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doi:10.1038/nature13976

β-catenin mediates stress resilience through Dicer1/microRNA regulation

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β-catenin is a multi-functional protein that has an important role in the mature central nervous system; its dysfunction has been implicated in several neuropsychiatric disorders, including depression. Here we show that in mice β-catenin mediates pro-resilient and anxiolytic effects in the nucleus accumbens, a key brain reward region, an effect mediated by D2-type medium spiny neurons. Using genome-wide β-catenin enrichment mapping, we identify *Dicer1*—important in small RNA (for example, microRNA) biogenesis—as a β-catenin target gene that mediates resilience. Small RNA profiling after excising β-catenin from nucleus accumbens in the context of chronic stress reveals β-catenin-dependent microRNA regulation associated with resilience. Together, these findings establish β-catenin as a critical regulator in the development of behavioural resilience, activating a network that includes Dicer1 and downstream microRNAs. We thus present a foundation for the development of novel therapeutic targets to promote stress resilience.

Despite decades of research, the molecular pathophysiology of depression remains elusive. One molecular player implicated in neuropsychiatric illnesses, including depression, is β-catenin[1–5]. In addition to having a structural role at synapses, β-catenin mediates the transcriptional output of canonical Wnt signalling[6–8]. This multi-functionality has made it difficult to untangle the mechanism through which β-catenin might contribute to pathological states. We recently demonstrated the involvement of upstream Wnt signalling in the nucleus accumbens (NAc) in mouse depression models, with impaired signalling mediating susceptibility to social stress and increased signalling mediating resilience[9]. We thus began by studying the behavioural role of β-catenin in this brain region.

β-catenin mediates resilience and anxiolytic responses

We overexpressed β-catenin in a herpes simplex virus (HSV) vector in NAc (Fig. 1a; Extended Data Fig. 1a), which increases β-catenin solely in the nuclear compartment, as measured by subcellular fractionation and immunohistochemistry (IHC), whereas global N-cadherin/β-catenin complexes were unaffected (Extended Data Fig. 1b, c). This suggests that HSV-β-catenin selectively activates the transcriptional function of the protein, without having direct effects on N-cadherin at synapses, consistent with earlier work in cultured cells[10].

We next overexpressed β-catenin in NAc during accelerated social defeat stress (ASD)[11,12]. We found that, while HSV-GFP injected control animals developed social avoidance, an indicator of depression-like behaviour, overexpression of β-catenin prevented this phenotype (Fig. 1b). Furthermore, in baseline behavioural assays, β-catenin mediated an antidepressant-like response in the forced swim test (FST) (Fig. 1c), and anxiolytic effects in the elevated plus maze (EPM) (Fig. 1d). We saw no changes in sucrose preference or cocaine conditioned place preference (data not shown), suggesting that β-catenin does not cause hedonic changes. To confirm the pro-resilient effect of β-catenin, we used a stabilized β-catenin mutant (S33Y)[13], and found identical results for wild-type β-catenin in the ASD and FST (Supplementary Notes), with no change in sucrose preference (data not shown). Finally, cell-type-specific overexpression of β-catenin in D2- but not D1-type medium spiny neurons (MSNs) in NAc (Fig. 1e, Extended Data Fig. 2a) induced a pro-resilient phenotype.

We also investigated the consequences of blocking β-catenin signalling in NAc with two approaches: excising β-catenin from NAc of conditional floxed mice (Extended Data Fig. 2b) and overexpressing a behaviourally validated dominant negative β-catenin mutant (Extended Data Fig. 2c)[14]. Both manipulations promoted susceptibility to stress in mice subjected to a sub-threshold defeat procedure (Fig 1f, g). Excising β-catenin from NAc caused no change in social interaction or locomotion in control animals, demonstrating a specific association with stress (Extended Data Fig. 3a–c). These results establish a critical role for β-catenin signalling in NAc in behavioural resilience.

To explore the endogenous activity of β-catenin in depression, we examined its transcriptional activity in post-mortem NAc of depressed humans. Axin2, a universal readout of activated canonical β-catenin signalling, was robustly suppressed in NAc of depressed humans (Fig. 2a, Supplementary Table 1, Extended Data Fig. 4a). In contrast, total N-cadherin and β-catenin messenger RNA levels were unchanged, pointing specifically to β-catenin nuclear function alterations in depression. There was also suppression of Tcf3 and Tcf4 (T cell transcription factors 3 and 4) levels in depressed patients (Fig. 2a); these are two of several transcription factors through which β-catenin acts. Together, these data demonstrate downregulation of the transcriptional output of β-catenin in NAc in human depression.

