Supplementary Methods

Human Studies

Sample

Of the patients included in our three previous GWASs, Operational Criteria Checklist for Psychotic Illness (OPCRIT (1)) data were available for 480 patients with schizophrenia (2), 641 patients with bipolar disorder (3), and 597 patients with major depression (4). All patients were recruited from consecutive hospital admissions. A DSM-IV (5) diagnosis was assigned in all patients using a consensus best-estimate procedure (6). This was based on multiple scales (7) including the OPCRIT checklist and the German version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I (8)). Over 96% of the patients reported that their parents or grandparents had been born in Germany. A detailed description of the recruitment procedures and phenotype characterization is provided elsewhere (2-4). The 1300 control subjects were drawn from three population-based epidemiological studies, as described elsewhere (9-11). The study protocol was approved by the Ethics Committees of the Faculties of Medicine of the Universities of Bonn and Heidelberg, and written informed consent was obtained from all participants following a detailed explanation of the study. All participants were genotyped using HumanHap550v3 BeadArrays and the Infinium II assay (Illumina, San Diego, CA, USA).

Clinical assessment

Symptoms were coded according to the OPCRIT version 3.3.2 (1). The OPCRIT is a polydiagnostic 90-item checklist that was designed for genetic research within the context of a collaborative study of the European Science Foundation. In the present study, the checklist was

rated by a trained psychologist or psychiatrist according to the information contained in the SCID-I (8) and the clinical records. All ratings were life-time.

The 90 OPCRIT variables were reduced to 69 by excluding all items referring to: data collection (items 1, 2, 84, and 86); demographic variables (item 3); premorbid characteristics (items 6, 7, 9-11); potential etiological correlates (items 12-16); or description of chronological course (items 4, 5, 8, 52, 87-90) (12). The remaining 69 variables were included in a Principle Component Analysis. In contrast to other rating scales, the OPCRIT has neither a positive nor a negative symptom subscale, either of which might bias symptom rating. Factors derived from OPCRIT ratings are therefore less likely to be statistical artifacts of scale development.

Statistical analysis

For the statistical analyses, we used the Statistical Package for the Social Sciences, Windows Version (SPSSW version 16.0, SPSS Inc., 2007). Missing data for the 69 OPCRIT items varied from approximately 4.2% (persecutory delusions) to 21% (diminished libido) (mean=6.5%). Diminished libido was often rated as missing since it was difficult to exclude the possibility that it was a side-effect of medication. Missing values were replaced by the median for that item, taking into account the ordinal characteristic of the OPCRIT data. A total of 69 OPCRIT items referring to symptoms entered the analysis as variables and the variables were later transformed to a binary scale using a value of 0 (symptom not present) or 1 (symptom present). Following this correction for missing data, principal component analysis was conducted on the 69 OPCRIT items for the combined sample, using the method of Dikeos et al. (12). The three sub-samples (bipolar disorder, schizophrenia, and major depression) were then analyzed separately. Since the principal component analysis was based on binary rather than continuous data, the resulting

components should be considered a transformation of the data, and their exploratory character should be kept in mind. Spearman correlation was used to compare factor dimensions derived from the three sub-samples. The scree test was used to determine the number of factors to be included in the model (13). The rationale of the scree test is that the battery of variables measures a limited number of factors well, and a larger number of trivial, specific, and error factors inaccurately. By computing the eigenvalues for the correlation matrix and plotting them in descending order of value along the ordinate with the eigenvalue number as the abscissa, a straight edge can then be laid across the lower eigenvalues, where they form an approximately straight line. The point at which the eigenvalue plot curves above the straight line formed by the lower values indicates the number of factors. The scree test has been shown to be a good determinant of the correct number of substantive factors in data for which the total number of underlying factors is known (13). Components extracted by the scree test are considerably easier to interpret than those extracted by the commonly used Kaiser-Guttman criterion (14). Principal component analyses of OPCRIT symptoms that are based on the Kaiser-Guttman criterion tend to generate an excessively large number of factors, which are often characterized by only one symptom (15). In contrast, the scree test tends to slightly underestimate the adequate factor number (14). We adopted the common cut-off for size of loading to be interpreted of 0.32 (10% of shared variance between variable and factor) (16)**.** The component solutions were extracted under both orthogonal (varimax) and oblique (direct oblimin) rotations. Correlations between factors resulting from the oblique rotation were examined further to define the most appropriate form of rotation for the data.

