Novel Candidate Genes Associated with Hippocampal Oscillations

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Abstract

The hippocampus is critical for a wide range of emotional and cognitive behaviors. Here, we performed the first genome-wide search for genes influencing hippocampal oscillations. We measured local field potentials (LFPs) using 64-channel multi-electrode arrays in acute hippocampal slices of 29 BXD recombinant inbred mouse strains. Spontaneous activity and carbachol-induced fast network oscillations were analyzed with spectral and cross-correlation methods and the resulting traits were used for mapping quantitative trait loci (QTLs), i.e., regions on the genome that may influence hippocampal function. Using genome-wide hippocampal gene expression data, we narrowed the QTLs to eight candidate genes, including Pcleb1, a phospholipase that is known to influence hippocampal oscillations. We also identified two genes coding for calcium channels, Cacna1b and Cacna1e, which mediate presynaptic transmitter release and have not been shown to regulate hippocampal network activity previously. Furthermore, we showed that the amplitude of the hippocampal oscillations is genetically correlated with hippocampal volume and several measures of novel environment exploration.

Introduction

The hippocampus is critical for a wide range of emotional and cognitive behaviors. Changes in hippocampal oscillatory activity have been established during hippocampus dependent behaviors, such as anxiety-related behavior and spatial orientation [1,2,3]. Furthermore, an increase in amplitude of gamma oscillations in the hippocampus has been associated with memory retrieval in humans [4] and rats [5]. Together, these data suggest an important role for gamma oscillatory activity in hippocampal function.

Oscillations can be pharmacologically induced in ventral hippocampal slices of rodents by applying the acetylcholine receptor agonist carbachol [6,7]. This in vitro activity, which we will refer to as “fast network oscillations”, shares many characteristics with gamma oscillations in vivo [8,9]. In particular, the amplitude of in vitro ventral hippocampal oscillations correlates with in vivo gamma amplitude and performance in a memory task [10]. Moreover, we recently reported differences among eight common inbred mouse strains in traits of carbachol-induced fast network oscillations in hippocampal slices, which implies the contribution of genetic variation to these traits [11]. Therefore, in vitro hippocampal activity is a physiologically relevant source of information to identify genetic variants affecting hippocampal function.

Here, we aimed at identifying genes that underlie variation in hippocampal spontaneous activity and carbachol-induced oscillations in vitro, using a population of 29 BXD recombinant inbred mouse strains [12]. The BXD strains were derived from an intercross of the common inbred mouse strains C57BL/6J and DBA/2J, which differ in many neurophysiologic hippocampal traits and hippocampus-related behavioral traits. For example, C57BL/6J outperforms DBA/2J in spatial memory tasks [13,14,15], which has been associated with their differences in synaptic plasticity [16], and hippocampal mossy fiber projections [17,18,19]. The BXD strains, therefore, form an excellent resource to identify the segregating genetic variants that affect hippocampus-related traits, and they enabled us to identify quantitative trait loci (QTLs) associated with these traits. These QTLs contained many candidate genes and, therefore, we used gene expression data to identify genes of which the expression is linked to hippocampal activity. Using this approach, we identified three genes that were linked to hippocampal activity previously and we identified five novel candidate genes.

In addition we questioned whether genetic predisposition for having a certain level of amplitude, frequency or coherence of hippocampal activity affects behavior. To address this, we computed correlations between the hippocampal activity traits and the behavioral phenotypes assembled in the GeneNetwork...
database (www.genenetwork.org). We found that several behavioral traits and hippocampal activity parameters were correlated in the mouse strains used, indicating a shared genetic component.

**Results**

To identify genes that affect hippocampal activity, we measured local field potentials (LFPs) in hippocampal slices from 29 BXD recombinant inbred strains. Measurements were performed using 60-channel multi-electrode arrays that covered the entire hippocampal cross-section in the slice (Fig. 1A), and the electrodes were classified as located in one of nine anatomical subregions (Fig. 1B). In the first condition, slices were perfused with artificial cerebrospinal fluid (ACSF), which gave rise to asynchronous activity characterized by 1/f-like amplitude spectra (Fig. 1C–E). We computed the integrated amplitudes in the frequency bands 1–4, 4–7, 7–13, 13–25, 25–35, and 35–45 Hz. These amplitudes differed considerably across mouse strains as illustrated with the two extreme mouse strains in Figure 2A.

Following the ACSF condition, we applied the acetylcholine receptor agonist carbachol (25 μM) to pharmacologically induce fast network oscillations (see Fig. 1C–E and Materials and Methods). The amplitude of these oscillations also differed conspicuously between strains (Fig. 2B). To selectively analyze the effect of carbachol on hippocampal activity, we divided the value of a trait in the carbachol condition by that obtained in the ACSF condition and computed heritability scores and genetic correlations.

**Hippocampal activity traits exhibit prominent heritability and genetic correlations**

The analysis of amplitude, peak frequency and inter-areal correlations (see Materials and Methods) for the two conditions in the nine hippocampal subregions define a total of 198 trait values per slice. Several traits were observed to exhibit prominent variation across the mouse strains, e.g., the peak amplitude in the presence of carbachol varied by a factor of three (Fig. 3A) in the CA1 stratum pyramidale. P-values from F statistics (ANOVA) and heritability scores were calculated for every trait (Tables S1 and S2). The heritabilities ranged from 1 to 25%.