We next investigated *Axin2* mRNA levels in mouse NAc 48 h after chronic social defeat stress (CSDS). We found no difference between

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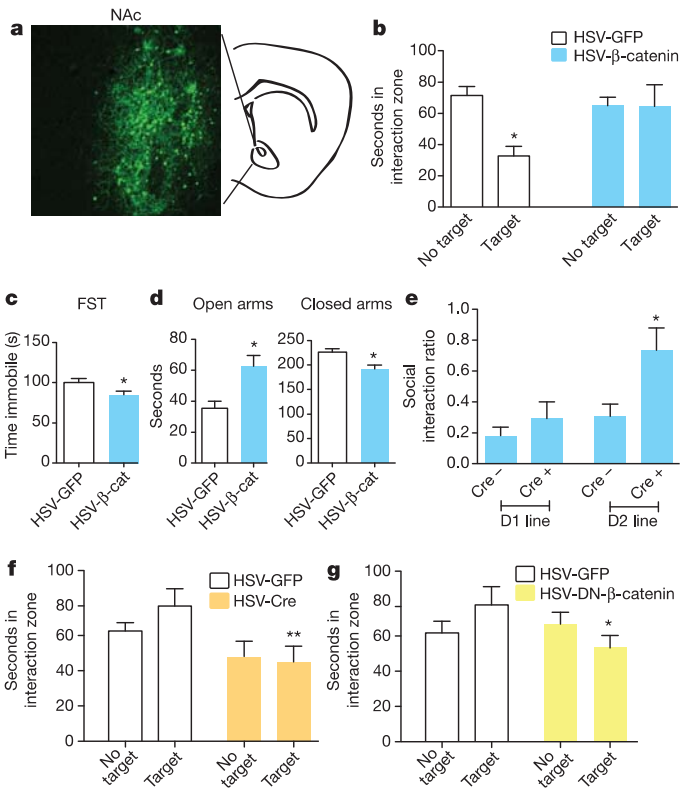

Figure 1 | β-catenin in NAc mediates pro-resilient, antidepressant, and anxiolytic responses. **a**, IHC illustrating viral transgene expression mediated by HSV-β-catenin with coronal cartoon of NAc highlighted. **b**, Pro-resilient effect of HSV-β-catenin on social interaction after ASD (*$P < 0.05$, two way ANOVA, $n = 8$ GFP, $n = 10$ β-catenin). **c**, Antidepressant-like effect of β-catenin in the forced swim test (*$P < 0.05$, two-tailed t-test, $n = 6$ GFP, $n = 7$ β-catenin). **d**, Anxiolytic-like effect of β-catenin in the elevated plus maze (closed arms: *$P < 0.01$, open arms: *$P < 0.01$, two-tailed t-test, $n = 6$ GFP, $n = 7$ β-catenin). **e**, Cell-type-specific overexpression of β-catenin in ASD (D2 Cre^- versus Cre^+: *$P < 0.05$, two-tailed t-test, $n = 13$ D2 Cre^-, $n = 8$ D2 Cre^+). **f**, Effect of knocking down β-catenin in a sub-threshold defeat procedure (**$P < 0.01$, two-way ANOVA, effect of virus only when target present, $n = 6$ GFP, $n = 5$ Cre). **g**, Effect of dominant negative β-catenin in sub-threshold defeat (*$P < 0.05$, two-way ANOVA, interaction effect, $n = 5$ GFP, $n = 4$ dominant negative). Data presented as mean and s.e.m. and are representative of at least two experiments. See Methods and Supplementary Table 9 for detailed statistics.

susceptible and resilient animals (Fig. 2b). However, resilient animals displayed increased Tcf3 and Tcf4, indicating that resilience may be associated with upregulation of β-catenin signalling (Fig. 2b). To probe this, we examined the levels of phospho-Ser 675 β-catenin, a form with enhanced transcriptional activity, as well as total β-catenin at this time point. We found upregulation in resilient versus susceptible animals of phospho-Ser 675 β-catenin but not total β-catenin (Extended Data Fig. 4b). At 10 days after CSDS, we found elevated levels of Axin2 in resilient mice only ($P < 0.05$, Supplementary Notes).

Cell-type-specific action of β-catenin in resilience

Given the small magnitude of change observed above, we questioned whether the cell-type-specific behavioural effects in Fig. 1e corresponded to differential regulation of β-catenin signalling in D2 versus D1 MSNs. Using fluorescence-assisted cell sorting-isolated NAc neurons from D2-GFP mice (whereby the D2 neurons are labelled with green fluorescent protein, GFP), we found robust induction of Axin2 expression in $D2^+$ neurons of resilient mice, and significantly reduced Axin2 levels in susceptible versus resilient mice, 48 h post CSDS, effects not seen in $D2^-$ cells (Fig. 2c). Furthermore, Axin2 IHC with D1- or D2-GFP transgenic mice subjected to CSDS revealed downregulation of β-catenin transcriptional activity in D2 versus D1 MSNs in susceptible mice (Fig. 2d). In sum, upregulation of β-catenin signalling occurs in D2 MSNs in resilient mice, with downregulation seen in susceptible animals.

