism of stress-dependent regulation of vHIP glutamate projections may reflect an interaction with alterations in dopaminergic input to NAc. Ventral tegmental area dopamine neuron burst firing is increased in susceptible mice and phasic dopamine release in NAc has been shown to facilitate vHIP-NAc inputs. Interestingly, vHIP-NAc stimulation may also increase VTA dopamine neuron population activity.

Our findings highlight a complex afferent-specific role for vHIP glutamatergic signalling in NAc in depression-associated behaviours. Chronic stress may shift the balance away from mPFC towards vHIP control, creating a reinforcing loop further enhancing vHIP-NAc synaptic transmission. Circuit-level therapeutic interventions that attenuate presynaptic vHIP over-activation in addition to targeting postsynaptic alterations in NAc may constitute more effective treatment strategies.

Methods

Experimental animals. Male 6–8 week-old C57BL/6J mice, and 6-month-old CD1 retired breeders, were maintained on a 12-h light-dark cycle (lights on at 0700 hours) at 22–25°C with ad libitum access to food and water. C57 mice were housed 5 per cage except following defeat experiments and after fiber implantation surgery at which point mice were singly housed. All experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee at Icahn School of Medicine at Mount Sinai. All behavioural testing occurred during the animals’ light cycle. Experimenter was blinded to experimental group and order of testing was counterbalanced during behavioural experiments and across days for electrophysiology experiments. For in vivo LTD experiments (Fig. 2), animals were randomized within cages before surgery. For acute stimulation experiments (Fig. 3), groups were matched on post-defeat social interaction scores to generate two groups randomized within cages before surgery. For acute stimulation experiments (Fig. 3), groups were matched on post-defeat social interaction scores to generate two groups with equivalent means and variance.

RNA isolation and qPCR. Mice were killed 48 h after CSDS (see below), brains were removed, coronally sliced and mPFC, vHIP and AMY tissue was rapidly dissected and frozen on dry ice. RNA isolation, qPCR and data analyses were performed as described. Briefly, RNA was isolated with TRIzol reagent (Invitrogen) and purified with RNAeasy micro kits from Qagen. All RNA samples were determined to have 260/280 and 260/230 values ≥ 1.8. Reverse transcription was performed using iScript (BioRad). qPCR using SYBR green (Quanta) was carried out with an Applied Biosystems 7900HT RT–PCR system with the C(t) method. qPCR primers: Egr1 FWD: 5’-GAGGAAGTGTGGCCAGGA GTG-3’, Egr1 REV: 5’-GAGTAGAAGGAGTGCCCAGG-3’; Arc FWD: 5’-GAAG TGTTGGAGGTACAGGC-3’, Arc REV: 5’-TTCCGTACCACTCAG-3’. Values of conditions tested (control versus susceptible or resilient mice) using the ΔΔC(t) method were ΔΔC(t) method values presented as described. Briefly, RNA was isolated with TRIzol reagent (Invitrogen) and purified with RNAeasy micro kits from Qagen. All RNA samples were determined to have 260/280 and 260/230 values ≥ 1.8. Reverse transcription was performed using iScript (BioRad). qPCR using SYBR green (Quanta) was carried out with an Applied Biosystems 7900HT RT–PCR system with the C(t) method. qPCR primers: Egr1 FWD: 5’-GAGGAAGTGTGGCCAGGA GTG-3’, Egr1 REV: 5’-GAGTAGAAGGAGTGCCCAGG-3’; Arc FWD: 5’-GAAG TGTTGGAGGTACAGGC-3’, Arc REV: 5’-TTCCGTACCACTCAG-3’. Immunohistochemistry. Forty-eight hours after CSDS (see below), mice were anaesthetized with chloral hydrate and transcardially perfused with 0.1% PBS followed by 4% paraformaldehyde in PBS. Brains were postfixed overnight and then cryopreserved in 30% sucrose. Brains were sectioned on a freezing microtome at 35 μm. Sections were rinsed three times in PBS and blocked in 4% normal