Interestingly, we observed a wide range of genetic correlations between the 198 traits, as illustrated by the scatter plots in Figure 3B.
suggests that traits have the same underlying genes. Influenced by different genes, whereas a high genetic correlation indicates that traits are all the interregional correlations (analyses (Fig. 4A–B). For the ACSF condition, one class contains main classes representing experimental conditions and type of clusters of 0.55, resulted in clusters that largely correspond to six 0.45, i.e., allowing for a maximal mean correlation between the clusters (see Materials and Methods). A threshold of the number of traits was reduced to six, and they will be referred to as: the six classes, for each class we calculated the mean over the strain performance of the clustering analysis in separating the six main subsets of phenotypes from the GeneNetwork database (Materials and Methods). See Tables S3 and S4 for descriptions of phenotypes in the subsets.

The first subset (n = 35) consisted of physiological traits of the hippocampus, such as the weight or volume of different subregions of the hippocampus. Interestingly, the trait amplitude 1–45 Hz (CCH) was negatively correlated with volume of the hippocampus. The four phenotypes from the subset with the most significant correlations with amplitude 1–45 Hz (CCH), were two measures of hippocampus volume (GeneNetwork ID 10457: r = −0.68, p < 0.002 (Fig. 5A) and ID 10456: r = −0.66, p < 0.002 [20], and two measures of ventral hippocampus volume (ID 10756: r = −0.57, p < 0.01 and ID 10757: r = −0.53, p < 0.05 [21], uncorrected p-values). The four correlations were significant at a false discovery rate of 0.125.

The second subset (n = 351) consists of a selection of behavioral traits from the database (see Materials and Methods). We found strong negative correlations between peak amplitude and four traits representing locomotion in a novel environment (ID 11510: r = −0.62, p < 0.0005 (Fig. 5B), ID 10916: r = −0.83, p < 0.0005, ID 10037: r = −0.76, p < 0.001, ID 10416: r = −0.89, p < 0.005, uncorrected p-values). The four locomotion traits were strongly correlated with each other, despite having been measured in different studies [22,23,24,25], which reflects that locomotion is a very reproducible trait [26]. The four locomotion traits were part of the top-10 of strongest correlations, which were all significant at a false discovery rate of 0.125. Interestingly, we also found a high positive correlation of peak amplitude with the performance in the Morris water maze task [27] (ID 10816, n = 7, r = 0.74, p < 0.05, uncorrected p-value). This correlation, however, did not survive correction for multiple testing, possibly because of the low number of observations.

We then measured locomotion in a novel open field in several BXD strains in our own laboratory. We used SEE software to dissect locomotion into lingering and progression segments (see Materials and Methods). Peak amplitude correlated negatively with total distance moved (r = −0.52, p < 0.005, data not shown) as it was found also using the GeneNetwork database (Fig. 5B), and with the duration of progression segments (r = −0.54, p < 0.005, Fig. 5C), but positively with the duration of lingering segments (r = 0.48, p < 0.01, Fig. 5D). Taken together, these findings indicate that the inverse relation between peak amplitude and locomotion in a novel environment is a robust effect.

QTL mapping identifies shared and unique genetic influences on hippocampal traits

We used the six main traits, as derived from the cluster analysis (Fig. 4C), for QTL mapping (see Materials and Methods). In total, we identified two significant QTLs (p < 0.05) and seventeen suggestive QTLs (p < 0.63) (Fig. 6). In Figures S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S19 close-ups of the QTLs are shown. See Tables S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S19, S20, S21, S22,
S23 for the location of the nineteen QTLs and the genes they contain. Table S24 contains the locations of all QTL intervals.

Amplitude 1–45 Hz (ACSF) and correlation (ACSF) had overlapping QTLs located on chromosome four (Fig. 6A, B). Amplitude 1–45 Hz (CCH), peak amplitude, and correlation (CCH) had overlapping QTLs on chromosome five; the one from peak amplitude overlapped a QTL from Amplitude 1–45 Hz (ACSF) (Fig. 6A, C–E and Fig. S3, S11, S14 and S17). Also, we identified for each trait one or more suggestive QTLs that were not found for other traits. The partially shared QTLs suggest that the traits share genetic components in addition to having unique genetic component(s). For example, peak frequency (Fig. 6F) had no QTLs in common with other traits. This suggests a dissimilar genetic underpinning of peak frequency and, e.g., peak amplitude.

Correlation with gene expression data points to candidate genes

The nineteen suggestive or significant QTLs identified (see above) varied in length from 2 to 19 Mb, and contained between 6 and 155 genes each. In order to evaluate these genes, we correlated the hippocampal activity traits with expression data from the hippocampus of BXD mice (see Materials and Methods).

