SUPPLEMENTARY METHODS

Behavioral measures

Fear conditioning. In the conditioning procedure, mice were placed in the cage for 120 s, and then a pure tone (2.9 kHz) was played for 20 s, followed by a 2-s, 0.5-mA foot shock. This procedure was then repeated and 30 s after the delivery of the second shock, mice were returned to their home cage. To test sensitivity to pain and the innate freezing response, immediate post-shock freezing was quantified over 30 s and compared to the freezing behavior during the initial 30 s of the conditioning procedure, before the tone and shock had been administered. Freezing (i.e., complete immobility), the dominant behavioral fear response, was quantified by measuring movements automatically using predefined activity and time thresholds. The conditioning context was cleaned with 100% ethanol between each mouse. Twenty-four hours later, associative fear learning was assessed. To test hippocampal-dependent contextual fear conditioning, mice were placed in the original conditioning cage. The immediate freezing response, measured for 30 s, was quantified and compared with the first 30 s of the initial conditioning trial as well as with the immediate post-shock period. Two hours later, mice were tested for the hippocampal-independent auditory-cued fear conditioning by placing them in a different context, shaped as an opaque colorful pyramid with a smooth floor. As a control for the influence of the novel environment, freezing was measured for 30 s in this new environment. Two min later, the conditioning tone was played for 30 s, during which conditioned freezing was measured. The investigators were fully blinded to group allocation during the entire battery of behavioral experiments by using automated video tracking and scoring software.
Relationship between *Ahi1* expression and fear learning across the BXD recombinant inbred strains

*Curating neocortical Ahi1 expression profiles.* A search within the GeneNetwork for the *Ahi1* gene was performed across three datasets, BIDMC/UTHSC Dev Neocortex P3 ILMv6.2 (Nov11) RankInv Database, BIDMC/UTHSC Dev Neocortex P14 ILMv6.2 (Nov11) RankInv Database and HQF BXD Neocortex ILM6v1.1 (Dec10v2) RankInv Database, which depict neocortical expression profiles across 43 and 72 inbred mouse strains at P3, P14 and P60, respectively. The RNA probe that had the higher expression across all three datasets was chosen for further analysis (Supplementary Figure 1a online).

*Curating fear conditioning-related behavioral traits.* A search within the BXD Published Phenotypes Database using the key words 'context', 'contextual' and 'cue' was performed, and reports depicting behavioral traits related to fear conditioning were curated. For each report, a principal component (PC) analysis was then carried out in attempt to identify one synthetic trait that could account for most of the variance in the traits described by that specific report (Supplementary Figure 1b online).

*Correlating Ahi1 expression with fear conditioning.* Each PC trait (or individual trait in case there was only one relevant trait per report) was correlated with each of the three neocortical expression profiles (Supplementary Figure 1c online). Notably, prior to the correlation analysis, the list of strains for which behavior was measured was compared with that derived from the expression datasets. In order to assure reasonable power to detect significance of correlations, reports depicting behavioral traits, for which the overlap with the expression datasets encompassed less than 10 strains, were omitted from the correlation analysis.
Mapping QTLs that modulate Ahi1 expression and fear learning across the BXD recombinant inbred strains

Interval mapping. Interval mapping is a process in which the statistical significance of a hypothetical QTL is evaluated at regular points across a chromosome, even in the absence of explicit genotype data at those points. The results are expressed as logarithm of the odds (LOD) scores. This score represents the ratio of likelihoods of a statistical model that includes a genetic effect at a particular locus versus a model that does not include that effect (the null expectation). In the case of WebQTL, significance is calculated using an efficient and very rapid regression method, the Haley-Knott regression equations, in which trait values are compared to the known genotype at a marker or to the probability of a specific genotype at a test location between two flanking markers\(^1\). The three genotypes are coded as -1, 0, and +1 at known markers. The inferred probability of the genotypes in regions that have not been genotyped can be estimated from genotypes of the closest flanking markers.

eQTL mapping of neonatal neocortical Ahi1 expression. Following the methodology previously described\(^2-4\), linkage mapping of the early neocortical Ahi1 expression trait (measured at P3) to genotypes was performed using a set of single nucleotide polymorphisms (SNPs) and microsatellite markers by scripts at http://www.genenetwork.org/\(^5\). At each marker locus, a LOD score was calculated as described above. The significance threshold was set by a permutation test\(^6\) at the LOD value that corresponds to a 5% probability of falsely rejecting the null hypothesis that there is no linkage anywhere in the genome. The suggestive LOD threshold was defined as that which yields, on average, one false positive per genome scan\(^7\). The consistency with which peak LOD scores cluster around a putative eQTL was evaluated using the Bootstrap Test (2000 bootstraps). If the position of an eQTL is firm, the histogram of
“best eQTLs” (yellow bars in the maps) that is displayed in WebQTL maps will tend to have a sharp peak. The additive allele effect (shown by the red/green lines in these plots) provides an estimate of the change in the average mRNA expression that is brought about by substituting a single allele of one type with that of another type. The additive effect is half of the difference between the mean of all cases that are homozygous for one parental allele (aa) compared to the mean of all cases that are homozygous for the other parental allele (AA): \[
\frac{([\text{mean of } AA \text{ cases}] - [\text{mean of } aa \text{ cases}])/2}{2}.
\]

**Determining whether the major eQTL regulating neonatal Ahi1 expression also serves as a QTL for associative fear learning.** In order to determine whether the highly-significant eQTL regulating neonatal Ahi1 expression in the developing neocortex also serves as a QTL for associative fear learning in adulthood we used the single marker test, which considers an individual marker or SNP without regard to information about adjacent markers\(^4\). The single marker test can be as simple as a \(t\) test between two sets of expression values, where each set represents expression values for a distinct genotype\(^6\). In this case, the phenotypic means for the relevant fear conditioning PC traits were compared between strain groups homozygous for either parent allele (BB vs. DD) at the Ahi1 eQTL. In order to assure a minimally-adequate group size for performing independent samples \(t\) tests, reports depicting behavioral traits, for which the overlap with the genotyped marker dataset yielded less than eight phenotyped mice per each homozygous genotype category, were excluded from the current analysis.

**Identifying genes that share their single best eQTL with Ahi1.** Identification of genes that share a single best eQTL with Ahi1 was performed using an advanced search option within GeneNetwork’s [BIDMC/UTHSC Dev Neocortex P3 database](https://www.genenetwork.org) using the following script: \(LRS=(17.5, 900, 1, 66, 72)\), which was based on the following command: \(LRS=(\text{Low}_LRS\_\text{limit}, \text{High}_LRS\_\text{limit}, \text{ChrNN}, \text{Mb}\_\text{Low}\_\text{Limit}, \text{Mb}\_\text{High}\_\text{Limit})\). This
command finds all transcripts that have a single best QTL that is located on Chr (ChrNN) between Mb_Low_Limit and Mb_High_Limit in the LRS range of Low_LRS_limit to High_LRS_limit. The selection of a specific Low_LRS_limit was based on the whole-genome significant LRS value obtained for the Ahi1 transcript. LRS (likelihood ratio statistics) values can be directly converted to LOD scores by dividing by 4.61.