First, we compared the mean factor scores across the diagnostic groups using the Kruskal Wallis H test, taking into account the non-normal distribution of the factor scores. We then applied the Mann-Whitney-U test to determine which dimension scores were enhanced in risk allele carriers compared to non-carriers. The Mann-Whitney-U test was performed under the assumption of a dominant model. The AA and AG genotypes were combined, since the frequency of the AA genotype in the individual diagnostic groups was low.#An overview of the association signals of *NCAN* with bipolar disorder, schizophrenia, and major depression is provided in ST1. The Cochran Armitage test was used for these association analyses, as implemented in the 1.06 version of PLINK (17) (see http://pngu.mgh.harvard.edu / ~purcell/plink/).

Derived Factor Dimensions

The varimax and direct oblimin factor solutions of the combined sample were very similar. Low correlations were observed between factors generated under the oblique model assumptions (correlation factors ranged from -0.150 to 0.222), suggesting that the factors could be treated as orthogonal. Factor solutions on imputed missing data did not differ from solutions calculated on the original data. Therefore only the results of the varimax rotation on imputed missing data were considered.

Although sixteen factors displayed eigenvalues greater than unity, the scree plot suggested a five-factor solution. The Kaiser-Meyer-Olkin (KMO) measures the covariance of variables and indicates whether principal component analysis is reasonable, and values above 0.9 indicate variables that are suitable for factor analysis. In our data, the KMO sampling adequacy was 0.909. The five-factor solution explained 38.3% of the total variance in the combined sample. In

the subsamples, both KMO (bipolar disorder=0.777; schizophrenia=0.739; major depression=0.616) and the explained variance (bipolar disorder=28.74%; schizophrenia=29.32%; major depression=26.66%) were slightly lower. The factors dimensions derived from the combined sample can be considered to represent *reality distortion, mania, depression, disorganization,* and *drug abuse/dependence*, as shown in ST2. Factor loadings above the threshold of 0.32 were considered substantial. This symptom structure, including the factor dimensions *reality distortion, mania, depression, disorganization,* and *abuse/dependency,* was observed very consistently in each of the diagnostic groups, although the *disorganization* factor dimension was not present in the bipolar disorder sample. The four consistently observed factor dimensions were comprised of similar items in all three diagnostic subsamples. Their correlations were significant (P= 0.01), and ranged from 0.406 to 0.796**.**

For the five factor dimensions derived in the combined sample, the mean scores differed significantly between the three diagnostic groups (P<0.001): (i) bipolar disorder patients scored highly on the *mania* and the *depression* dimensions; schizophrenia patients scored highly on the *disorganization*, the *reality distortion*, and the *abuse/dependency* dimensions; and (iii) major depression patients scored highly on the *depression* and the *disorganization* dimensions.

Refinement analysis

Of the five symptom dimensions derived in the combined sample, only the scores on the mania dimension were significantly elevated in risk allele carriers. This association withstood Bonferroni correction for multiple testing for the five dimensions tested. To refine the mania dimension, we included items with high loadings (defined as ≥ 0.32) on that dimension in a

subsequent principal component analysis. In the combined sample, none of the derived subdimensions fulfilled the Kaiser-Guttman criterion. This means that the subdimensions derived in the combined sample did not explain more of the variance in manic items than any single manic item, rendering the inclusion of the subdimensions unfeasible. Therefore a principal component analysis was performed in each diagnostic group separately in order to dissect out the mania dimension.

For bipolar disorder and schizophrenia, refinement of the mania dimension resulted in three subdimensions (irritability, overactivity, and grandiosity). For major depression, the mania dimension was refined to four subdimensions (irritability, overactivity, grandiosity, and self-esteem). Analyses were then performed to identify association between these derived subdimensions and the NCAN risk genotype. In the bipolar disorder sample, no significant differences in manic subdimensions were found between risk allele carriers and non-carriers. However, in the schizophrenia sample, a significant difference in factor scores for the subdimension overactivity was observed between risk allele carriers and non-carriers (Mann–Whitney U=22100.5, n1=162, n2=318, p=0.015, multiple testing corrected for three subdimensions tested). In major depression patients, a trend towards association with the subdimension overactivity was observed (Mann–Whitney U=34699, n1=180, n2=417, p=0.052, multiple testing corrected for the four subdimensions tested). The main items of the overactivity subdimension were excessive activity, elevated mood, a reduced need for sleep, and reckless activity (Table 1). Although differences for the overactivity subdimension did not reach statistical significance in the bipolar disorder sample, risk allele carriers showed higher scores on the overactivity subdimension (Mann–Whitney U=45618.5, n1=223, n2=414, p=0.395).

