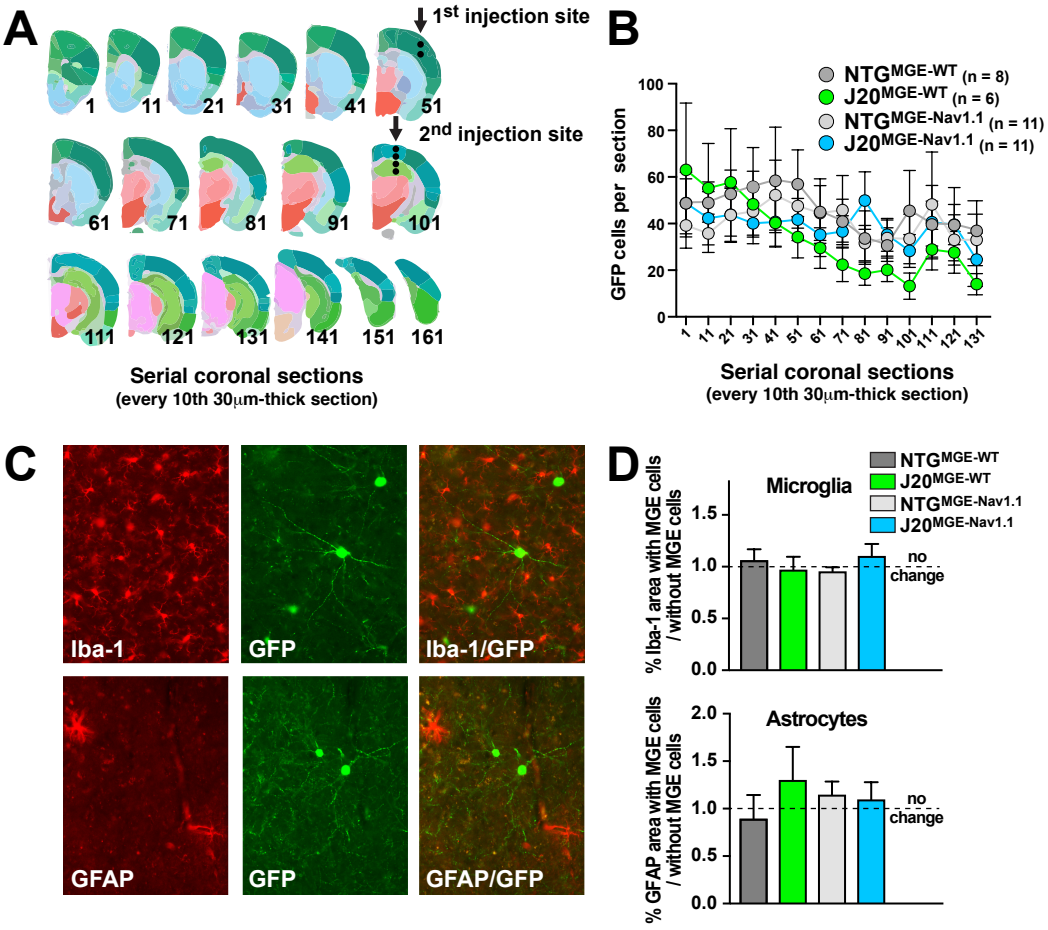
A
1st injection site
2nd injection site
1
11
21
31
41
51
61
71
81
91
101
111
121
131
141
151
161
Serial coronal sections
(every 10th 30μm-thick section)
B
NTGMGE-WT (n = 8)
J20MGE-WT (n = 6)
NTGMGE-Nav1.1 (n = 11)
J20MGE-Nav1.1 (n = 11)
GFP cells per section
Serial coronal sections
(every 10th 30μm-thick section)
C
Iba-1
GFP
Iba-1/GFP
GFAP
GFP
GFAP/GFP
D
Microglia
% Iba-1 area with MGE cells / without MGE cells
no change
Astrocytes
% GFAP area with MGE cells / without MGE cells

Figure S1

Supplemental Figure S1. Related to Figure 1. MGE-Derived Cell Distribution and Glia Response.

(**A**) Diagram indicating the injection sites. We transplanted cells bilaterally in the somatosensory cortex (1st injection site; two levels indicated by black dots) and in the dorsal hippocampus and the above cortical region (2nd injection site; four levels indicated by back dots). See methods for the stereotaxic coordinates.