**Enrichment analysis.** Enrichment analysis based on GO terms was performed for the genes identified above using the WEB-based GEne SeT AnaLysis Toolkit (WebGestalt)\(^8\)\(^9\). The mmusculus__genome was chosen as the reference gene set. For the statistical analysis, the hypergeometric method was chosen. Minimum number of genes for a category was set at two. Significantly enriched GO terms (i.e., those with adjusted \(p< 0.05\)) were presented using REVIGO\(^10\).

**Generation of QTL heat maps.** QTL heat maps (also termed cluster maps) are a unique feature of GeneNetwork\(^11\). These heat maps are essentially sets of QTL maps for a group of traits that can be either mRNA expression traits, behavioral traits, or any combination of such traits. The QTL maps for the individual traits are run side by side to enable easy detection of common and unique QTLs. The genome location is shown along the long axis of the cluster map, marker by marker, from Chromosome 1 to Chromosome X. Colors are used to encode the probability of linkage, as well as the additive effect polarity of alleles at each marker. These QTL maps are computed using the fast Marker Regression algorithm. P values for each trait are computed by permuting each trait 1000 times. QTL heat maps could be considered trait gels because each lane is loaded with a trait that is run out along the genome. Using this feature, a heat map loaded with traits that represent both the gene transcripts that comprise the highly-enriched GO categories identified above and the relevant fear conditioning PC traits was created.
Resting state functional networks

Acquisition of fMRI data. The mice were anesthetized with isoflurane (~1.5% + 30 : 70 O2 : N2O). Respiration rates were monitored continuously and maintained between 55 and 65/min by small adjustments of the isoflurane concentration. Body temperature was kept stable (37 ± 1 °C) using a heating bed. Two-dimensional (2D) T2-weighted coronal images were acquired for anatomy. Functional blood oxygen level-dependent (BOLD) contrast MRI was collected with EPI-FID (TR=3.5, TE=20ms, 200 repetitions, matrix=128×128×12, FOV=1.8×1.8 cm², 1 mm slice width, 1.2 mm inter-slice gap, 90° flip angle and three sequential sets).

Graph-theory approach. In recent years, graph-theory-based complex network analysis, which describes important properties of complex systems by quantifying topologies of their respective network representations, has been increasingly used in the study of the functional and structural organization of the nervous system. Graph theory analysis of functional brain imaging data exploits the complexity of brain connections to characterize the overall functional architecture of the brain network. By treating the brain as one integrated network, this analysis asks whether the architecture of communication patterns within that network is altered under various conditions and disorders. For graph-theoretical analysis of neural networks through fMRI, anatomical brain regions are considered as nodes, linked by edges, which represent the connectivity measured by the temporal correlation of BOLD signal fluctuations between the nodes. Network integration and segregation are measured by the characteristic path length and the clustering coefficient, respectively. Networks which display a balance between these two measures are considered to be small-world networks, characterized by high local specialization (high clustering) and some global “shortcuts” (low path length), allowing fast information transfer with reduced energy expenditure. Small-world topology has
been described in human brain functional and structural networks\textsuperscript{15}. In fact, whole brain functional network analysis has been widely used to study human brain development and to detect alterations of brain function in a wide spectrum of brain disorders\textsuperscript{16}.

**Network analysis.** The topological properties of the networks derived by thresholding the matrix of inter-regional BOLD signal correlations depend on the choice of threshold value. If the threshold is high and the number of edges is low, the network will be sparsely connected and some regional nodes may be disconnected; if the threshold is low and the number of edges is high, the network will be more densely connected but will also have a random topology\textsuperscript{13}. Our first effort was therefore to define a range of thresholds that yielded fully connected networks with a small-world topology. After defining this range, analysis was performed in networks held at minimum density as well as in networks derived from parameters averaged (by the AUC approach) across densities, using the graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks\textsuperscript{17}. Networks were visualized using BrainNet Viewer, a network visualization tool for human brain connectomics\textsuperscript{18}. Notably, the anatomical and heat map visualizations included both positive and negative (anti) correlations, given an emerging understanding of the latter's biological meaning\textsuperscript{19}. However, the negative correlations were excluded from the graph-based analysis because of biological ambiguity in the context of this specific approach\textsuperscript{18}.

**Local and global network topology.** In contrast to anatomical networks, for functional networks, a set of regional network measures including node degree and local clustering coefficient are quantified per each individual network (i.e. mouse), rather than for a whole group of mice\textsuperscript{17}. Similarly, global network measures, such as global clustering, mean shortest path length, small-world index, assortativity and hierarchy are first quantified for each mouse individually and only then averaged. The clustering coefficient quantifies the number of connections that exist between the nearest
neighbors of a node as a proportion of the maximum number of possible connections\textsuperscript{13}.

Shortest path length is the minimum number of edges that must be traversed to go from one node to another. Averaging local network parameters then enables quantification of global network topology.

*Small world organization.* Small-world networks combine the highly segregation characteristic of regular networks with the high integration of random networks, thus seen as systems that are both globally and locally efficient\textsuperscript{20}. The small-world index is defined as the ratio of the clustering coefficient to the mean shortest path length after both metrics have been standardized by comparing their values to those in equivalent random networks. Thus, these networks are significantly more clustered than random networks but have approximately same characteristic mean shortest path length as random networks simultaneously\textsuperscript{13}. For each fully connected network, we calculated the small-world index $\sigma$, which provides a convenient summary of the small-world property of a network compared with equally sized random graphs: if $\sigma \gg 1$, the network in question displays the small-world property.

*Assortativity.* The assortativity coefficient is the Pearson correlation coefficient of degree between pairs of linked nodes\textsuperscript{21}. A degree correlation $\alpha$ which is close to 0 implies that the hubs of the network are not preferentially connected to each other, and this is a characteristic of a non-assortative network\textsuperscript{22} (Supplementary Figure 5a online). A positive value of degree correlation, $\alpha > 0$, indicates that nodes are likely to be connected to other nodes with the same degree and therefore that the high degree nodes or hubs of the network are likely to be connected to each other. This is characteristic of an assortative network (Supplementary Figure 5b online).