We then explored whether the risk allele was associated with overactivity in the combined sample, rather than only in individual diagnostic groups. An overactivity subdimension was constructed by a principal component analysis of the four items excessive activity, elevated mood, a reduced need for sleep, and reckless activity. Risk allele carriers differed significantly from non-carriers in the combined sample (Mann–Whitney U=261529, n1=523, n2=1062, p=0.015). We further explored whether subdimensions constructed on irritability and grandiosity items were associated with the NCAN risk genotype. Only the subdimension overactivity was associated with the NCAN risk genotype.

The bipolar disorder sample had limited power for the analysis of the overactivity subdimension, since overactivity is a core dimension of bipolar disorder and nearly all patients with bipolar disorder displayed overactivity symptoms (62 showed the highest possible scores). Therefore we postulated that the non significant finding in this diagnostic sample may have been due to a ceiling effect in bipolar disorder.

Additionally, since bipolar disorder patients did not differ in terms of manic subdimensions, we investigated whether the association signals with schizophrenia (P= 0.00041, OR=1.44) and major depression (P= 0.0419; OR=1.22) were mainly attributable to patients with high loadings on manic subdimensions (results see ST4). #

Animal Studies

Mice

The generation of Ncan$^{-/-}$ mice on C57BL/6J has been described elsewhere (18). Ncan $^{-/-}$ and

Ncan$^{+/+}$ male and female littermates aged 8-10 weeks were used in all experiments. Mice were housed in groups of three to five on a 12h/12h reversed light/dark cycle with full spectrum daylight lamps (LifeLite®, best-lite Neu Eichenberg, Germany). The conditions were 200 lux during the day and no light during the dark period (9 to 21h); 19–21 °C; and 30–50% humidity. Animals received food and water *ad libitum* unless otherwise specified. Animal procedures followed the guidelines of the German Animal Protection Legislation, and the Local Committee for Animal Health (LANUV NRW) approved the experiments.

Behavioral tests

Open Field

Locomotor activity was investigated in a dimly illuminated (20 lux at the ground level of the arena) and sound-attenuated room. Each mouse was placed in the center of the open field arena (45 x 45 x 22 cm). The animals were monitored by a video camera that was connected to a computer operated video tracking software (TSE Systems GmbH, Germany). Total distance travelled (in minutes) and time spent in the center (seconds) were measured and evaluated by repeated measurements two-way ANOVA. Data were collected over a period of 30 minutes. The open field arenas were wiped and allowed to dry between mice.

Home cage motor activity

Home cage behavior was recorded using an infrared sensor connected to a recording and data storing system (Mouse-E-Motion by Infra-e-motion, Henstedt-Ulzburg, Germany; separation distance 1.5 cm). A sensor was positioned on each 21 x 21 x 24 cm cage. Mouse movements were sampled every second and averaged over 30 minutes. Recordings were made for a total of

48 hours over two consecutive days. Groups were compared using repeated measurements two-way ANOVA.

Elevated Zero Maze

The elevated zero maze consisted of an annular white platform (inner diameter 46 cm; inner width 5.6 cm) which was elevated 40 cm above ground level and divided into four equal quadrants. The two opposite quadrants were enclosed by white walls (height 13 cm) on both edges of the platform. The behavior of the mice was videotaped using a camera fixed above the maze and analyzed with a video-tracking system (Videomot, TSE Systems, Bad Homburg, Germany). We evaluated time spent in the open area, distance travelled in the open and closed parts, and number of visits. The maze was cleaned with wet and dry paper towels between mice. Data were analyzed using one-way or two-way ANOVA.