For each of the six main traits, we selected genes within the QTLs of the trait, and correlated the expression of these genes with the trait. The significance of the correlations was determined with permutation tests (see Materials and Methods). Table 1 gives an overview of the eight genes from these nineteen QTLs that had significant expression correlations. Peak amplitude was associated with \textit{Plcb1} (phospholipase C, beta 1) and \textit{Cacna1b}, the gene coding for calcium channel alpha1B. The gene coding for calcium channel alpha1E (\textit{Cacna1e}) was linked to amplitude 1–45 Hz (CCH). \textit{Plcb1} is known to influence hippocampal oscillations [28]. \textit{Cacna1b} and \textit{Cacna1e} have been implicated in hippocampal LTP [29,30], but not in the formation of synchronous network activity. For peak frequency, we identified Eps15-homology domain protein 3 (\textit{Ehd3}), which, like the other genes identified (\textit{Creb3}, \textit{Psmc2}, \textit{Dctn3}, and \textit{Ralgps2}) has not yet been related to hippocampal activity.

Discussion

Neuronal oscillations have been implicated in cognitive and emotional behavior [1,31,32] and are heritable [11,33,34] which make quantitative traits derived from oscillatory activity potentially useful in gene-finding strategies. Here, we searched for genes that underlie variation in hippocampal network activity \textit{in vitro} based on...
29 recombinant inbred strains from the BXD population [35]. QTL mapping pointed to regions on the genome associated with variability in amplitude of oscillatory and non-oscillatory activity, as well as in functional coupling between hippocampal areas. To evaluate genes in the QTLs for a potential contribution in hippocampal activity, we correlated their expression in the hippocampus with the hippocampal activity traits, and identified eight candidate genes.

Hippocampal activity traits have relatively low heritability in BXD strains

The heritability estimates of amplitude and functional coupling ranged from 1 to 25%, which is similar to what we found in a population of eight inbred mouse strains [11]. Higher-order statistical measures of oscillatory dynamics, such as long-range temporal correlations [36] and markers from Langevin dynamics [37] exhibit low—albeit significant—heritability, and were not included in the present QTL analysis [38].

To our knowledge, heritability of in vivo hippocampal gamma-band amplitude has not been estimated yet, but EEG studies in humans show that the early auditory gamma-band response has a heritability of 65% [39], and heritability of amplitude in the classical delta-, theta-, alpha- and beta-frequency bands ranges from 40 to 90% [33]. Thus, the heritability we observed here may be considered low. This may be explained by the environmental noise introduced by the experimental procedure, e.g., the slicing of the hippocampus. Moreover, heritability depends also on the population in which it is measured; the heritability we estimated holds for the offspring of the strains C57BL/6J and DBA/2J, which obviously does not comprise the genetic variation as present in the human population.

Reduction of traits inspired by cluster analysis

We used cluster analysis to evaluate the genetic correlations of the 198 hippocampal activity traits. The clusters showed which traits are strongly correlated and, therefore, could be merged. The clusters we identified exhibited a great overlap with six main classes of traits as indicated by the color-coding in (c), i.e., the peak frequency and peak amplitude for the carbachol (CCH) condition, and the broad-band amplitude (1–45 Hz) and the inter-regional correlations for both conditions. We based the QTL mapping on the mean of the traits within these six classes (see labeling below the cluster diagram).

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classes of traits representing experimental conditions and type of analyses. We chose to supervise the merging of traits by using the classes instead of the exact clusters. This approach had the advantage over commonly used unsupervised methods, such as principal component analysis, that the resulting traits have a straightforward analytic and physiological interpretation. By collapsing the information on hippocampal subregions and frequency bands, we reduced the amount of traits to six. The cluster analysis showed that the genetic correlation between the traits measured during the ACSF condition and those during the CCH condition is relatively low. The QTL mapping, however, showed that this correlation is substantial: the traits from the ACSF condition have some overlapping and some non-overlapping QTLs with the traits from the carbachol condition, suggesting a partially unique and partially shared genetic architecture. Therefore, it is also likely that partially shared and partially unique downstream mechanisms underlie the traits from the two conditions."

Genetic correlations with behavioral traits from the GeneNetwork

The negative genetic correlation between hippocampal volume and hippocampal activity traits suggests that there are genes that influence both traits. In two subsequent BXD studies [20,40], a QTL for hippocampal volume was reported at chromosome 1, which overlaps with one of the QTLs we identified for amplitude 1–45 Hz (CCH). This QTL might contain genes that influence both hippocampal activity and hippocampal volume. Recently it has been reported that tenascin-C deficient mice have smaller hippocampal subregions and higher gamma oscillation amplitude compared to wild-type mice [41], which corroborates our finding that small hippocampal volume is associated with high amplitude oscillations.

Locomotion in a novel open field is a complex trait used as a measure for, e.g., exploration, anxiety and hyperactivity. The locomotor behavior of a mouse that is placed in a novel environment can be divided in lingering and progressing segments [42]. During lingering, the animal is actively gathering information about the environment by sniffing, rearing and looking around. During progression, the animal moves from one location to the next. We observed that peak amplitude was negatively correlated with the duration of progression segments, but positively with the duration of lingering segments. Future studies should test whether the same relation holds between locomotion and network oscillations in freely behaving mice. This is not unlikely, because hippocampal oscillations in the 20–40 Hz range are prominent when mice enter a novel environment [43], and gamma oscillations have been associated with novelty in rats [44].