*Hierarchy.* The hierarchical structure of the networks was quantified by the $\beta$ coefficient, which is a parameter of the power-law relationship between the clustering coefficient $C$ and degree $k$ of the nodes in the network\textsuperscript{23}: $C \sim k^{-\beta}$. A large positive value
of $\beta$ means that the hubs of the network have high degree (total connectivity) but low clustering (local connectivity), indicating that they are connected predominantly to nodes not otherwise connected to each other. Such networks are said to be hierarchical. When $\beta$ values approximate 0, the network is thought to display a non-hierarchical pattern, while large negative values indicate a dis-hierarchical topology. The iterative construction leading to a hierarchical network is presented in Supplementary Figure 5c online.

Statistics

Determining adequate sample size. Based on our previous experience with the effect sizes relating to stress-resilient phenotypes in the $Ahi1^{+/}$ mouse, we estimated that a sample of ~20 mice (10 from each genotype) should ensure adequate power to reveal between-genotype differences. As we had no prior experience with the effect size relating to fear learning deficits in $Ahi1^{+/}$ mice, we a-priori chose to conduct this experiment with a larger cohort (i.e. 30 mice total).

Detecting outliers in the behavioral data derived from the $Ahi1$ knockout model. When analyzing the behavioral data from our $Ahi1$ knockout mouse model, dealing with significant outlier values provides a more normal distribution of the data, and hence enhances the validity of the more powerful parametric approaches (i.e. t-test and ANOVA). In order to identify outliers, we first determined the Q1(25%) and Q3(75%) values and then multiplied by a constant (in our case 1.5; a higher constant is less sensitive to outliers). This value was then subtracted from the Q1 value and added to the Q3 value in order to determine the lower and upper bounds. Values that fell above the upper bound or below the lower bound were considered outliers.
Dealing with outliers in the behavioral data derived from the Ahi1 knockout model. Options for handling outliers in our knockout mouse model include: (1) do nothing, (2) delete the outliers (trimming), (3) transform the data, or (4) winsorize the distribution of values. Winsorising is not equivalent to simply excluding data, which is a simpler procedure, called trimming, but is a method of censoring data. In a trimmed estimator, the extreme values are discarded; in a Winsorised estimator, the extreme values are instead replaced to match that of the next highest or lowest value that falls within the predefined boundaries. When analyzing the behavioral data from our Ahi1 knockout mouse model, we preferred modifying (winsorizing) outliers over deleting them, as the former represents a more conservative approach that does not totally disregard outlier values, which could in fact possess some biological meaning. A detailed summary of outliers detected and winsorized in the behavioral tests (open field, Morris water maze and fear conditioning) is provided in Supplementary Table 19.

Dealing with outliers in the context of the GeneNetwork-based neonatal expression × adult behavior correlations analysis. The Pearson correlation coefficients can indeed be highly sensitive to outlier values, including both univariate and bivariate outliers; the latter outliers are outliers that occur within the joint combination of two variables. In order to address the issue the following steps were implemented: i) Examination of univariate outliers using the abovementioned criteria. In the case of the neonatal expression × adult behavior correlations analysis, two minor outliers were detected in the BIDMC/UTHSC Dev Neocortex P3 dataset, while no outliers were detected in the BIDMC/UTHSC Dev Neocortex P14 and HQF BXD Neocortex P60 datasets, as well as in the principal component datasets derived from Owen et al24 (PC_Owen), from Philip et al6 (PC_Philip) and in the single trait dataset reported by Yang et al25 (10901_Yang). Examination of Pearson correlations between neonatal Ahi1 expression and the relevant behavioral traits yielded similar results when either the original BIDMC/UTHSC Dev Neocortex P3 dataset or a modified P3 dataset, in which the two minor outliers
were winsorized, were used. **ii)** Examination of bivariate outliers using visual inspection of the relevant scatterplots, in which outlier data points can often be easily identified. With respect to the neonatal expression × adult behavior correlations analysis, no such outliers could be readily identified (Figure 4e-g, i-k). **iii)** Comparing Pearson and Spearman correlations. All relevant neonatal expression × adult behavior relationships were quantified using both Pearson and Spearman correlations. The results, depicted in Supplementary Tables 9-10, are very similar indeed. Specifically, the Spearman correlation coefficients are almost as high as the Pearson values in most significant correlations. Thus, we assume that the Spearman coefficients are slightly lower than Pearson's due to the fact that the former is less powerful (albeit more robust), and not as a result of significant (bivariate) outliers.

**Justification of statistical tests.** Following the handling of outliers, as described above, the Shapiro-Wilk test suggested that data were normally distributed throughout the experimental groups. To check whether the group variances were equal, we performed the "Levene's Test for Equality of Variances". According to the results obtained from Levene's test, we chose to employ the equal or the unequal variance t-test. An exclusion to the above is the novel object recognition test, for which the $Ahi^{t+}$ data significantly deviated from the normal distribution ($p_{Shapiro-Wilk} = 0.013$). Hence, the data from this experiment was analyzed with both parametric and nonparametric tests (i.e. t-test and Mann-Whitney U test). When using mixed-ANOVAs, the assumption of sphericity was tested with Mauchly's test for sphericity. If violated, tests of within-subjects effects were interpreted using the "Greenhouse-Geisser" correction. When performing Pearson's correlations or linear regressions, a linear relationship between the two variables was first sought, followed by inspection for bivariate outliers, as noted above.
Controlling for multiple testing. In order to avoid chance findings obtained through multiple tests, we routinely employed the Bonferroni correction when ≤ 5 comparisons were made (such as in the Ahi1 eQTL x fear conditioning t-tests). When more than five comparisons were made (such as in the enrichment and QTL analyses), we employed the BH procedure for controlling the False Discovery Rate\textsuperscript{26}.

Software used for statistical analysis. For the behavioral tests, statistics were performed using IBM SPSS 20. The analysis based on the GeneNetwork database was performed using the relevant online tools (www.genenetwork.org). For the graph-based network analysis we used GAT, a graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks\textsuperscript{17}.
Supplementary Figure 1: Methodological steps for correlating gene expression and behavior using GeneNetwork.

Cartoon depicting the methodology employed for determining the relationship between Ahi1 expression and fear learning across the BXD recombinant inbred strains. (a) Curating neocortical Ahi1 expression profiles. The RNA probe that had the higher expression across all three datasets was chosen for further analysis (marine-blue bars). (b) Curating fear conditioning-related behavioral traits (olive-green bars) and deriving Principal Component traits when more than one trait per report was available (green bars). (c) Correlating Ahi1 expression with fear conditioning. Each PC trait (or individual trait in case there was only one relevant trait per report) was correlated with each of the three neocortical expression profiles. The √ and × marks represent reports depicting behavioral traits, for which the overlap with the expression datasets encompassed ≥ 10 strains (green √ marks) or ≤ 9 strains (red × mark).
Supplementary Figure 2: Ahi1 expression across developmental time-points.