Because glutamatergic neurotransmission regulates β-catenin transcriptional activity and stress susceptibility[15,16], we tested whether medial prefrontal cortex (PFC) or hippocampus, two important glutamatergic inputs to NAc, control β-catenin signalling in NAc. Using previously validated constructs and stimulation protocols[17,18], we found that optogenetic stimulation of glutamatergic PFC terminals robustly suppressed β-catenin activity in NAc as indicated by decreased Axin2, Tcf3, and Tcf4, whereas stimulation of hippocampus terminals had no effect (Fig. 2e, f). Repeated burst firing of dopamine afferents from the ventral tegmental area (VTA) also had no effect (Extended Data Fig. 5). Thus, PFC to NAc stimulation specifically elicited a molecular 'signature' of susceptibility, indicating that activation of this circuit could mediate the maladaptive suppression of β-catenin activity in NAc.

Genome-wide mapping of β-catenin after social defeat

We next conducted β-catenin chromatin immunoprecipitation followed by deep sequencing (ChIP-seq) on NAc of control, susceptible, and resilient mice after CSDS. We first validated our β-catenin ChIP protocol by examining an LEF/TCF consensus sequence in the promoter of a known β-catenin target gene, *CaMKIV* (also known as *Camk4*). We found enrichment of β-catenin at the LEF/TCF site, but not a distant site, in NAc of resilient mice only (Fig. 3a). Through ChIP-seq[19,20] we then examined global β-catenin enrichment after CSDS, and found major differences in peak numbers (Fig. 3b, Supplementary Data 1). Control and resilient conditions were associated with 10–15-fold higher absolute peak numbers compared to susceptible conditions, suggesting profound global alterations in β-catenin activity, consistent with our biochemical data (Fig. 2). Enrichment of β-catenin in resilient animals (Fig. 3b) only occurred at transcriptionally active sites, as indicated by high basal binding of two transcriptional activation marks H3K4me3 and H4K16ac (Fig. 3c, Extended Data Fig. 6). However, we did not observe global changes in these two histone marks after CSDS (Extended Data Figs 7, 8), suggesting that β-catenin may be recruited to active, open regions of chromatin through the presence of other, direct DNA-binding transcription factors.

Using Ingenuity pathway analysis, we demonstrated a predicted β-catenin network to be upregulated in NAc of resilient versus susceptible mice (Extended Data Fig. 9), a prediction specific to β-catenin. Concomitantly, there were nearly twice as many increases as decreases in β-catenin binding in resilient versus control mice at promoter regions. In contrast, susceptible versus control animals displayed equivalent numbers of upregulated and downregulated β-catenin binding events (Fig. 3d). These results support our hypothesis that resilience is associated with genome-wide enrichment of β-catenin. Examining the distribution of β-catenin peaks across the genome (Fig. 3e) revealed similar results: redistribution of β-catenin binding towards promoters and gene bodies in resilience, and redistribution away from promoters/gene bodies and towards gene deserts in susceptibility.

To validate the β-catenin ChIP-seq data, we conducted quantitative ChIP (qChIP) on independent biological samples at genes that showed significant peaks in resilience or upregulation in resilient versus susceptible animals, thus confirming significant β-catenin enrichment at several promoters (Fig. 3f). As further validation, we examined mRNA levels of genes found in our ChIP-seq list that coincided either with *in silico* lists of predicted or known β-catenin targets[21,22] (Supplementary Table 2) or with the H3K4me3 and H4K16ac ChIP-seq data sets (Supplementary Data 2). We found robust upregulation of many of these genes in NAc of resilient mice (Fig. 3g).

Regulation of Dicer1 and microRNA by β-catenin

One gene validated by qChIP and quantitative PCR (qPCR) was *Dicer1*, a critical component of microRNA (miRNA) biogenesis[23]. Thus, selective enrichment of β-catenin binding at *Dicer1* in resilient mice (Fig. 4a),