Elevated Plus Maze

The elevated plus-maze consisted of two open arms (38.5 x 5 cm) and two enclosed arms of the same size (height of walls 15 cm). The arms extended from a common central platform (5 x 5 cm). They were elevated to a height of 39 cm above the floor. Arms of the same type were arranged opposite to each other. Each mouse was placed in the central square of the maze facing one of the open arms. Mouse behavior was recorded over a period of 5 minutes. We measured the number of entries into-, and the time spent in the open and closed arms. The maze was cleaned with wet and dry paper towels between mice. Groups were compared using Student's t-test.

Porsolt forced swim test

Mice were placed in a Plexiglas cylinder (internal diameter 10 cm; height 50 cm) filled with a 40cm high column of water (23-24°C). Immobility time was measured between the second- and the sixth minute of the test. A mouse was judged to be immobile when it remained floating in the water, making only those movements necessary to keep its head above the water (19, 20). The water was changed between mice. Data were analyzed using one-way or two-way ANOVA, followed by Fisher's least-significant-difference post hoc test.

Saccharin Preference

The mice remained individually housed for seven days prior to- and 8 days after the start day. We followed the procedure described previously with minor changes (21). Briefly, on the first day, we replaced the water bottles with two identical bottles. These were fitted with bottle stoppers containing two-balled sipper tubes. The positions of the bottles were switched daily to avoid a side bias, and the fluid consumed from each bottle was measured daily. On the first two days, both bottles were filled with drinking water (w/w). On the next two days, both bottles were filled with a solution of 0.1% saccharin dissolved in drinking water. On days 5 to 9, one bottle contained 0.1% saccharin and the other contained drinking water. Preference for saccharin was expressed as the amount of saccharin consumed divided by the total (saccharin plus water) liquid consumption. Groups were compared using repeated measurements two-way ANOVA.

Lithium treatment

Lithium was administered to the mice as described previously (21). Briefly, lithium chloride (Sigma-Aldrich) was mixed into the drinking water at a dose of 220 mg/kg/day and administered for a minimum of 10 days. Control mice received drinking water only.

Pre-pulse Inhibition (PPI)

The startle response apparatus (TSE Systems GmbH, Germany) consisted of a cage (11 x 5.5 x 6 cm) with metal bars on the floor (4 mm diameter, 6 mm apart), located on a vibration-sensitive platform in a ventilated, sound-attenuated chamber. Two 7 cm speakers, located on either side and 3 cm from the cage, delivered the background white noise (65 dB) and the startle-eliciting signal of 120 dB 12 kHz 40 ms. A pre-pulse signal (12 kHz 16 dB above the background noise) preceded the startle-eliciting signal by 100 ms. Five-five startle signals, with and without pre-pulse, were used in a random order after five minutes habituation. Data were analyzed using two-way ANOVA, followed by Fisher's least-significant-difference post hoc test.

Marble burying

The marble burying test was performed in a polypropylene box (21 x 21 x 24 cm), in which 16 glass marbles (diameter 2.3 cm, ordered 4 x 4) were spaced evenly over the bedding. Mice were placed individually in a cage and left undisturbed for 15 minutes. The number of unburied marbles was counted every 3 minutes. Data were analyzed using two-way ANOVA, followed by Fisher's least-significant-difference post hoc test.

Amphetamine

D-amphetamine (Sigma-Aldrich, St. Lewis, MI) was dissolved in saline. Mice received a single intraperitoneal injection of amphetamine (2 mg/kg, 10 ml/kg) or saline (10 ml/kg). After a baseline period of 30 minutes, amphetamine- or vehicle-induced locomotor activity was monitored during 30 minutes in the open field arena described above. Data were analyzed using two-way ANOVA, followed by Fisher's least-significant-difference post hoc test.

Statistical Analysis

All statistical analyses were performed using Statistica software (version 7.2, Statsoft Hamburg, Germany). Data are shown as means ±s.e.m. The significance level was set at $p < 0.05$.

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TABLE S1. Association signalling of *NCAN* in the present samples compared with previous studies.