The positive correlation between the performance in the Morris water maze and the peak amplitude suggests that BXD strains capable of producing high-amplitude gamma have good spatial
Memory. Elevated activity of gamma oscillations during encoding and retention of information in working memory has been reported in humans [4,45] and in rodents [5]. Our results, however, provide the first indication that genetic predisposition for high-amplitude gamma oscillations is beneficial for working-memory performance.

Genes previously associated with carbachol-induced hippocampal oscillations

Genetic influences on hippocampal carbachol-induced oscillations in vitro have been studied extensively and it has pointed to several genes involved, including *Chrm1* [46], *Gabra5* [47], *Gabrb2* [48], *Pck1* [28]. *Pck1* is essential for the genesis of carbachol-induced oscillations as indicated by the inability to induce oscillations with carbachol in the hippocampus of *Pck1* knockout mice [28]. *Pck1* is one of the candidate genes we identified, which can be regarded as an internal validation of our experimental and statistical procedures.

Our paradigm did not reveal other genes previously associated with hippocampal oscillations. A reason for this may be that the influence of such a gene may be caused by only a few single-nucleotide polymorphisms (SNPs). If C57BL/6J and DBA/2J do not differ in these SNPs, the paradigm we followed would not have revealed these genes. Moreover, most of the studies that try to link genes to brain activity use knockout-mice, in which the effect of the particular gene is likely to be stronger than in the BXD population. Also, the effect sizes of the genes known to be involved in hippocampal oscillations may be too small to be detected by our analysis.

Novel candidate genes associated with hippocampal activity

Our combined use of QTL mapping and correlation with expression data has some notable advantages. The QTL mapping was merely used to select stretches of the genome for further analysis, which justifies the use of suggestive significance. We qualified our findings with the significance level of the correlation with the expression data of genes within these QTLs.

We identified two candidate genes for shaping hippocampal network that code for calcium channels: the alpha1b subunit (*Caca1b*), and the alpha1e subunit (*Caca1e*). Calcium channels mediate synaptic transmission [49], and are essential in the formation of thalamo-cortical gamma band activity [50]. Also, *Caca1e* and *Caca1b* facilitate hippocampal long-term potentiation (LTP) [29,30], and the *Caca1b* knock-out mouse exhibits impaired long-term memory and LTP [51]. Thus, *Caca1e* and *Caca1b* are interesting candidates for playing a role in hippocampal oscillations. Moreover, *Caca1b* has been associated with schizophrenia in three recent linkage studies [52,53,54]. Thus, we may hypothesize that alterations in *Caca1e* and *Caca1b* affect hippocampal network activity such as to impair memory performance in, for example, schizophrenia patients known to suffer from memory impairment.

In a QTL for correlations (ACSF) we identified the gene *Creb3*, coding for the transcription factor cAMP responsive element-binding protein 3. *Creb1* plays an important role in (spatial) memory [53]; increasing the expression level of *Creb1* in the hippocampus facilitates long-term memory [56]. Therefore, it might well be that *Creb3* is involved in hippocampal activity as well. The other gene identified for this trait is *Dctn3*, which has a function in the cytoskeleton [57]. Peak frequency was linked to *Ehd3* which is involved in endosome to Golgi transport [58]. *Psmc2*, associated with amplitude 1–45 Hz (ACSF), is involved in developmentally programmed cell death [59]. *Ralgps2*, linked to amplitude 1–45 Hz (CCH), affects neurite outgrowth [60].

In summary, we identified eight candidate genes for influencing different aspects of hippocampal network activity. Future research, by means of knockout mice or pharmacological manipulations, should reveal the mechanisms by which these genes affect hippocampal activity and related cognitive functions.

Table 1. QTL mapping and correlation with gene expression revealed eight candidate genes for influencing hippocampal activity.

| Table 1. QTL mapping and correlation with gene expression revealed eight candidate genes for influencing hippocampal activity. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| trait           | location QTL    | LRS             | genes           | Correlation     | p-value         |
| Amplitude 1–45 Hz (ACSF) | chr 5 16.522–22.723 | 14.6           | Psmc2           | −0.63           | 0.01           |
| Correlation (ACSF)   | chr 4 39.167–44.254 | 15.1           | Dctn3           | −0.59           | 0.04           |
| Amplitude 1–45 Hz (CCH) | chr 1 156.371–160.384 | 12.4           | Ralgps2         | 0.61            | 0.03           |
| Peak amplitude     | chr 2 132.507–135.784 | 18.2           | Pck1            | 0.58            | 0.02           |
| Peak frequency     | chr 2 22.673–25.693 | 12.2           | Caca1b          | 0.57            | 0.03           |
|                  | chr17 72.002–76.447 | 12.6           | Ehd3            | 0.60            | 0.005          |

Each row contains the information belonging to one candidate gene. Indicated are the hippocampal activity trait associated with the gene, the location of the QTL (chr = chromosome, location in Megabases) that harbors the gene found, the LRS score of the QTL, the gene symbol, the correlation between trait and level of expression of the gene, and finally the p-value from the correlation, computed with a permutation test. doi:10.1371/journal.pone.0026586.t001
Materials and Methods