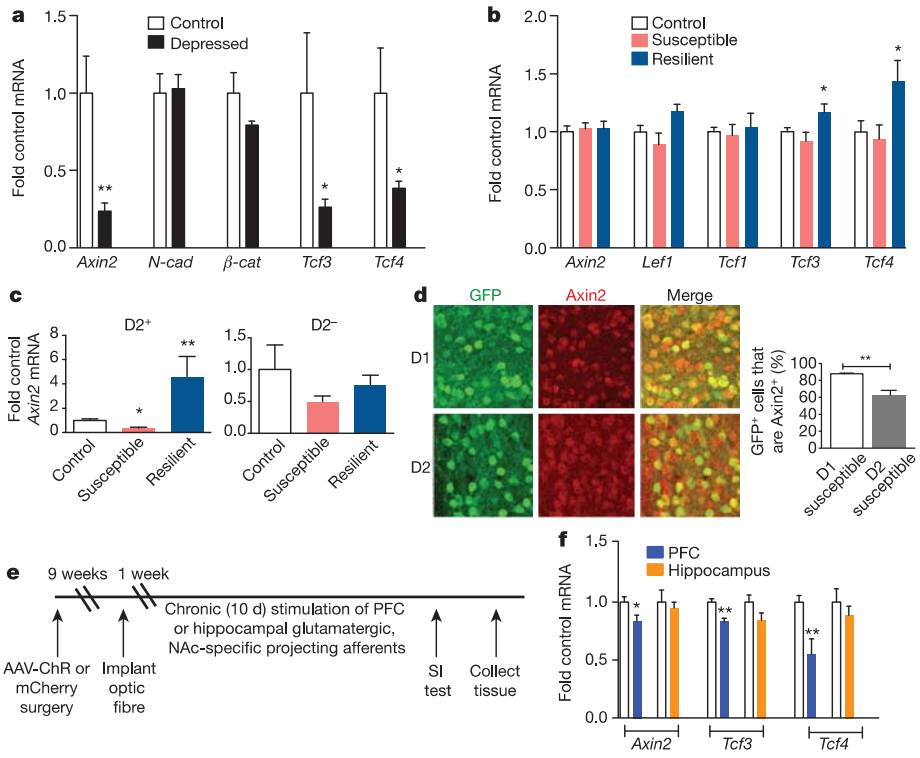

Figure 2 | Regulation of β-catenin signalling in human depression and mouse CSDS. **a**, mRNA from human NAc (*Axin2*: $^{**}P < 0.01$; *Tcf3*: $^{*}P < 0.05$; *Tcf4*: $^{*}P < 0.05$, two-tailed *t*-test, $n = 6$ control, $n = 10$ depressed). **b**, mRNA from mouse control, susceptible, and resilient NAc 48 h post CSDS (*Tcf3*: $^{*}P < 0.05$; *Tcf4*: $^{*}P < 0.05$, one-way ANOVA, $n = 16$ control, $n = 12$ susceptible, $n = 9$ resilient). **c**, *Axin2* is upregulated in $D2^{+}$ MSNs only in resilience (*Axin2* $D2^{+}$:$^{**}P < 0.01$, control versus resilient $P < 0.05$, $^{*}P < 0.01$ susceptible versus resilient, $n = 4$ control, $n = 5$ susceptible, $n = 3$ resilient; *Axin2* $D2^{-}$: not significant, $P > 0.05$, $n = 3$ control, $n = 5$ susceptible, $n = 3$ resilient, one-way ANOVA). **d**, Percentage of cells positive for Axin2 plus GFP in D1- or D2-GFP susceptible mice after CSDS ($^{**}P < 0.01$, two-tailed *t*-test, $n = 3$ per group). **e**, Optogenetic stimulation protocol. **f**, mRNA expression in NAc after repeated stimulation from PFC or hippocampus in ChR2 versus mCherry (*Axin2*: $^{*}P < 0.05$, $n = 6$ mCherry, $n = 5$ ChR; *Tcf3*: $^{**}P < 0.01$, $n = 6$ mCherry; $n = 4$ ChR; *Tcf4*: $^{**}P < 0.01$, $n = 6$ mCherry, $n = 4$ ChR, two-tailed *t*-test). Human data are from one experiment, all other data are representative of at least two experiments. All data presented as mean and s.e.m.

and subsequent validation of this effect (Fig. 3f, g), indicated that *Dicer1* represents a robust target of β-catenin in NAc. To study the behavioural effects of Dicer1, we knocked it down locally in NAc (Extended Data Fig. 10), and conducted sub-threshold defeat. Control animals injected with HSV-GFP displayed normal social interaction; however, animals with Dicer1 knockdown demonstrated social avoidance (Fig. 4b), which mimicked the effects of blocking β-catenin signalling (Fig. 1). Importantly, we can rule out confounding effects of long-term Dicer1 loss on neuronal viability[24], because our experimental paradigm was limited to two weeks.