(a) Bar graph depicting expression of the Ahi1 3' UTR probe (Y-axis, arbitrary units $[\log_2]$) across the BXD recombinant inbred strains and parent strains assessed in the neocortex at postnatal day 60. (b+c) Pearson correlation plots depicting the correlations between expression of the Ahi1 3' UTR probe measured at P60 (ILM 460520, Y axis) and expression of the Ahi1 3' UTR probes (X axis) measured at (a) P3 and (b) P14 (ILM_2813712, X axis). Only strains for which expression data measured at both time-points was available were entered into the correlation. Note that correlations are moderate-to-weak.
Supplementary Figure 3: Manhattan plots displaying eQTLs controlling the expression of Ahi1.

Manhattan plots displaying the eQTLs controlling the expression of Ahi1 in the neocortex during early neonatal life, identified by interval mapping the Ahi1 probe (ILMN_2813712) from the BIDMC/UTHSC Dev Neocortex P3 database against dense genotype data for 43 BXD strains. The x-axis represents the physical maps for the whole genome (a, Chr number) and for Chr 1 (b, position in Mb); the y-axis provides the LRS (likelihood ratio statistics) values of the association between Ahi1 expression and the genotypes of markers, which can be directly converted to LOD scores by dividing by 4.61. Each little circle denotes a marker.
Supplementary Figure 4: Global network measures derived from whole-brain functional networks.

(a-c) Based upon whole-brain functional networks, average global network parameters were calculated across network densities in wildtype (blue circles) and $Ahi1^{+/}$ (yellow squares) mice. Values were normalized to random networks. Brain networks of mice from both genotypes displayed average normalized global clustering coefficients higher than in random networks (a), although average shortest path lengths were similar to those expected in random networks (b). Taken together, networks of mice from both genotypes displayed average small-world indices that were higher than those expected in random networks, most prominent across lower network densities (c). (d-f) Confidence intervals for between-group comparison of the global network measures described above. Using the resampling procedure with 1000 permutations, between-group differences in global clustering (d), path length (e) and small-world index (f) were deemed non-significant.
Supplementary Figure 5: Assortative and hierarchical organization of the functional brain networks.

(a-b) Cartoon depicting scale-free networks with different degrees of assortativity. Note that while in a non-assortative network (a) nodes tend to connect to other nodes irrespective of their degree, in the assortative network (b) nodes tend to connect preferentially to other nodes with a similar degree. Image credit: Yang et al, 2010. (c) The iterative construction leading to a hierarchical network. The network is made of numerous small, highly integrated five node modules, which are assembled into larger 25-node modules. These 25-node modules are less integrated but each of them is clearly separated from the other 25-node modules when combined into the even larger 125-node modules. These 125-node modules are even less cohesive, but again will appear separable from their replicas if the network expands further. The nodes at the center of the numerous 5-node modules have a clustering coefficient $C = 1$. Those at the center of a 25-node module have $k = 20$ and $C = 3/19$, while those at the center of the 125-node modules have $k = 84$ and $C = 3/83$, indicating that the higher a node’s degree the smaller is its clustering coefficient, asymptotically following the $1/k$ law. Image credit: Barabasi et al, 2002. (d) A correlation plot depicting the relationship between a network’s hierarchy coefficient and its assortativity coefficient across all 27 mice. Note the highly significant, negative correlation between the two.
### Supplementary Table 1: Neocortical *Ahi1* probes available at GeneNetwork.

Outlined are *Ahi1* probes within the developing (DevNeocortex\_ILM6.2P3RInv\_1111 and DevNeocortex\_ILM6.2P14RInv\_1111) and adult (HQFNeoc\_1210v2\_RankInv) neocortex datasets available at GeneNetwork. Outlined are the names of the datasets explored, the trait IDs and gene symbol, description of the relevant probes, their chromosomal locations, the mean probe expression values (as log₂) and the number of inbred strains analyzed within this dataset.

Data source: BXD Published Phenotypes at [www.genenetwork.org](http://www.genenetwork.org)

Accessed on: October 16, 2015
| Neocortical Ahi1 expression measured at P3 | 0.969 | 34 | 0.441 |
|------------------------------------------|-------|----|-------|
| Neocortical Ahi1 expression measured at P14 | 0.969 | 34 | 0.427 |
| Neocortical Ahi1 expression measured at P60 | 0.974 | 34 | 0.590 |

**Supplementary Table 2:** Tests of normality for Ahi1 probe at three developmental stages.

Outlined are tests of normality for the distribution of Ahi1 probe expression across strains measured at three developmental stages.

Data source: BXD Published Phenotypes at [www.genenetwork.org](http://www.genenetwork.org)

Accessed on: October 16, 2015
Supplementary Table 3: Traits related to contextual fear conditioning.

Outlined are traits related to contextual fear conditioning derived by searching the BXD Published Phenotypes Database for all records that match the terms central, nervous, system, fear, conditioning, response, and contextual. Irrelevant traits, such as that pertaining to nociception, were removed. The table includes the record number, phenotype and publication information (authors, year and Pubmed ID).

Data source: BXD Published Phenotypes at www.genenetwork.org
Accessed on : October 16, 2015

| Record | Phenotype                                                                 | Authors                                                                 | Year | Pubmed Id   |
|--------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|------|-------------|
| 11651  | Central nervous system, behavior: Fear conditioning response, contextual activity for females [units] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391    |
| 11908  | Central nervous system, behavior: Fear conditioning response, contextual activity for males and females [units] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391    |
| 11394  | Central nervous system, behavior: Fear conditioning response, contextual activity for males [units] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391    |
| 10901  | Central nervous system, behavior, learning and memory: Fear conditioning, freezing in response to context exposure 48 hr after conditioning [%] | Yang RJ, Mozhui K, Karlsson RM, Cameron HA, Williams RW, Holmes A        | 2008 | 18185497    |
| 10445  | Central nervous system, behavior: Fear response control (unconditioned auditory stimulus stimulus, US) in a contextualized fear conditioning paradigm [% freezing] | Owen EH, Christensen SC, Paylor R, Wehner JM                            | 1997 | 9106670     |
| 10446  | Central nervous system, behavior: Fear response to context [% freezing] | Owen EH, Christensen SC, Paylor R, Wehner JM                            | 1997 | 9106670     |
| 10447  | Central nervous system, behavior: Fear response to preconditioned (altered) context stimulus [% freezing] | Owen EH, Christensen SC, Paylor R, Wehner JM                            | 1997 | 9106670     |
| 11011  | Central nervous system, behavior, learning and memory: Fear conditioning, freezing response to context after 48 hours [%] | Brigman JL, Mathur P, Lu L, Williams RW, Holmes A                      | 2009 | 18830130    |
## Supplementary Table 4: Traits related to cued fear conditioning.

Outlined are traits related to cued fear conditioning derived by searching the BXD Published Phenotypes Database for all records that match the terms central, nervous, system, fear, conditioning, response, and cued. Irrelevant traits, such as those pertaining to suppression, were removed. The table includes the record number, phenotype and publication information (authors, year and Pubmed ID).