Animals, hippocampal slice preparation and extracellular recording

All experiments were performed in accordance with the guidelines and under approval of the Animal Welfare Committee of the VU University Amsterdam. BXD strains were originally purchased from Jackson Lab, or from Oak Ridge Laboratory (BXD43, BXD51, BXD61, BXD65, BXD68, BXD69, BXD73, BXD75, BXD87, BXD90), and were bred by the NeuroBsk consortium. In this study we used in total 586 slices from 322 animals (62% male), from 29 BXD strains: BXD01 (n = 20), BXD02 (n = 28), BXD08 (n = 18), BXD11 (n = 12), BXD12 (n = 20), BXD13 (n = 16), BXD16 (n = 22), BXD27 (n = 13), BXD28 (n = 13), BXD29 (n = 8), BXD31 (n = 14), BXD32 (n = 23), BXD33 (n = 19), BXD34 (n = 24), BXD39 (n = 17), BXD40 (n = 18), BXD42 (n = 28), BXD43 (n = 17), BXD51 (n = 36), BXD55 (n = 22), BXD61 (n = 16), BXD65 (n = 18), BXD68 (n = 20), BXD69 (n = 28), BXD73 (n = 27), BXD75 (n = 23), BXD87 (n = 31), BXD90 (n = 19), and BXD96 (n = 17). Per animal, maximally 2 slices were used. Unanesthetized mice were decapitated at postnatal day 13–15. The brains were quickly dissected and placed in ice-cold artificial cerebrospinal fluid (ACSF) containing 125 mM NaCl, 25 mM NaHCO3, 3 mM KCl, 1.2 mM NaH2PO4, 1 mM CaCl2, 3 mM MgSO4, and 10 mM D(+)-glucose (carboxygenated with 5% CO2/95% O2). Horizontal slices (400 μm thick) from the ventral hippocampus were cut by a microtome (Microm, Waldorf, Germany). Slices were stored in an interface storage chamber at room temperature and placed in ACSF containing 2 mM CaCl2 and 2 mM MgSO4. After 1 hour, slices were placed on 8-by-8 planar electrode grids with 200 μm spacing between electrodes (the 4 corners of the grid did not contain electrodes; see Fig. 1A) and polyethyleneimine coating (Sigma, St. Louis, MO, USA). The slices were left for 1 hour in a chamber with humidified carbogen gas before they were placed in the recording unit. During recordings the flow rate was 4–5 ml/min and the temperature was kept at 30±0.3°C. Carbachol was purchased from Sigma. Local field potentials (LFPs) were measured at each of the 60 electrodes, sampled at 1 kHz, down-sampled off-line to 200 Hz and converted into Matlab (The Mathworks, USA) file format. Off-line analysis was done using custom written scripts in Matlab.

Slice selection and subregion classification

For each experiment a photograph was taken of the slice in the recording unit, to visualize the locations of the electrodes in the hippocampus (Fig. 1A). The hippocampus consists of three main anatomical regions: CA1, CA3 and dentate gyrus (DG). We divided CA3 and CA1 into the subregions stratum oriens, stratum pyramidale and stratum radiatum/lacunosum-moleculare, and DG into stratum molecular, stratum granulosum and hilus (Fig. 1B). To classify electrode locations into one of these nine subregions, we used an in-house written interactive Matlab procedure based on the photograph of the electrode grid. Using Fourier analysis (see below), we determined for each electrode whether oscillatory activity was present. A slice was excluded from further analysis if none of the 60 electrodes showed oscillations.

For each condition, in order to detect electrodes producing noisy signals and transient artifacts before the quantitative trait analysis, each slice recording was subjected to a principal component analysis. If noisy signals were present, then the first few spatial components had high values only for one or a few of these signals. These signals were identified and excluded. The time series of the remaining signals were averaged; this average was used to identify noisy segments. Samples from this average with absolute values exceeding five times the standard deviation of the averaged signal, were excluded from each signal before the analysis.

Experimental protocol to measure hippocampal network activity

After placing the slices in the recording units with ACSF, 15 minutes of spontaneous activity was recorded (see Fig. 1C). These first 15 minutes will be referred to as the “ACSF condition”. Then, carbachol (25 μM) was bath applied to the slice. Carbachol-induced oscillations at around 20 Hz were initially unstable in frequency and amplitude, but stabilized after 45 minutes. After this 45-minute wash-in period fast network oscillations were recorded for a period of 30 minutes, which will be referred to as the “carbachol condition”. In Figure 1C a time-frequency representation of a representative signal is shown for a complete recording. Example LFP traces for the two conditions are shown in Figure 1D. The frequency of oscillations increased with temperature (Fig. 1F), which has been observed previously [61,62]. Thus, the oscillations at around 20 Hz, which were recorded at 30°C in the present experiments, are expected to have frequencies in the gamma range (>30 Hz) at the physiological temperature of 36.9°C. However, the amplitude of oscillations at higher temperatures was markedly lower than at 30°C, resulting in an unfavorable signal-to-noise ratio. Therefore, all experiments were performed at 30°C.