To assess whether the behavioural effect of Dicer1 was related to β-catenin signalling, we first expressed HSV-Cre or HSV-GFP in NAc of floxed *Dicer1* mice and found no difference in social interaction under baseline, non-stressed conditions (Fig. 4c). We then injected all mice with HSV-β-catenin in NAc and subjected them to ASD. β-catenin overexpression blocked the development of social avoidance in mice

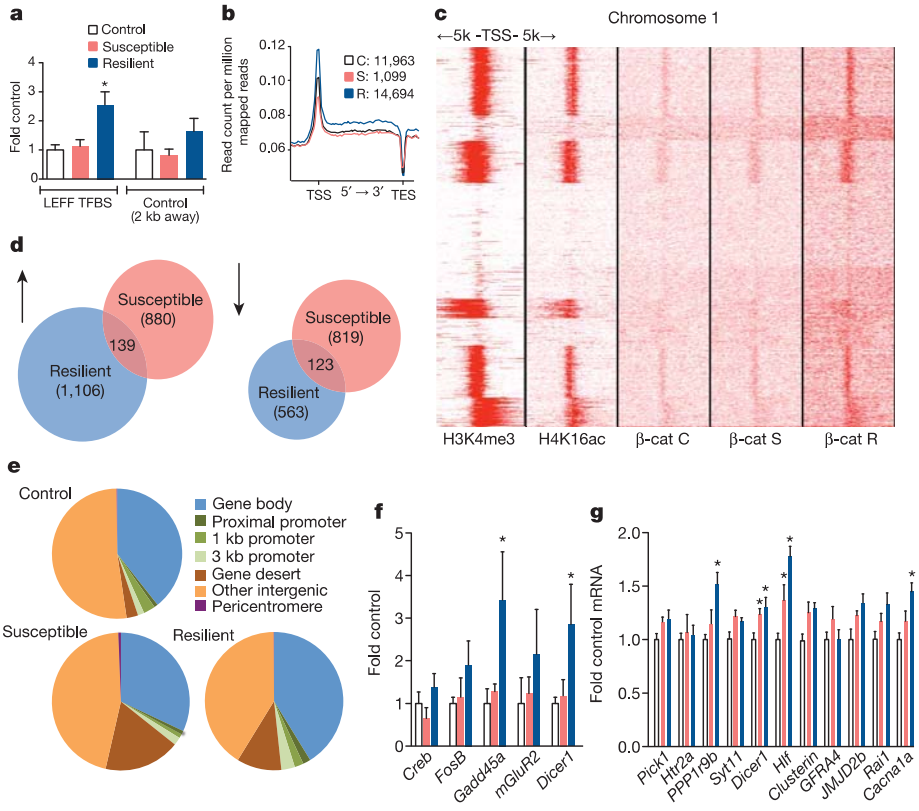

Figure 3 | β-catenin ChIP-seq in NAc 48 h post CSDS. **a**, qChIP validation of β-catenin ChIP ($^{*}P < 0.05$, one-way ANOVA, post-hoc test control versus resilient and susceptible versus resilient at LEFF transcription factor binding site (TFBS) of a CaMKIV gene, $n = 4$ per group). **b**, Plot of β-catenin binding across genic regions. TSS, transcription start site; TES, transcription end site. Individual peak numbers per condition indicated in inset. **c**, Heat map showing β-catenin binding 5 kb up- and downstream of TSSs on chromosome 1 in control (C), susceptible (S), and resilient (R) NAc; binding profiles of H3K4me3 and H4K16ac under basal conditions are also shown. **d**, Number of increased (up arrow) versus decreased (down arrow) β-catenin binding sites at promoters in resilient versus control or susceptible versus control conditions. **e**, Genome-wide distribution of β-catenin binding. **f**, qChIP validation of ChIP-seq (*Gadd45a*: $^{*}P < 0.05$, one-way ANOVA; *Dicer1*: $^{*}P < 0.05$, one-way ANOVA, $n = 4$ control, susceptible, $n = 3$ resilient). **g**, mRNA validation of β-catenin ChIP-seq (*Dicer1*: $^{*}P < 0.01$, one-way ANOVA, $n = 13$ control, $n = 11$ susceptible, $n = 7$ resilient). Data presented as mean and s.e.m. and are representative of at least two experiments. Colour-coding in **f** and **g** as in **a**.