Data source: BXD Published Phenotypes at www.genenetwork.org
Accessed on: October 16, 2015

| Record | Phenotype                                                                 | Authors                                                                                     | Year | Pubmed Id  |
|--------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------|------------|
| 11909  | Central nervous system, behavior, learning and memory: Fear conditioning response, activity in altered context during presentation of cue for males and females [units] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391   |
| 11652  | Central nervous system, behavior: Fear conditioning response, activity in altered context during presentation of cue for females [units] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391   |
| 11395  | Central nervous system, behavior: Fear conditioning response, activity in altered context during presentation of cue for males [n beam breaks] | Philip VM, Ansah TA, Blaha CD, Cook MN, Hamre KM, Lariviere WR, Matthews DB, Mittleman G, Goldowitz D, Chesler EJ | 2010 | 19958391   |
| 11010  | Central nervous system, behavior, learning and memory: Fear conditioning, freezing response time to conditioned cue after 24 hours [%] | Brigman JL, Mathur P, Lu L, Williams RW, Holmes A                                           | 2009 | 18830130   |
| 11009  | Central nervous system, behavior, learning and memory: Fear conditioning, freezing response time to conditioned cue after 48 hours [%] | Brigman JL, Mathur P, Lu L, Williams RW, Holmes A                                           | 2009 | 18830130   |
**Supplementary Table 5:** Traits related to fear conditioning reported by Owen et al.

Outlined are Pearson's correlations between the three fear conditioning traits reported by Owen et al\(^{24}\) as well as the 1\(^{st}\) principal component derived from these three traits, and which accounts for 75% of the total variability in these traits.

Data source for raw data: BXD Published Phenotypes at www.genenetwork.org

Accessed on: October 16, 2015

|                      | Owen_10445 | Owen_10446 | Owen_10447 |
|----------------------|------------|------------|------------|
| **Owen_10445:** Fear response control (unconditioned auditory stimulus stimulus, US) in a contextualized fear conditioning paradigm [% freezing] | Pearson Correlation | 1 | .524* | .413* |
|                      | Sig. (2-tailed) | .010 | .050 | |
|                      | N | 23 | 23 | 23 |
| **Owen_10446:** Fear response to context [% freezing] | Pearson Correlation | .524* | 1 | .866** |
|                      | Sig. (2-tailed) | .010 | .000 | |
|                      | N | 23 | 23 | 23 |
| **Owen_10447:** Fear response to preconditioned (altered) context stimulus [% freezing] | Pearson Correlation | .413* | .866** | 1 |
|                      | Sig. (2-tailed) | .050 | .000 | |
|                      | N | 23 | 23 | 23 |
| *PC_Owen* derived from traits 10445+10446+10447 accounting for 75% of total variability in these traits | Pearson Correlation | -.760** | -.949** | -.908** |
|                      | Sig. (2-tailed) | .000 | .000 | .000 |
|                      | N | 22 | 22 | 22 |

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).
### Supplementary Table 6: Traits related to fear conditioning reported by Philip et al.

Outlined are Pearson's correlations between the six fear conditioning traits reported by Philip et al. as well as the 1st principal component derived from these six traits, and which accounts for 70% of the total variability in these traits.

Data source for raw data: BXD Published Phenotypes at www.genenetwork.org
Accessed on: October 16, 2015
Supplementary Table 7: Traits related to fear conditioning reported by Brigman et al.

Outlined are Pearson's correlations between the six fear conditioning traits reported by Brigman et al\textsuperscript{27} as well as the 1\textsuperscript{st} principal component derived from these three traits, and which accounts for ~65% of the total variability in these traits.

Data source for raw data: BXD Published Phenotypes at www.genenetwork.org

Accessed on: October 16, 2015

|                            | Brigman_11010 | Brigman_11009 | Brigman_11011 |
|-----------------------------|---------------|---------------|---------------|
| **Pearson Correlation**     |               |               |               |
| **Sig. (2-tailed)**         |               |               |               |
| **N**                       | 25            | 25            | 25            |
| **Brigman_11010**           |               |               |               |
| Fear conditioning, freezing response time to conditioned cue after 24 hours [%] | 1             | .461\*        | .473          |
| **Brigman_11009**           |               |               |               |
| Fear conditioning, freezing response time to conditioned cue after 48 hours [%] | .461\*        | 1             | .378          |
| **Brigman_11011**           |               |               |               |
| Fear conditioning, freezing response to context after 48 hours [%] | .473\*        | .378          | 1             |
| **PC_Brigman derived from 3 traits and accounting for ~65% of variability in traits** | -.827**       | -.770**       | -.784**       |
| **Sig. (2-tailed)**         | .000          | .000          | .000          |
| **N**                       | 24            | 24            | 24            |

\* Correlation is significant at the 0.05 level (2-tailed).
\** Correlation is significant at the 0.01 level (2-tailed).
**Supplementary Table 8**: Correlations between the synthetic principal components derived from individual fear conditioning reports.

Outlined are Pearson’s correlations between the major principal components derived from fear conditioning traits reported by Owen et al\(^\text{24}\) (PC\_Owen derived from 3 traits), Philip et al\(^\text{6}\) (PC\_Philip derived from 6 traits), Brigman et al\(^\text{24}\) (PC\_Brigman derived from 3 traits) and Yang et al\(^\text{28}\) (single trait, 10901).

Data source for raw data: BXD Published Phenotypes at www.genenetwork.org
Accessed on: October 16, 2015

|                  | PC\_Owen | PC\_Philip | PC\_Brigman | Yang\_10901 |
|------------------|----------|------------|-------------|-------------|
| PC\_Owen         |          |            |             |             |
| Pearson Correlation | 1       | -.476      | .386        | -.162       |
| Sig. (2-tailed)  |          | .085       | .449        | .598        |
| N                | 22       | 14         | 6           | 13          |
| PC\_Philip       |          |            |             |             |
| Pearson Correlation | -.476   | 1          | -.647\(*)^*  | -.215       |
| Sig. (2-tailed)  |          | .085       | .005        | .482        |
| N                | 14       | 57         | 17          | 13          |
| PC\_Brigman      |          |            |             |             |
| Pearson Correlation | .386    | -.647\(*)^* | 1           | .579        |
| Sig. (2-tailed)  |          | .449       | .005        | .421        |
| N                | 6        | 17         | 24          | 4           |
| Yang\_10901      |          |            |             |             |
| Pearson Correlation | -.162   | -.215      | .579        | 1           |
| Sig. (2-tailed)  |          | .598       | .482        | .421        |
| N                | 13       | 13         | 4           | 17          |

\(*\text{Correlation is significant at the 0.01 level (2-tailed).}

**Correlations**

- PC\_Owen
- PC\_Philip
- PC\_Brigman
- Yang\_10901

27
**Supplementary Table 9:** Pearson's product-moment correlations between *Ahi1* expression profiles and fear conditioning traits.