(**B**) NTG and J20 mice received MGE^{WT} or MGE$^{Nav1.1}$ cell transplants into the hippocampus and cortex at P3–5. After 7–8 months, GFP^{Lhx6}-positive MGE-derived cells were counted in every 10th serial coronal 30µm-section throughout the rostrocaudal extent of the right forebrain. Distribution of GFP^{Lhx6}-positive MGE-derived interneurons throughout the rostrocaudal extent of the forebrain. 21,696 MGE-derived cells were counted (n = 6–11 mice per group, 537 brain sections, and 13–18 sections per mouse). Data are means ± SEM.

(**C** and **D**) Brain sections from 7–8-month-old NTG and J20 mice transplanted at P3–5 with MGE^{WT} or MGE$^{Nav1.1}$ cells were labeled for Iba-1 (red, microglia) or GFAP (red, astrocytes) and GFP (green, MGE cells) (**C**). % Area occupied by microglia (top) or astrocytes (bottom) in adjacent areas with or without GFP-MGE-derived interneurons (internal control) was quantified and the ratio calculated. The presence of MGE^{WT}- or MGE$^{Nav1.1}$-derived cells did not change microglia or astrocyte levels in NTG or J20 mice (n = 3 mice per group). $P > 0.05$ by one-way ANOVA and Bonferroni *post hoc* test.

Values are mean ± SEM.

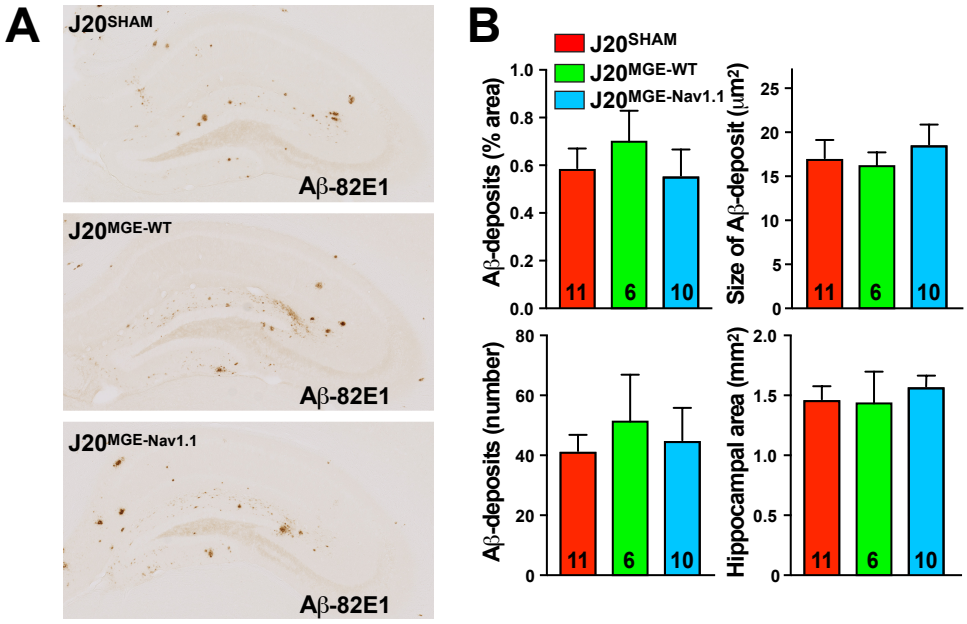
A
J20SHAM
Aβ-82E1
J20MGE-WT
Aβ-82E1
J20MGE-Nav1.1
Aβ-82E1
B
J20SHAM
J20MGE-WT
J20MGE-Nav1.1
Aβ-deposits (% area)
1.0
0.8
0.6
0.4
0.2
0.0
11
6
10
Size of Aβ-deposit (μm²)
25
20
15
10
5
0
11
6
10
Aβ-deposits (number)
80
60
40
20
0
11
6
10
Hippocampal area (mm²)
2.0
1.5
1.0
0.5
0
11
6
10

Figure S2

Supplemental Figure S2. Related to Figure 1. MGE Cell Transplants Do Not Alter Early Hippocampal Amyloid Deposition in J20 Mice.

(**A**) J20 mice were sham-treated or transplanted with MGE^{WT} or $MGE^{Nav1.1}$ cells into the hippocampus and cortex at P3–5. After 7–8 months, hippocampal Aβ-positive deposits were measured by immunohistochemistry analyses using the anti-Aβ 82E1 antibody.

(**B**) Compared to sham-treated mice, MGE^{WT}- or $MGE^{Nav1.1}$-derived cell transplants did not change the % area occupied by Aβ-deposits, size of Aβ-deposits or number of Aβ-deposits in the hippocampus of J20 mice. Hippocampal area was also not altered by MGE transplants. $P > 0.05$ by one-way ANOVA and Bonferroni *post hoc* test. Values are mean ± SEM. Numbers in bars indicate numbers of mice.