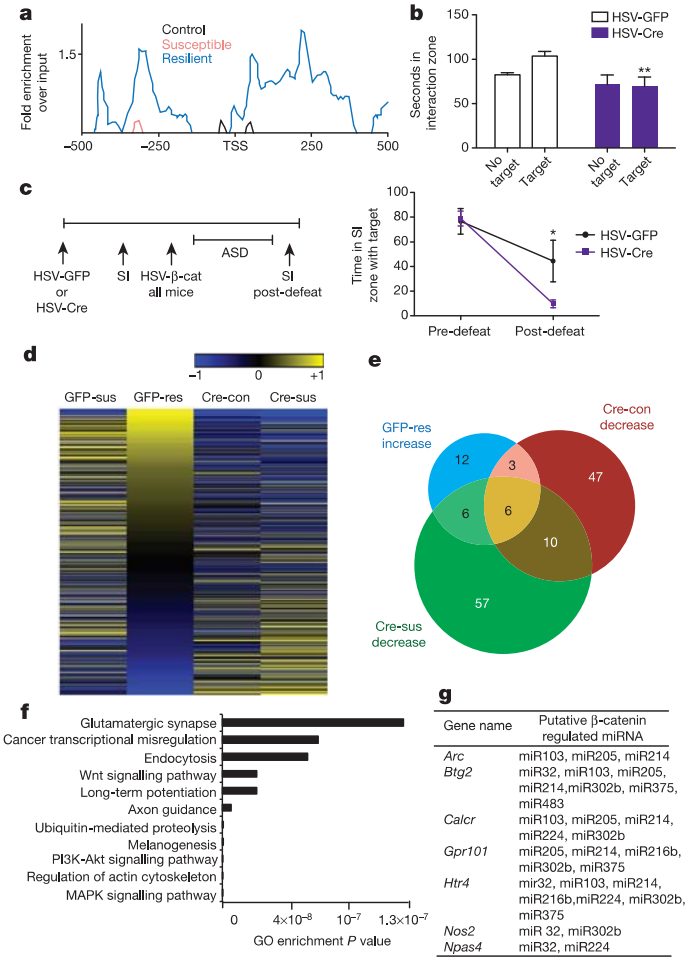

Figure 4 | Dicer1 bridges β-catenin and miRNA regulation in CSDS. **a**, β-catenin ChIP-seq enrichment around the Dicer1 TSS. **b**, Effect of NAc Dicer1 knockdown (HSV-Cre) in sub-threshold defeat with HSV-GFP as control (**$P < 0.01$, effect of virus, two-way ANOVA, $n = 7$ Cre, $n = 8$ GFP). **c**, Left, schematic of floxed Dicer1 deletion followed by β-catenin rescue; right, social interaction (SI) before and after ASD with HSV-β-catenin (*$P < 0.05$, interaction effect, matching two-way ANOVA, $n = 7$ per group). **d**, Heat map of CSDS-regulated miRNA expression changes with (Cre) or without (GFP) β-catenin knockdown. Log_2-fold changes of all altered miRNAs among all groups are shown. **e**, Venn diagram showing increased miRNAs in GFP-resilient mice (GFP-res) overlap with decreased miRNAs in β-catenin knockout in non-stressed (Cre-con) or susceptible (Cre-sus) animals. **f**, Top 11 most enriched gene ontology terms of target genes of overlapping miRNAs in panel **e**. **g**, Predicted targets of β-catenin-dependent miRNAs display downregulation by mRNA-seq in resilient mice after CSDS. Data presented as mean and s.e.m. and are representative of at least two experiments.

expressing normal Dicer1 levels, but not in mice with NAc Dicer1 knockdown (Fig. 4c). This indicates that at least part of the pro-resilient effect of β-catenin is mediated through Dicer1.

Finally, these data prompted us to examine the global miRNA profile in NAc in response to CSDS and study its dependence on β-catenin. We injected an adeno-associated virus (AAV) vector expressing GFP or Cre in NAc of floxed β-catenin mice, subjected them to CSDS or control conditions, and performed small RNA sequencing (Supplementary Table 3). We first compared each group—GFP susceptible (GFP-sus), GFP resilient (GFP-res), Cre control (Cre-con), and Cre susceptible (Cre -sus)—to the 'GFP-con' condition. We could not study the Cre resilient condition, because virtually no mice are resilient upon β-catenin knockout from NAc. We found downregulation of numerous miRNAs, including many that were upregulated in resilience, when β-catenin was knocked out from control animals (Cre-con, Fig. 4d, Supplementary Table 4). Interestingly, a smaller subset of miRNAs was upregulated following β-catenin knockout, which may represent miRNAs that are regulated by repressive factors under β-catenin control. We identified 66 miRNAs that were significantly downregulated in NAc after β-catenin deletion (Cre-con, Fig. 4e). We also identified downregulated miRNAs ($n = 79$) in the Cre-sus condition, many of which were decreased in Cre-con, further substantiating our hypothesis that pro-adaptive miRNA responses are lost in the absence of β-catenin, enhancing susceptibility to stress (Fig. 4e). miRNAs that overlapped between any two groups (up in GFP-res, but down in Cre-con or Cre-sus), presumably represent the most biologically important β-catenin- and stress-regulated miRNAs (Fig. 4e, Supplementary Table 5). This subset controls several meaningful gene categories (Fig. 4f), including Wnt and glutamatergic signalling. Finally, to identify potential miRNA targets, we overlapped predicted targets of these β-catenin-regulated miRNAs (Supplementary Table 5) with mRNA-seq data from NAc after CSDS. We thus found several interesting, novel genes to be significantly repressed in resilience (Fig. 4g).