Fourier analysis

For the two conditions (ACSF and carbachol), and for each electrode that was classified into one of the nine regions, we calculated the Fourier amplitude spectrum using Welch’s method [63]. Figure 1E shows representative spectra in the two conditions. For the ACSF condition, we calculated the integrated amplitude in the frequency bands 1–4, 4–7, 7–13, 13–25, 25–35, and 35–45 Hz. In the carbachol condition, we observed oscillations at around 20 Hz, which is similar to previous reports using a temperature of around 30°C in mouse hippocampus [11,64,65]. We calculated the amplitude and the frequency of these oscillations, which we will refer to as the peak amplitude and the peak frequency, respectively. Moreover, a 1/f curve was fitted to the spectrum outside the interval at which the peak occurred, and from this curve we calculated the integrated amplitude in the frequency bands 1–4, 4–7, 7–13, 13–25, 25–35, and 35–45 Hz. For each of these measures, the traits we used for the cluster analysis (see below) were the mean trait values across electrodes per anatomical subregion (n = 54 traits for the ACSF condition, n = 72 traits for the carbachol condition).

To establish whether oscillations were detected at a given electrode, we applied the following procedure. First, a frequency interval in which the peak of the spectrum occurred was determined visually, e.g., for the spectrum in Figure 1E this interval would be from 10 to 25 Hz. Next, a 1/f curve was fitted to the spectrum outside this interval. This 1/f curve was then subtracted from the original spectrum. Finally, a Gaussian curve was fitted to the remaining spectrum. If the peak of this Gaussian curve did not exceed the 95% confidence interval of the fitted 1/f curve, we classified the signal as not oscillating. Slices were excluded from further analysis when none of the electrodes detected oscillations.

Interaction between hippocampal regions

To quantify the interaction between two hippocampal subregions, e.g., between CA1 stratum oriens and CA3 stratum oriens, we calculated a suitable cross-correlation measure (as described
the normality assumption for ANOVA. For inbred strains, we 
can estimate the genetic correlation between two traits as the 
Pearson’s linear correlation between the 29 mouse strain 
means of one trait and the 29 mouse strain means of the 
other trait [69,70]. The mouse strain means were taken over 
all slices from a given mouse strain. The estimated genetic 
correlations were used in a cluster analysis, as explained 
below.

Cluster analysis of traits

In order to identify clusters of genetically correlated traits, 
hierarchical clustering was performed on the complete set of 
\( n = 198 \) traits. In this analysis, traits are clustered based on a 
distance measure between the traits. To measure the distance 
between two traits, we subtracted the estimated genetic 
correlation between the two traits from 1, so traits with high genetic 
correlation are close to each other. No strong negative correlations 
were present; using absolute genetic correlation yielded similar 
results. Average linkage was used as a clustering method. This 
method starts with as many clusters as there are traits, and 
then sequentially joins the two clusters that are closest to each other 
in terms of the mean of distances between all possible pairs of traits 
in the two clusters; the procedure ends when all traits are joined in 
one cluster. A particular classification of traits into clusters is 
obtained by setting a threshold for the minimal distance that the 
clusters are allowed to have between them. The result of the 
cluster analysis was visualized in a dendrogram, in which the 
sequential union of clusters was depicted together with the distance 
value (the height of the horizontal lines that connect the objects or 
clusters) leading to this union. The threshold procedure can be 
visualized by a horizontal line in the dendrogram; the clusters 
under this line correspond to that particular threshold.

BDX recombinant inbred strains and QTL mapping

The BDX strains were created by crossing the inbred mouse 
strains C57BL/6J and DBA/2J and by inbreeding several groups 
of the crossed offspring [35]. It is one of the largest mammalian 
recombinant inbred strain panels currently available. Genetically, 
each of these BDX strains is a unique combination of the C57BL/ 
6J and DBA/2J strains. The chromosomes of the BDX strains 
consist of haplotypes (stretches of chromosomes inherited intact 
from the parental strains). Each BDX strain was genotyped at 
3795 markers covering the entire genome; each marker was 
classified as originating from C57BL/6J or DBA/2J. In order to 
calculate the correlation between a trait and these markers, 
the markers were encoded, \(-1\) for DBA/2J version of the marker and 
1 for C57BL/6J version of the marker. Markers that correlate with 
a trait are called QTLs. We used WebQTL (www.genenetwerk. 
org) to compute and visualize the QTL interval mapping. In 
WebQTL, the correlation between a marker and a trait was 
transformed into likelihood ratio statistics (LRS) in the following 
way: \( LRS = N \log (1/(1-r^2)) \), where \( N \) is the number of strains, and \( r \) 
the correlation [71]. For intervals with unknown genotype, LRS 
scores of flanking markers were linearly interpolated. Threshold 
for significant LRS scores were computed using a permutation 
test: the \( N \) strain means from the trait were permuted, and for this 
permutation the maximum LRS score over all markers was 
computed, which resulted in an observation of the null-
distribution. Significance of LRS scores was computed by 
comparing them with the empirical null-distribution. LRS scores 
were termed significant if \( p<0.05 \), and suggestive if \( p<0.63 \). The 
QTL mapping was used to select regions of the genome for further 
analysis, which justifies the use of suggestive significance. The 
QTL intervals were determined with the 1 LOD drop-off method 
[72]; the interval ends where the LRS score drops more than 4.61
Correlations with traits from the GeneNetwork phenotype database