Figure 3 | Acute stimulation of vHIP versus mPFC or AMY terminals in NAc promotes opposite behavioral responses to CSDS. (a). Schematic of experimental time course. Representative traces validating that 4 Hz stimulation of vHIP (b) (scale bar 200 pA, 1 s), mPFC (c) (scale bar 50 pA, 1 s) and AMY (d) (scale bar 50 pA, 1 s) terminals in NAc slices evokes EPSCs. Blue squares indicate light pulse delivery. In vivo, 4 Hz stimulation of vHIP terminals in NAc shell (e) reduced time spent interacting with a target mouse (F1,39 = 4.274 interaction effect, P < 0.05, post hoc P < 0.05, n = 20, 21) and (h) increased time spent in corners (F1,39 = 6.560 target effect, F1,39 = 4.271, stimulation effect, P < 0.05, post hoc P < 0.05, n = 20, 21). Stimulation of mPFC terminals in NAc (f) increased time spent interacting with a target mouse (F1,26 = 9.174 stimulation effect, P < 0.01, post hoc P < 0.01, n = 13, 15) and (i) decreased time spent in corners (F1,26 = 7.735, P < 0.01, post hoc P < 0.05, n = 13,15). Stimulation of AMY axons in NAc (g) increased time spent interacting with a target mouse (F1,14 = 5.4284 interaction effect, P < 0.01, post hoc P < 0.01, n = 8) but (j) did not affect time spent in corners. Two-way repeated-measures ANOVAs with Bonferroni post hoc tests. ‘No stim’ and ‘4 Hz’ denote non-stimulated controls versus 4 Hz stimulated mice. ‘No target’ and ‘Target’ indicate absence or presence of a target mouse during testing. Error bars represent s.e.m.
donkey serum (NDS) with 0.5% Triton-X in PBS (PBST) for 2 h at room temperature. Sections were then incubated in primary antibodies overnight at 4 °C (chicken anti-CaMKIIa (Aivis, A-284, S; Cell Signaling, 1:1,000) in PBST). Sections were then washed three times in PBST and incubated with secondary antibodies (donkey anti-rabbit Cy3, donkey anti-chicken Alexa Fluor 488; 1:500, Jackson Immunoresearch) for 2 h at room temperature. Sections were then washed three times in PBS. Hoechst stain (Invitrogen) was added to the final wash for 25 min. Sections were washed one final time before mounting and coverslapping with ProLong Gold (Invitrogen).

**Stereotaxic surgery and viral vectors.** Adenoassociated virus (AAV) vectors expressing channelrhodopsin-2 (ChR2) fused with enhanced yellow fluorescent protein (EYFP) under the control of the CaMKIIa promoter (AAV5–CaMKIIa–ChR2–EYFP) were used for optical activation of glutamatergic afferent terminals of NAc (mPFC, vHIP, and AMY). CaMKIIa expression is specific to excitatory glutamatergic neurons29. To take advantage of this property in viral vectors, CaMKIIa has been shown to target such neurons30,31. AAV5–CaMKIIa–ChR2–EYFP and AAV5–CaMKIIa–EYFP were purchased from the University of North Carolina Vector Core. To label neurons projecting to NAc, retrograding AAV2/5–CaMKIIa–EYFP purchased from University of Pennsylvania Viral Core was infused into NAc. (Note that AAV2/5 expresses a different serotype than the AAV5 vectors used in this study.) Sections were then incubated in primary antibodies overnight at 4 °C in 2% donkey serum (NDS) with 0.5% Triton-X in PBS (PBST) for 2 h at room temperature. Sections were then incubated in primary antibodies overnight at 4 °C. Sections were washed three times in PBST, Hoechst stain (Invitrogen) was added to the final wash for 25 min. Sections were washed one final time before mounting and coverslapping with ProLong Gold (Invitrogen).