We also examined other small RNAs for regulation by CSDS. Piwi-interacting RNAs (piRNAs), small RNAs widely studied in germ line cells, were detected recently in brain and found to play a functional role in spine morphology and synaptic plasticity[25,26]. 163 piRNAs were detectable in our data set with read counts in at least one condition, supporting the notion of piRNA expression in brain (Supplementary Table 6). Although the majority of them were expressed at low levels, approximately 20 piRNAs appear to be regulated by CSDS (Supplementary Table 7). Examining additional small RNA categories that might be regulated by Dicer1 revealed several differentially expressed candidates (Supplementary Table 8), laying the groundwork for future investigation.

Discussion

The present study demonstrates that β-catenin in D2 MSNs activates a network in NAc that mediates behavioural resilience, whereas deficits in this pathway contribute to depression-related pathology. PFC inputs to NAc appear to be particularly important in controlling this β-catenin regulation. D2 MSNs, which comprise the indirect or 'no-go' pathway[27–30], may be more important for mediating flexible behavioural choices in aversive contexts compared to reward-motivated behaviour[31–33]. We thus posit that enhanced β-catenin signalling in NAc D2 MSNs of resilient mice permits increased behavioural flexibility, which allows them, despite having the same experience as susceptible mice, to overcome generalizing avoidance of all mice, a process independent of hedonic responses. This has parallels in humans: resilient individuals are more successful at managing stress and recovering from it[34].

Our β-catenin ChIP-seq approach provides a valuable resource for mining the molecular targets that drive resilience. One validated target is Dicer1, which establishes a novel connection between β-catenin signalling and miRNAs in brain. Among the regulated miRNAs are those that feedback and regulate β-catenin signalling[35]. The cell type-specific role of β-catenin, and the inherent complexity of stress susceptibility versus resilience, which involves many additional regulatory steps beyond Dicer1, presumably explains the relatively small number of β-catenin-dependent miRNAs observed in this study. miRNAs provide a crucial layer of post-transcriptional gene regulation in neural development, plasticity, and in an increasing number of brain disorders[36–38]. The present study, by identifying specific miRNAs associated with stress susceptibility or resilience, offers a template for future studies to induce resilience in inherently more susceptible individuals.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Received 12 August 2013; accepted 20 October 2014.
Published online 12 November 2014.

1. Madsen, T. M., Newton, S. S., Eaton, M. E., Russell, D. S. & Duman, R. S. Chronic electroconvulsive seizure up-regulates β-catenin expression in rat hippocampus: role in adult neurogenesis. *Biol. Psychiatry* **54,** 1006–1014 (2003).