The GeneNetwork database (www.genenetwork.org) contains more than 2000 phenotypes from previous studies using BXD strains. We computed genetic correlations between the hippocampal activity traits and two subsets of phenotypes from this database. By using subsets, the correction for multiple testing is reduced. To further reduce the risk of chance correlations, we only included phenotypes from the database that were reported for more than six BXD strains that were also used in the present study. The first subset ($n=35$) contained physiological traits of the hippocampus. The second subset ($n=351$) contained the behavioral traits that do not involve pharmacological manipulations. See Tables S1 and S2 for trait description and GeneNetwork IDs of both subsets.

To correct the significance for multiple testing, we used the false discovery rate (FDR) [75,76]. The FDR controls the expected proportion of erroneously rejected hypothesis. It is the number of falsely rejected hypotheses divided by the total number of rejected hypotheses. In our case, the total number of rejected hypotheses is the number of observed correlations with $p$-values lower than a threshold. The number of falsely rejected hypotheses was estimated with a permutation paradigm. The hippocampal activity trait was permuted thousand times across strains, and the correlation between the permuted trait and the traits from the subsets was computed. The number of falsely rejected hypotheses was estimated as the average number of correlations with $p$-values smaller than the threshold.

Gene expression data

Data on gene expression in hippocampal tissue of adult mice, measured with Affymetrix Mouse Exon 1.0 ST Arrays, were accessed through GeneNetwork (UMUTAffy Hippocampus Exon (Feb09) RMA, accession number GN206, from www.genenetwork.org). The original data set contained over 1.2 million probe sets that contain SNPs that differed between the two parental strains (according to databases snp_celera_b37 and snp_perlegen_b37 (2008) downloaded from http://phenome.jax.org). Probe sets targeting introns and intergenic regions were also removed, which reduced the amount of probe sets to 340318. We analyzed the expression per gene by taking the mean over all probes that target the same gene. For each hippocampal activity trait, we only calculated correlations with expression of genes from the QTLs of the trait. Significance levels for these correlations were determined with a permutation test; the hippocampal activity trait was permuted across strains, and the maximum of the correlations between the permuted trait and the expression of the genes was computed. This was done a thousand times; the thousand maxima so obtained formed the empirical null distribution against which the significance of a correlation was tested.

Subjects for locomotion in open field test

Six-week-old male mice ($n>10$ per strain, see section “animals, slice preparation and recording” for strain names) arrived in the facility in different batches in a period spanning 2 years. Mice were housed individually in Macrolon cages on sawdust bedding, which were, for the purpose of animal welfare, enriched with cardboard nesting material and a curved PVC tube. Food (Harlan Teklad) and water was provided ad libitum. All mice were habituated to the facility for at least 7 days before testing started.

Prior to the open field testing described below, mice had been exposed to novelty tests in the home cage, an elevated plus maze and a light dark box apparatus, as described previously [79]. Housing and testing rooms were controlled for temperature, humidity and light-dark cycle (7 AM lights on, 7 PM lights off; testing during the light phase).

Locomotion in open field

All experimental procedures were approved by the local animal research committee and complied with the European Council Directive (86/609/EEC). Mice were introduced into a corner of a white square open field (50x50 cm, walls 35 cm high) illuminated with a single white fluorescent light bulb from above (130 lx), and exploration was tracked for 10 minutes (12.5 frames/s; EthoVision 3.0, Noldus Information Technology). The SEE software (Strategy for the Exploration of Exploration [42,80] was used to smoothen progress segments, which together constitute the total distance moved. Furthermore, SEE uses the distribution of speed peaks to parse the locomotor data into lingering segments (slow local movements) and progression segments, which together constitute the total distance moved.

Supporting Information

Figure S1  Zoom in of the QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr4 40.937–49.610 Mb. The LRS scores ($y$-axis) quantify the relation between genomic markers ($x$-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S2  Zoom in of the QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr4 53.915–65.605 Mb. The LRS scores ($y$-axis) quantify the relation between genomic markers ($x$-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S3  Zoom in of the QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr5 16.516–22.717 Mb. The LRS scores ($y$-axis) quantify the relation between genomic markers ($x$-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S4  Zoom in of the QTL for the trait Correlation (ACSF), located at Chr4 38.926–44.246 Mb. The LRS scores ($y$-axis) quantify the relation between genomic markers ($x$-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S5  Zoom in of the QTL for the trait Correlation (ACSF), located at Chr4 58.377–62.347 Mb. The LRS scores ($y$-axis) quantify the relation between genomic markers ($x$-axis) and the trait. Parental allele effect is shown in green and red:...
a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S6 Zoom in of the QTL for the trait Correlation (ACSF), located at Chr14 56.052–59.824 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S7 Zoom in of the QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr2 19.000–25.727 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S8 Zoom in of the QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr1 135.653–160.478 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S9 Zoom in of the QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr2 57.639–60.486 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S10 Zoom in of the QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr2 65.6704–72.240 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S11 Zoom in of the QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr3 1343–12.371 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S12 Zoom in of the QTL for the trait Peak amplitude, located at Chr2 19.000–25.727 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S13 Zoom in of the QTL for the trait Peak amplitude, located at Chr2 132.641–135.954 MB. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S14 Zoom in of the QTL for the trait Peak amplitude, located at Chr5 3.143–20.086 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S15 Zoom in of the QTL for the trait Correlation (CCH), located at Chr2 76.832–80.436 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S16 Zoom in of the QTL for the trait Correlation (CCH), located at Chr2 133.463–135.918 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S17 Zoom in of the QTL for the trait Correlation (CCH), located at Chr5, Chr5 4.468–12.371 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S18 Zoom in of the QTL for the trait Peak frequency, located at Chr12 30.140–35.762 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Figure S19 Zoom in of the QTL for the trait Peak frequency, located Chr17 72.196–76.447 Mb. The LRS scores (y-axis) quantify the relation between genomic markers (x-axis) and the trait. Parental allele effect is shown in green and red: a green line indicates that DBA/2J alleles increase trait values. A red line indicates that C57BL/6J alleles increase trait values. (PNG)