Outlined are Pearson's product-moment correlations across the BXD strains between the three *Ahi1* expression profiles (Ahi1_P3, Ahi1_P14 and Ahi1_P60) and the synthetic principal components, PC_Owen and PC_Philip, derived from the three and six fear conditioning traits reported by Owen et al\(^{24}\) and Philip et al\(^{6}\). The last column outlines the correlations between the *Ahi1* expression profiles and the single relevant fear-conditioning trait reported by Yang et al\(^{28}\). Note that the correlations between P3 *Ahi1* expression profile and PC_Owen or PC_Philip (tests #1 and #2, bottom table) were the only ones to withstand FDR correction for multiple testing.

Data source for raw data: BXD Published Phenotypes at [www.genenetwork.org](http://www.genenetwork.org).
Accessed on: October 16, 2015.
**Supplementary Table 10**  
Spearman rank-order correlations between *Ahi1* expression profiles and fear conditioning traits.

Outlined are Spearman rank-order correlations across the BXD strains between the three *Ahi1* expression profiles (*Ahi1* P3, *Ahi1* P14 and *Ahi1* P60) and the synthetic principal components, PC_Owen and PC_Philip, derived from the three and six fear conditioning traits reported by Owen et al\(^6\) and Philip et al\(^6\) as well as the single relevant fear-conditioning trait reported by Yang et al\(^8\). Note that, as with the Pearson's product-moment correlation, the Spearman rank-order correlation between P3 *Ahi1* expression profile and PC_Owen withstands FDR correction for multiple testing (tests #1, Correction for Multiple Testing tables in Supplementary Tables 9 and 10, \(p_{adj}=0.009\) and 0.018, respectively). However, unlike Pearson's correlation between P3 *Ahi1* expression profile and PC_Philip, which yielded a marginal p-value following FDR correction, the Spearman rank-order correlation, being less powerful, albeit more robust to outliers, produces only a suggestive p-value following correction for multiple testing (tests #2, Correction for Multiple Testing tables in Supplementary Tables 9 and 10, \(p_{adj}=0.0495\) vs. 0.072).

Data source for raw data: BXD Published Phenotypes at [www.genednetwork.org](http://www.genednetwork.org).  
Accessed on: October 16, 2015.
Supplementary Table 11: Prediction of PC_Owen according to Ahi1 expression profiles.

Outlined are results of a hierarchical regression analysis with PC_Owen as the dependent variable and Ahi1_P3, Ahi1_P14 and Ahi1_P60 as predictors. Note that while Ahi1 expression at P3 predicted 48% of the total variance in PC_Owen, addition of the P14 and P60 time-points to the earlier one did not improve model strength.

Data source for raw data: BXD Published Phenotypes at [www.genenetwork.org](http://www.genenetwork.org).
Accessed on: October 16, 2015.
Supplementary Table 12: Prediction of PC_Philip according to *Ahi1* expression profiles.

Outlined are results of a hierarchical regression analysis with PC_Philip as the dependent variable and Ahi1_P3, Ahi1_P14 and Ahi1_P60 as predictors. Note that while *Ahi1* expression at P3 predicted 23% of the total variance in PC_Philip, addition of the P14 and P60 time-points to the earlier one did not improve model strength.

Data source for raw data: BXD Published Phenotypes at [www.genenetwork.org](http://www.genenetwork.org).
Accessed on: October 16, 2015.
Supplementary Table 13: Group statistics of fear conditioning traits grouped according to genotype.

Outlined are the group statistics for the fear conditioning traits grouped into homozygote carriers of the parental B or D allele at the rs6312657 marker. Notice that PC_Owen, PC_Philip and PC_Brigman traits include strain-specific data that partially overlaps the rs6312657-genotyped dataset, so that at least eight phenotyped mice could be grouped into each homozygous genotype category. The '10901_Yang' trait does not fulfil this criterion.

Data source for raw data: BXD Published Phenotypes at www.genenetwork.org. Accessed on: October 16, 2015.
Supplementary Table 14: Independent samples test of fear conditioning traits grouped according to genotype.

Outlined are the independent samples tests for the fear conditioning traits grouped into homozygote carriers of the parental B or D allele at the rs6312657 marker. Notice that of the three PC traits, rs6312657 genotype shows a significant effect on PC_Brigman, which remains significant following Bonferroni correction for multiple testing.

|                  | Equality of Variances | t-test for Equality of Means |
|------------------|------------------------|-----------------------------|
|                  | F         | Sig. | t        | df | Sig. (2-tailed) | Sig. (2-tailed, Bonferroni adjusted) |
| PC_Brigman       |            |      |          |    |                |                                      |
| Equal variances assumed | .918 | .351 | -2.687 | 18 | .015 | .045 |
| Equal variances not assumed |     |      | -2.579 | 13.423 | .022 | .067 |
| PC_Owen          |            |      |          |    |                |                                      |
| Equal variances assumed | .109 | .745 | -1.100 | 18 | .286 | .857 |
| Equal variances not assumed |     |      | -1.084 | 14.367 | .296 | .889 |
| PC_Philip        |            |      |          |    |                |                                      |
| Equal variances assumed | .010 | .920 | 1.360 | 54 | .179 | .538 |
| Equal variances not assumed |     |      | 1.360 | 49.767 | .180 | .539 |
Supplementary Table 15: Transcripts regulated by the Chr1: 69.048453 locus during neocortical development.

Outlined are the 41 transcripts that have a single best trans-QTL that can be mapped to the Chr1: 69.048453 locus (marker rs6312657) with LOD scores >3.80, derived from QTL analysis of the entire BIDMC/UTHSC Dev Neocortex P3 dataset. For each transcript, its symbol, description, chromosomal location and LOD score for its association with the Chr1: 69.048453 locus are presented. Transcripts are presented in descending order according to LOD scores. The Ahi1 transcript, which is the focus of the current research, is highlighted.