Samples	N Patients	P-value TREND	OR
Bipolar disorder [1]	2,411	$3.02*10^{-8}$	1.31
Bipolar disorder reanalysis	641	$8.792*10^{-7}$	1.58
Schizophrenia [2]	464	0.0015	1.38
Schizophrenia reanalysis	480	0.00041	1.44
Major depression[3]	597	0.0419	1.22
Major depression reanalysis	597	0.0419	1.22

1=(3); 2=(2); 3=(4)
TREND, Cochran-Armitage test
OR, Odds Ratio

TABLE S2. Animal Number and Sex Distribution Across the Behavioral Tests

	$Ncan^{+/+}$ Mice		$Ncan^{-/-}$ Mice	
Behavioral Test	Male	Female	Male	Female
Baseline home cage	5	5	5	5
Baseline saccharin preference	5	5	5	5
Baseline open field	6	4	5	5
Baseline Porsolt	5	5	5	5
Baseline zero maze	6	4	5	5
Porsolt control	6	4	5	5
Porsolt lithium	4	6	6	4
Marble burying control	5	5	5	5
Marble burying lithium	6	4	6	4
Psychomotor stimulation control/vehicle	5	5	5	5
Psychomotor stimulation control/amphetamine	6	4	4	6
Psychomotor stimulation lithium/vehicle	4	6	5	5
Psychomotor stimulation lithium/amphetamine	4	6	5	5
PPI control	6	4	5	5
PPI lithium	6	4	6	4

TABLE S3. Five-factor solution. Item loadings after varimax rotation.

Item	*Reality Distortion*	*Mania*	*Depression*	*Disorganization*	*Abuse/Dependence*
Bizzare Behavior	**0.504**	0.181	-0.074	**0.435**	0.022
Catatonia	0.283	0.028	0.066	**0.310**	-0.096
Excessive Activity	-0.081	**0.890**	0.016	-0.018	-0.030
Reckless Activity	-0.057	**0.730**	-0.022	-0.013	0.005
Distractibility	0.075	**0.734**	0.008	0.068	0.058
Reduced Need for Sleep	-0.080	**0.858**	0.030	-0.030	-0.065
Agitated Activity	0.030	0.295	0.215	0.160	0.033
Slowed Activity	0.045	0.096	**0.509**	0.075	-0.108
Tiredness	-0.108	-0.003	**0.652**	-0.054	-0.070
Speech Difficult to Understand	0.232	0.227	-0.118	**0.481**	0.170
Incoherence	0.202	0.305	0.001	**0.393**	0.092
Positive Formal Thought Disorder	0.302	**0.359**	-0.083	**0.390**	0.137
Negative Formal Thought Disorder	**0.507**	-0.058	0.021	**0.439**	-0.062
Pressured Speech	-0.069	**0.852**	0.017	-0.008	-0.001
Thoughts Racing	0.002	**0.827**	-0.010	-0.003	0.006
Restricted Affect	0.293	0.128	0.078	**0.428**	-0.072
Blunted Affect	0.142	-0.047	-0.064	**0.393**	-0.042
Inappropriate Affect	0.268	0.176	-0.080	**0.425**	0.013
Elevated Mood	-0.087	**0.857**	0.031	-0.049	-0.038
Irritable Mood	0.157	**0.606**	0.038	0.219	0.020
Dysphoria	-0.135	0.047	**0.628**	-0.166	0.038
Diurnal Variation	-0.125	0.003	**0.531**	-0.078	-0.100
Loss of Pleasure	-0.220	0.017	**0.679**	-0.160	-0.022
Altered Libido	-0.063	-0.004	**0.416**	-0.098	-0.023
Poor Concentration	0.107	0.020	**0.401**	0.038	0.026
Excessive Self Reproach	-0.112	0.106	**0.418**	-0.152	0.078
Suicidal Ideation	0.057	0.027	**0.368**	-0.152	0.084
Initial Insomnia	-0.024	-0.051	**0.471**	0.009	-0.005
Middle Insomnia	-0.067	-0.145	**0.488**	-0.002	0.001
Early Morning Awakening	-0.188	0.028	**0.427**	-0.046	0.009
Excessive Sleep	0.169	0.266	0.109	-0.036	-0.003
Poor Appetite	-0.228	-0.097	**0.512**	0.002	0.081