Table S1 Heritability scores (h) and P-values from F statistics from the ANOVAs of all the traits derived in the ACSF condition (spontaneous activity). The trait names are coded: Amplitude a_b_Hz_c indicates the integrated amplitude between a and b Hz, in region number c. Corr(a,b) indicates the correlation of activity between region a and region b. The numbers refer to the following regions: 1 = CA3 stratum radiatum/lacunosum moleculare, 2 = CA3 stratum pyramidale, 3 = CA3 stratum oriens, 4 = CA1 stratum radiatum/lacunosum moleculare, 5 = CA1 stratum pyramidale, 6 = CA1 stratum oriens, 7 = Dentate Gyrus hilus, 8 = Dentate Gyrus stratum granulosum, 9 = Dentate Gyrus stratum moleculare.

Table S2 Heritability scores (h) and P-values from F statistics from the ANOVAs of all the traits derived in the carbachol condition (oscillations). The trait names are coded: Amplitude a_b_Hz_c indicates the integrated amplitude between a and b Hz, in region c. Amplitude_a is the peak amplitude in region a, Frequency_a indicates the peak frequency in region a.
PLF(a,b) is the phase locking factor of the activity between region a and region b. The numbers refer to the following regions: 1 = CA3 stratum radiatum/lacunosum moleculare, 2 = CA3 stratum pyramidal, 3 = CA3 stratum oriens, 4 = CA1 stratum radiatum/lacunosum moleculare, 5 = CA1 stratum pyramidale, 6 = CA1 stratum oriens, 7 = Dentate Gyrus hilus, 8 = Dentate Gyrus stratum granulosum, 9 = Dentate Gyrus stratum molecular.

Table S3 Description and IDs of first subset of phenotypes from the GeneNetwork phenotype database: physiological hippocampal traits.

Table S4 Description and IDs of second subset of phenotypes from the GeneNetwork phenotype database: behavioral traits.

Table S5 List of genes in a QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr4 40.937–49.610 Mb.

Table S6 List of genes in a QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr4 53.915–65.605 Mb.

Table S7 List of genes in a QTL for the trait Amplitude 1–45 Hz (ACSF), located at Chr5 16.516–22.717 Mb.

Table S8 List of genes in a QTL for the trait Correlation (ACSF), located at Chr4 38.926–44.246 Mb.

Table S9 List of genes in a QTL for the trait Correlation (ACSF), located at Chr4 58.377–62.347 Mb.

Table S10 List of genes in a QTL for the trait Correlation (ACSF), located at Chr14 56.052–59.824 Mb.

Table S11 List of genes in a QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr1 156.053–160.478 Mb.

Table S12 List of genes in a QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr1 109.358–128.626 Mb.

Table S13 List of genes in a QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr2 57.639–60.486 Mb.

Table S14 List of genes in a QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr2 65.6704–72.240 Mb.

Table S15 List of genes in a QTL for the trait Amplitude 1–45 Hz (CCH), located at Chr3 3.143–12.371 Mb.

Table S16 List of genes in a QTL for the trait Peak amplitude, located at Chr2 19.000–25.727 Mb.

Table S17 List of genes in a QTL for the trait Peak amplitude, located at Chr2 132.641–135.954 MB.

Table S18 List of genes in a QTL for the trait Peak amplitude, located at Chr3 3.143–20.086 Mb.

Table S19 List of genes in a QTL for the trait Correlation (CCH), located at Chr2 76.832–80.436 Mb.

Table S20 List of genes in a QTL for the trait Correlation (CCH), located at Chr2 133.463–135.918 Mb.

Table S21 List of genes in a QTL for the trait Correlation (CCH), located at Chr5 4.468–12.371 Mb.

Table S22 List of genes in a QTL for the trait Peak frequency, located Chr17 72.196–76.447 Mb.

Table S23 List of genes in a QTL for the trait Peak frequency, located at Chr12 30.140–35.762 Mb.

Table S24 The locations of the 19 QTLs.

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