| Symbol       | Description                                      | Chr Mb | Max_LOD        |
|--------------|--------------------------------------------------|--------|----------------|
| Unc80        | unc-80 homolog                                   | 1      | 66.7           | 9.940018354 |
| 1700011M02Rik | RIKEN cDNA 1700011M02 gene                        | X      | 100            | 6.972034752 |
| Shh          | sonic hedgehog                                   | 25     | 28.8           | 6.225316196 |
| Kcnh6        | potassium voltage-gated channel, subfamily H (eg-related), member 6 | 10     | 109            | 5.649131729 |
| Pes1         | pescadillo homolog 1, containing BRCT domain (zebrafish) | 11     | 3.88           | 5.391397001 |
| I16          | interleukin 16                                   | 17     | 7.90           | 5.261593964 |
| Hap1         | huntingtin-associated protein 1                  | 11     | 100            | 4.85768757  |
| Iqsec3       | IQ motif and Sec7 domain 3                        | 6      | 121            | 4.708624579 |
| **Ahi1**     | Abelson helper integration site                  | 10     | 20.8           | 4.587740465 |
| Rtnr4l1      | reticulon 4 receptor-like 1                       | 11     | 75.1           | 4.46088423  |
| Rai1         | retinoic acid induced 1                           | 11     | 59.9           | 4.43653363  |
| E430013K19Rik | RIKEN cDNA E430013K19 gene                        | X      | 38.9           | 4.43684092  |
| Rhbd1        | rhomboid family 1 (Drosophila)                   | 11     | 32.1           | 4.43687587  |
| Lass4        | longevity assurance homolog 4 (S. cerevisae)      | 8      | 4.33           | 4.43523363  |
| Gna-rs1      | guanine nucleotide binding protein, related sequence 1 | 17 | 36.1           | 4.40573023  |
| A930038C07Rik | RIKEN cDNA A930038C07 gene                       | 6      | 65.7           | 4.405725875 |
| Ccdc92       | coiled-coil domain containing 92                 | 5      | 125            | 4.38197168  |
| Zic2         | Zic finger protein of the cerebellum 2           | 14     | 123            | 4.32498732  |
| Pscd4        | pleckstrin homology, Sec7 and coiled/coil domains 4 | 15     | 78.4           | 4.23979165  |
| Zpf291       | zinc finger protein 291                          | 9      | 55.7           | 4.237418053 |
| Rab31        | RAB31, member RAS oncogene family                | 17     | 66             | 4.18461313  |
| Raly         | hRNAP-associated with lethal yellow              | 2      | 155            | 4.15696267  |
| Cenpk        | centromere protein K                             | 13     | 105            | 4.11752542  |
| Sgs1         | small G protein signaling modulator 1 (RUN and TBC1 domain containing 2) | 5 | 114            | 4.07355596  |
| Peci         | peroxisomal delta3, delta2-enzyl-Coenzyme A isomerase | 13 | 35.1           | 4.07303426  |
| Kcnt1        | potassium channel, subfamily T, member 1 (slack, low threshold slowly adapting) | 2 | 25.8           | 4.01956089  |
| 3110082D06Rik | RIKEN cDNA 3110082D06 gene                       | 17     | 42.5           | 4.01277763  |
| Ngf          | nerve growth factor                              | 3      | 102            | 3.97813847  |
| Rsrc1        | arginine-serine-rich coiled-coil 1               | 3      | 66.9           | 3.93763152  |
| A930034L06Rik | RIKEN cDNA A930034L06 gene                       | 5      | 72.8           | 3.92716609  |
| 4922503N01Rik | RIKEN cDNA 4922503N01 gene                       | 4      | 109            | 3.90451649  |
| A930034L06Rik | RIKEN cDNA A930034L06 gene                       | 2      | 158            | 3.89459006  |
| Rasgrf1      | RAS protein-specific guanine nucleotide-releasing factor 1 | 9 | 89.9           | 3.88001669  |
| Ddc          | 3,4-dihydoxyphenylalanine/lalanine (DOPA) decarboxylase (catecholamine biosynthesis, DOPA decarboxylase) | 11 | 11.7           | 3.869602106 |
| A930026H04Rik | RIKEN A930026H04Rik                              | 10     | 62.8           | 3.86422582  |
| Zdhdc14      | zinc finger, DHR domain containing 14            | 17     | 57.5           | 3.86328272  |
| Aebp2        | AE binding protein 2                             | 6      | 141            | 3.84534663  |
| Plekhm2      | pleckstrin homology domain containing, family M (with RUN domain) member 2 | 4 | 141           | 3.82993435  |
| Tce2a        | transcription elongation factor A (Sil), 2       | 2      | 181            | 3.8231225   |
| Rbic1        | RB1-inducible coiled-coil 1                      | 1      | 62.4           | 3.81437714  |
| Rasgrf1      | RAS protein-specific guanine nucleotide-releasing factor 1 | 9 | 89.9           | 3.80361339  |
Supplementary Table 16: Top GO terms associated with genes regulated by the Chr1: 69.048453 locus.

Outlined are the three top Gene Ontology (GO) terms that contain genes which are significantly over-represented among the 41 transcripts that have a single best trans-

```markdown
### Supplementary Table 16: Top GO terms associated with genes regulated by the Chr1: 69.048453 locus.

Outlined are the three top Gene Ontology (GO) terms that contain genes which are significantly over-represented among the 41 transcripts that have a single best trans-
```
QTL that can be mapped to the Chr1: 69.048453 locus (marker rs6312657) with LOD scores >3.8 (see above). For each GO category, the first row lists its sub-root (biological process, molecular function, or cellular component), category name, and corresponding GO ID. The second row lists the following statistics:

- C: the number of reference genes in the category
- O: the number of genes in the gene set and also in the category
- E: the expected number in the category
- R: ratio of enrichment
- rawP: p value from hypergeometric test
- adjP: p value adjusted by the multiple test adjustment

Finally, genes in the category are listed. For each gene, the table lists Entrez ID, Ensembl Gene Stable ID, Gene symbol, and description.
Supplementary Table 17: Regions of Interest (ROIs) preselected based on the Paxinos Mouse Brain Atlas\textsuperscript{29}.  

3-D coordinates are depicted in mm together with structure names and abbreviations. Structures are color-coded as following: cortex, green; caudoputamen, light blue; pallidum, marine blue; amygdala, light green; hippocampus, olive; midbrain, pink; diencephalon, red. R and L denote right and left, respectively.
### Supplementary Table 18: Tests of normality for global network measures.