Weight Loss	-0.128	0.039	**0.389**	0.038	0.052
Increased Appetite	0.113	0.223	-0.002	-0.263	0.086
Weight Gain	0.074	0.179	-0.021	-0.275	0.096
Increased Sociability	0.056	**0.682**	0.026	0.185	0.033
Persecutory Delusion	**0.678**	0.185	-0.139	0.189	0.028
Organised Delusion	**0.660**	0.029	-0.073	0.173	-0.014
Increased Self Esteem	0.095	**0.767**	-0.029	-0.013	0.030
Grandiose Delusion	0.252	**0.524**	-0.039	0.009	0.083
Delusion of Influence	**0.643**	0.186	-0.129	0.125	0.059
Bizarre Delusion	**0.520**	0.091	-0.080	0.192	0.090
Widespread Delusion	**0.718**	-0.020	-0.123	0.213	0.003
Delusion of Passivity	**0.543**	0.133	-0.051	0.031	0.164
Primary Delusional Perception	**0.696**	0.122	-0.082	0.177	0.011
Other Primary Delusions	**0.716**	0.074	-0.071	0.222	-0.007
Delusion & Hallucination lasting for 1 Week	**0.784**	0.010	-0.147	0.091	0.047
Persecutory Delusion & Hallucinations	**0.775**	-0.030	-0.110	0.073	-0.027
Thought Insertion	**0.537**	0.018	-0.146	-0.082	0.137
Thought Withdrawal	**0.460**	-0.031	-0.130	-0.094	0.203
Thought Broadcast	**0.540**	0.030	-0.053	-0.051	0.155
Delusions of Guilt	0.249	0.082	0.144	0.037	-0.003
Delusions of Poverty	-0.007	0.090	0.157	0.080	-0.067
Nihilistic Delusions	0.126	0.010	0.027	0.127	-0.002
Thought Echo	0.304	0.018	-0.133	-0.026	0.088
Third Person Auditory Hallucinations	**0.681**	-0.046	-0.082	0.051	-0.043
Running Commentary Voices	**0.704**	-0.034	-0.074	0.038	-0.016
Abusive/Accusatory/Persecutory Voices	**0.661**	-0.089	-0.053	0.030	-0.036
Other Auditory Hallucinations	**0.696**	0.004	-0.066	0.070	0.019
Non-affective Hallucination in any Modality	**0.740**	0.012	-0.023	0.071	-0.002
Alcohol Abuse/Dependence	0.041	0.076	0.023	-0.036	**0.540**
Cannabis Abuse/Dependence	0.208	-0.004	-0.077	0.025	**0.629**
Other Abuse/Dependence	0.064	-0.049	0.032	0.038	**0.646**
Alcohol Abuse/Dependency with Psychopathology	-0.041	0.059	0.059	0.015	**0.571**
Cannabis Abuse/Dependency with Psychopathology	0.087	0.020	-0.052	0.053	**0.700**
Other Abuse/Dependency with Psychopathology	0.034	0.002	0.017	0.062	**0.688**
Information not Credible	-0.060	0.019	-0.114	**0.384**	0.083
Lack of Insight	0.086	0.071	-0.236	**0.494**	0.171

Rapport Difficult	0.090	-0.014	-0.104	**0.600**	0.063

Bold type indicates the item loadings that contribute to each factor

TABLE S4. Comparison of behavioral phenotypes between Ncan knockout mice and previously described mouse models of mania

Behavioral assay	Ncan	GluR6	Clock	Erk1	Gsk-3β	Bcl-2
Less anxious or more risk-taking type behavior	Yes	Yes	Yes	Yes	n.t.	n.t.
Open field overactivity	Yes	Yes	Yes	Yes	Yes	n.t.
Home cage overactivity	Yes	Yes	n.t.	Yes(a)	n.t.	n.t.
More aggressive during social interaction	n.o.	Yes	n.t.	n.t.	n.t.	n.t.
Increased locomotor response to amphetamine	Yes	Yes	n.t.	Yes	n.t.	Yes(b)
Less despair-type manifestations in the forced swim test	Yes	Yes	Yes	Yes	Yes	n.t.
Increased reward-seeking behavior for sucrose	Yes	n.t.	Yes	Yes	n.t.	Yes
Pre-pulse inhibition	Yes	n.t.	n.t.	n.t.	a.s.r.	n.t.
Marble burying	Yes	n.t.	n.t.	n.t.	n.t.	n.t.
Response to lithium treatment	Yes	Yes	Yes	Yes	n.t.	Yes