**In vivo optogenetic stimulation.** Custom optical fiber patch cords attached to implanted fibers46 with ceramic zirconia sleeves (Precision Fiber Products) were connected using an FC connector and to a 473-nm blue laser diode (OEM Laser Systems; 100 mW) and a stimulator to generate blue light pulses. LFS to induce LTD consisted of 10 min, 1 Hz, 4 ms pulse width 15–20 mW, 473 nm stimulation 45 min before social interaction testing. In separate experiments, synaptic transmission was acutely increased during behavioural testing using 4 Hz, 5 ms pulse width, 15–20 mW 473 nm stimulation. This stimulation protocol has previously been shown to reliably modulate synaptic transmission by ChR2-expressing glutamatergic terminals in NAc12. Comparison of EYFP-injected stimulated controls and ChR2-injected non-stimulated controls showed no differences in social interaction behaviour (Supplementary Fig. 5).

**CSDS and social interaction.** All experiments utilized an established CSDS protocol to induce depressive-like behaviours in mice4. C57BL/6 J mice were subjected to 10 daily, 5-min defeats by a novel CD1 aggressor mouse and were then housed across a plexiglass divider to allow for sensory contact. Control mice were housed in cages separated from other control mice by a plexiglass divider and were rotated to a different cage daily. Resident and susceptible mice were identified by their respective preference for, or avoidance of, interaction with a novel mouse after 10 days of defeat in a social interaction test. In vivo optogenetic experiments used the entire population of defeated mice and did not specifically select for resilient or susceptible to facilitate the detection of bidirectional shifts in social interaction behaviour. Social-avoidance behaviour was assessed with a novel CD1 mouse in a two-stage social-interaction test. In the first 2.5-min test (no target), the experimental mouse was allowed to freely explore an arena (44 × 44 cm) containing a plexiglass anodized membrane wall (12 cm). For the second 2.5-min test (target), the experimental mouse was returned to the arena with a novel CD1 mouse enclosed in the plexiglass wire mesh cage. Time spent in the ‘interaction zone’ (14 × 26 cm) surrounding the plexiglass wire mesh cage, ‘corner zones’ (10 × 10 cm) and ‘distance travelled’ within the arena was measured by video tracking software (Ethisoft 5.0, Noldus). We utilized a single-forced swim paradigm as extensively used and validated in mice5.
Statistics. No statistical methods were used to predetermine sample sizes but sample sizes are consistent with those reported in previous publications from our laboratory and sufficient for the types of experiments. Variance was similar between groups being statistically compared and data were normally distributed supporting the use of parametric statistics. Some animals or data points were lost in the course of social defeat, due to cage-flooding post-surgery, loss of fiber implant or equipment failure during behavioural testing. Grabov’s test was used to identify and remove significant outliers from qPCR data. qPCR and paired-pulse data were analysed by one-way ANOVA and social interaction data were analysed by two-way repeated measures ANOVA. In all instances, Bonferroni post-hoc tests were used to resolve significant main effects or interactions. In one-way designs all pairwise comparisons were tested and in two-way repeated measures designs the effect of the between subjects variable was compared at each level of the within subjects variable. Two group comparisons (open field and forced swim test) were analysed by unpaired two-tailed Student’s t-tests. Significance was set at P<0.05 for all tests and only comparisons with P<0.05 are explicitly reported. Detailed statistics are provided in figure legends. All data expressed as mean ± s.e.m.

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and M.H.H. provided reagents and technical training necessary to perform the research; R.C.B. & E.J.N. wrote the paper.

**Additional information**

**Supplementary Information** accompanies this paper at http://www.nature.com/naturecommunications

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Corrigendum: Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression

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In the original version of this Article, the middle initial of the author Joseph F. Cheer was omitted from the author information. The affiliation details for this author were also incorrect. These errors have now been corrected in both the PDF and HTML versions of the article.