Both the network assortativity and network hierarchy coefficients were normally distributed across mice from both genotypes, as evidenced by non-significant Shapiro-Wilk tests.
| Test  | Variable           | Figure | N tested \((Ahi1^{+/+}, Ahi1^{+-})\) | N Outliers deleted \((Ahi1^{+/+}, Ahi1^{+-})\) | N Outliers winsorized \((Ahi1^{+/+}, Ahi1^{+-})\) | N included = N tested - N Outliers deleted \((Ahi1^{+/+}, Ahi1^{+-})\) |
|-------|-------------------|--------|------------------------------------|---------------------------------------------|------------------------------------------------|------------------------------------------------|
| OF    | Thigmotaxis       | 1b     | 12, 13                             | 0, 0                                        | 0, 1                                           | 12, 13                                          |
|       | Velocity          | 1g     | 12, 13                             | 0, 0                                        | 0, 0                                           | 12, 13                                          |
| MWM   | Thigmotaxis       | 1d     | 12, 13                             | 0, 0                                        | 0, 0                                           | 12, 13                                          |
|       | Escape latency    | 1e     | 12, 13                             | 0, 0                                        | 0, 2                                           | 12, 13                                          |
|       | Distance to platform | 1f   | 12, 13                             | 0, 0                                        | 0, 2                                           | 12, 13                                          |
|       | Swimming Velocity | 1h     | 12, 13                             | 0, 0                                        | 0, 0                                           | 12, 13                                          |
| NOR   | Discrimination ratio | 2a   | 7, 9                               | 0, 0                                        | 0, 0                                           | 7, 9                                            |
| FC    | Contextual        | 2b     | 15, 15                             | 0, 0                                        | 2, 0                                           | 15, 15                                          |
|       | Cued              | 2c     | 15, 15                             | 0, 0                                        | 0, 0                                           | 15, 15                                          |
| fMRI  | Global network topology | 5,6 | 13, 12                             | 0, 0                                        | 0, 0                                           | 13, 12                                          |

**Supplementary Table 19:** Size of experimental groups and outlier handling.

For variables measured in each of the behavioral and imaging tests comparing wildtype \((Ahi1^{+/+})\) and Ahi1 knockout \((Ahi1^{+-})\) mice, the table depicts the number of animals tested in each experimental group, the number of outliers that were deleted or modified (winsorized) and the net number of animals included in the final analysis and relevant figure(s). Note that no outliers were removed and a maximum of two outlier values per experiment were modified. OF, open field; MWM, Morris water maze (visible platform); NOR, novel object recognition; FC, fear conditioning; fMRI, functional magnetic resonance imaging.
SUPPLEMENTARY REFERENCES

1. Haley CS, Knott SA. A simple regression method for mapping quantitative trait loci in line crosses using flanking markers. Heredity (Edinb) 1992; 69(4): 315-324.

2. Heimel JA, Hermans JM, Sommeijer JP, Neuro-Bsik Mouse Phenomics c, Levelt CN. Genetic control of experience-dependent plasticity in the visual cortex. Genes, Brain and Behav 2008; 7(8): 915-923.

3. Geisert EE, Lu L, Freeman-Anderson NE, Templeton JP, Nassr M, Wang X et al. Gene expression in the mouse eye: an online resource for genetics using 103 strains of mice. Molecular Vision 2009; 15: 1730-1763.

4. Pandey AK, Williams RW. Genetics of Gene Expression in CNS. Int Rev Neurobiol 2014; 116: 195-231.

5. Chesler EJ, Lu L, Shou S, Qu Y, Gu J, Wang J et al. Complex trait analysis of gene expression uncovers polygenic and pleiotropic networks that modulate nervous system function. Nat Genet 2005; 37(3): 233-242.

6. Philip VM, Duvvuru S, Gomero B, Ansah TA, Blaha CD, Cook MN et al. High-throughput behavioral phenotyping in the expanded panel of BXD recombinant inbred strains. Genes, Brain and Behav 2010; 9(2): 129-159.

7. Wang J, Williams R, Manly K. WebQTL. Neuroinformatics 2003; 1(4): 299-308.

8. Zhang B, Kirov S, Snoddy J. WebGestalt: an integrated system for exploring gene sets in various biological contexts. Nucleic Acids Res 2005; 33(Web Server issue): W741-748.

9. Wang J, Duncan D, Shi Z, Zhang B. WEB-based GEne SeT AnaLysis Toolkit (WebGestalt): update 2013. Nucleic Acids Res 2013; 41(W1): W77-W83.

10. Supek F, Bosnjak M, Skunca N, Smuc T. REVIGO summarizes and visualizes long lists of gene ontology terms. PLoS One 2011; 6(7): e21800.

11. Gaglani SM, Lu L, Williams RW, Rosen GD. The genetic control of neocortex volume and covariation with neocortical gene expression in mice. BMC Neurosci 2009; 10: 44.

12. Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage 2010; 52(3): 1059-1069.

13. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature reviews Neuroscience 2009; 10(3): 186-198.
14. Sporns O, Honey CJ. Small worlds inside big brains. *Proc Natl Acad Sci U S A* 2006; 103(51): 19219-19220.

15. Sporns O. Structure and function of complex brain networks. *Dialogues Clin Neurosci* 2013; 15(3): 247-262.

16. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Nature reviews Neuroscience* 2015; 16(3): 159-172.

17. Hosseini SM, Hoeft F, Kesler SR. GAT: a graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks. *PLoS One* 2012; 7(7): e40709.

18. Xia M, Wang J, He Y. BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. *PLoS ONE* 2013; 8(7): e68910.

19. Goelman G, Gordon N, Bonne O. Maximizing Negative Correlations in Resting-State Functional Connectivity MRI by Time-Lag. *PLoS ONE* 2014; 9(11): e111554.

20. Latora V, Marchiori M. Efficient behavior of small-world networks. *Phys Rev Lett* 2001; 87(19).

21. Newman MEJ. Assortative mixing in networks. *Phys Rev Lett* 2002; 89(20).

22. Yang Y, Xiang L, Zhihai R. Assortative degree-mixing patterns inhibit behavioral diversity of a scale-free structured population in high-mutation situations. *EPL (Europhysics Letters)* 2010; 89(1): 18006.

23. Ravasz E, Barabási A-L. Hierarchical organization in complex networks. *Phys Rev E* 2003; 67(2): 026112.

24. Owen EH, Christensen SC, Paylor R, Wehner JM. Identification of quantitative trait loci involved in contextual and auditory-cued fear conditioning in BXD recombinant inbred strains. *Behav Neurosci* 1997; 111(2): 292-300.

25. Yang RJ, Mozhui K, Karlsson RM, Cameron HA, Williams RW, Holmes A. Variation in mouse basolateral amygdala volume is associated with differences in stress reactivity and fear learning. *Neuropsychopharmacology* 2008; 33(11): 2595-2604.

26. Benjamini Y, Yekutieli D. Quantitative trait Loci analysis using the false discovery rate. *Genetics* 2005; 171(2): 783-790.

27. Brigman JL, Mathur P, Lu L, Williams RW, Holmes A. Genetic relationship between anxiety-related and fear-related behaviors in BXD recombinant inbred mice. *Behav Pharmacol* 2009; 20(2): 204-209.
28. Yang RJ, Mozhui K, Karlsson R-M, Cameron HA, Williams RW, Holmes A. Variation in Mouse Basolateral Amygdala Volume is Associated With Differences in Stress Reactivity and Fear Learning. *Neuropsychopharmacology* 2008; 33(11): 2595-2604.

29. Paxinos G, Franklin KBJ. *The mouse brain in stereotaxic coordinates*. Compact 2nd edn. Elsevier Academic Press: Amsterdam; Boston, 2004.