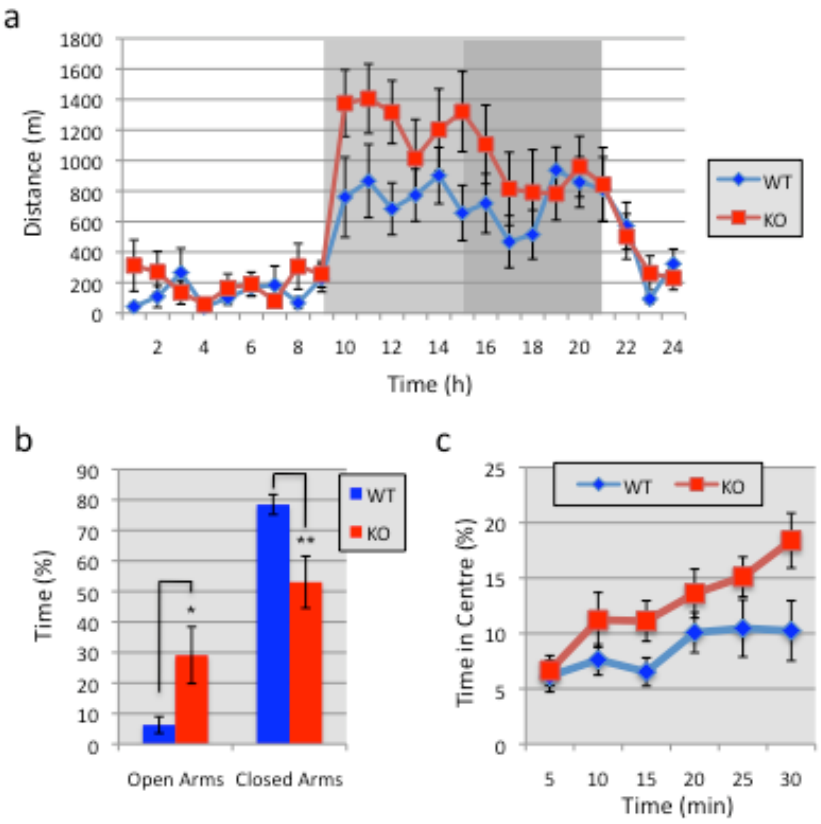
(a) : Home cage voluntary wheel running
(b) : Yes for amphetamine sensitization, but not for acute amphetamine
a.s.r.: Increased acoustic startle response at 100, 105 and 110 dB
n.t.: not tested

TABLE S5. Association with *NCAN* in patients with schizophrenia or major depression, based on their scoring on the *overactivity* subdimensions.

Samples	N Patients	P-value FISHER	OR
Schizophrenia *overactive*	335	0.00033	1.51
Schizophrenia *nonoveractive*	145	0.176	1.26
Major depression *overactive*	546	0.015	1.28
Major depression *nonoveractive*	51	0.2828	0.69

Overactive scoring above 0 on the *overactivity* subdimensions; *nonoveractive* scoring less than 0 on the *overactivity* subdimension; FISHER; Fisher's exact test

FIGURE S1. Ncan$^{-/-}$ mice showed increased activity in the home cage as well as lower anxiety levels and increased risk-taking behavior.



(*a*) Home cage activity was monitored on a second consecutive day (for day 1, see Figure 1b). During the active phases, Ncan$^{-/-}$ mice initially displayed higher locomotor activity than Ncan$^{+/+}$ mice. This later declined until similar levels were observed in both groups (genotype effect in the first half of the active phases, F=8.1, df=1, 18, p=0.011). During the inactive light phase, the activity profiles did not differ between the two genotypes. Dark phase: 9-21h; light phases: rest of the 24 h period. Gray areas represent the first and the second halves of the active phases. (*b*) In the elevated plus maze, Ncan$^{-/-}$ mice spent more time in the open arms of the elevated plus maze (F= 6.2, df=1, 16, p= 0.024), and less time in the closed arms (F=8.6, df=1, 16, p=0.010), with no difference in the number of visits (open arms, F=2.5, df=1, 16, p=0.13, closed arms, F=0.4, df=1, 16, p=0.530). (*c*) In the open field test, the time spent in center of the arena by Ncan$^{-/-}$ mice did not reach significance (F=3.6, df=1, 18, p=0.073). Blue squares or bars: Ncan$^{+/+}$ mice (WT). Red squares or bars: Ncan$^{-/-}$ mice (KO). Results are means±s.e.m. *: p≤0.05, **: p≤0.01.