2. Beaulieu, J.-M. *et al.* Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc. Natl Acad. Sci. USA* **101,** 5099–5104 (2004).
3. Gould, T. D. *et al.* Beta-catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors. *Neuropsychopharmacology* **32,** 2173–2183 (2007).
4. Li, X. & Jope, R. S. Is glycogen synthase kinase-3 a central modulator in mood regulation? *Neuropsychopharmacology* **35,** 2143–2154 (2010).
5. Brennand, K. J. *et al.* Modelling schizophrenia using human induced pluripotent stem cells. *Nature* **473,** 221–225 (2011).
6. Behrens, J., von Kries, J., Kühl, M. & Bruhn, L. Functional interaction of β-catenin with the transcription factor LEF-1. *Nature* **382,** 638–642 (1996).
7. Molenaar, M. *et al.* XTcf-3 transcription factor mediates β-catenin-induced axis formation in *Xenopus* embryos. *Cell* **86,** 391–399 (1996).
8. van de Wetering, M. *et al.* Armadillo coactivates transcription driven by the product of the *Drosophila* segment polarity gene dTCF. *Cell* **88,** 789–799 (1997).
9. Wilkinson, M. B. *et al.* A novel role of the WNT-dishevelled-GSK3β signaling cascade in the mouse nucleus accumbens in a social defeat model of depression. *J. Neurosci.* **31,** 9084–9092 (2011).
10. Sadot, E. *et al.* Regulation of S33/S37 phosphorylated β-catenin in normal and transformed cells. *J. Cell Sci.* **115,** 2771–2780 (2002).
11. Berton, O. *et al.* Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* **311,** 864–868 (2006).
12. Krishnan, V. *et al.* Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* **131,** 391–404 (2007).
13. Kolligs, F. T., Hu, G., Dang, C. V. & Fearon, E. R. Neoplastic transformation of RK3E by mutant β-catenin requires deregulation of Tcf/Lef transcription but not activation of c-*myc* expression. *Mol. Cell. Biol.* **19,** 5696–5706 (1999).
14. Wang, Z. *et al.* β-catenin promotes survival of renal epithelial cells by inhibiting Bax. *J. Am. Soc. Nephrol.* **20,** 1919–1928 (2009).
15. Rada, P. *et al.* Glutamate release in the nucleus accumbens is involved in behavioral depression during the Porsolt swim test. *Neuroscience* **119,** 557–565 (2003).
16. Abe, K. & Takeichi, M. NMDA-receptor activation induces calpain-mediated β-catenin cleavages for triggering gene expression. *Neuron* **53,** 387–397 (2007).
17. Tye, K. M. *et al.* Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature* **471,** 358–362 (2011).
18. Britt, J. P. *et al.* Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* **76,** 790–803 (2012).
19. Feng, J. *et al.* Chronic cocaine-regulated epigenomic changes in mouse nucleus accumbens. *Genome Biol.* **15,** R65 (2014).
20. Shen, L. *et al.* diffReps: detecting differential chromatin modification sites from ChIP-seq data with biological replicates. *PLoS ONE* **8,** e65598 (2013).
21. Hödar, C. *et al.* Genome-wide identification of new Wnt/β-catenin target genes in the human genome using CART method. *BMC Genomics* **11,** 348 (2010).
22. Wexler, E. M. *et al.* Genome-wide analysis of a Wnt1-regulated transcriptional network implicates neurodegenerative pathways. *Sci. Signal.* **4,** ra65 (2011).
23. Bernstein, E., Caudy, A. A., Hammond, S. M. & Hannon, G. J. Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature* **409,** 363–366 (2001).
24. Cuellar, T. L. *et al.* Dicer loss in striatal neurons produces behavioral and neuroanatomical phenotypes in the absence of neurodegeneration. *Proc. Natl Acad. Sci. USA* **105,** 5614–5619 (2008).
25. Lee, E. J. *et al.* Identification of piRNAs in the central nervous system. *RNA* **17,** 1090–1099 (2011).
26. Rajasethupathy, P. *et al.* A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. *Cell* **149,** 693–707 (2012).
27. Graybiel, A. M. The basal ganglia. *Curr. Biol.* **10,** R509–R511 (2000).
28. Gerfen, C. R. The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annu. Rev. Neurosci.* **15,** 285–320 (1992).
29. Kravitz, A. V., Tye, L. D. & Kreitzer, A. C. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nature Neurosci.* **15,** 816–818 (2012).
30. Lobo, M. K. & Nestler, E. J. The striatal balancing act in drug addiction: distinct roles of direct and indirect pathway medium spiny neurons. *Front. Neuroanat.* **5,** 41 (2011).
31. Hikida, T., Kimura, K., Wada, N., Funabiki, K. & Nakanishi, S. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. *Neuron* **66,** 896–907 (2010).
32. Darvas, M. & Palmiter, R. Contributions of striatal dopamine signaling to the modulation of cognitive flexibility. *Biol. Psychiatry* **69,** 704–707 (2011).
33. Yawata, S., Yamaguchi, T., Danjo, T., Hikida, T. & Nakanishi, S. Pathway-specific control of reward learning and its flexibility via selective dopamine receptors in the nucleus accumbens. *Proc. Natl Acad. Sci. USA* **109,** 12764–12769 (2012).
34. Southwick, S. M. & Charney, D. S. The science of resilience: implications for the prevention and treatment of depression. *Science* **338,** 79–82 (2012).
35. Veronese, A. *et al.* Mutated β-catenin evades a microRNA-dependent regulatory loop. *Proc. Natl Acad. Sci. USA* **108,** 4840–4845 (2011).
36. Kosik, K. S. The neuronal microRNA system. *Nature Rev. Neurosci.* **7,** 911–920 (2006).
37. Im, H.-I. & Kenny, P. J. MicroRNAs in neuronal function and dysfunction. *Trends Neurosci.* **35,** 325–334 (2012).
38. Issler, O. *et al.* MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. *Neuron* **83,** 344–360 (2014).

Supplementary Information is available in the online version of the paper.

Acknowledgements We thank O. Jabado and M. Mahajan for support and S. Borkan for providing β-catenin constructs. This work was supported by grants from the National Institute of Mental Health and the Hope for Depression Research Foundation (HDRF).

Author Contributions C.D. and J.F. conceived the project, designed research, conducted experiments, interpreted the results, and wrote the manuscript; H.S., M.S.M.-R., D.D.-W., K.S., R.B., B.L., E.R., P.K., V.V., D.F., C.P., E.C., J.K. and E.M. conducted experiments; S.G., C.T. provided reagents and tools; R.N. conducted experiments and provided reagents; N.S., X.L. performed bioinformatic analysis; L.S. performed and supervised bioinformatic analysis; E.J.N. conceived the project, designed and supervised research, interpreted the results, and wrote the manuscript. All authors discussed the results and commented on the manuscript.

Author Information All sequencing data have been deposited into the Gene Expression Omnibus with accession numbers GSE61294 and GSE61295. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to E.J.N. (eric.nestler@mssm.edu) or L.S. (li.shen@mssm.edu).