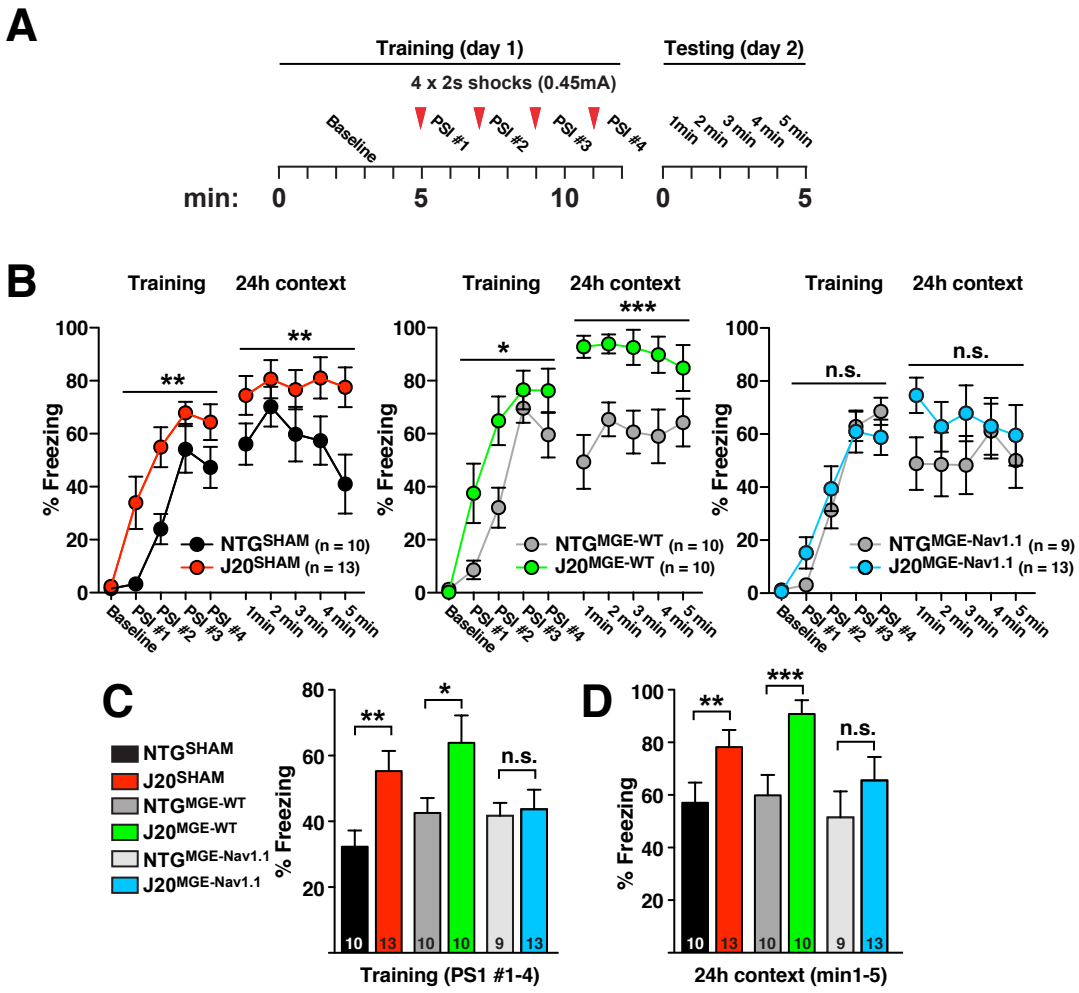
A
Training (day 1)
4 x 2s shocks (0.45mA)
Testing (day 2)
Baseline
PSI #1
PSI #2
PSI #3
PSI #4
1min
2 min
3 min
4 min
5 min
min:
0
5
10
0
5
B
Training
24h context
% Freezing
NTGSHAM (n = 10)
J20SHAM (n = 13)
NTGMGE-WT (n = 10)
J20MGE-WT (n = 10)
NTGMGE-Nav1.1 (n = 9)
J20MGE-Nav1.1 (n = 13)
n.s.
C
NTGSHAM
J20SHAM
NTGMGE-WT
J20MGE-WT
NTGMGE-Nav1.1
J20MGE-Nav1.1
Training (PS1 #1-4)
D
24h context (min1-5)

Figure S3

Supplemental Figure S3. Related to Figure 2. MGE$^{Nav1.1}$ Cell Transplants Prevent Excessive Freezing in J20 Mice. Mice were sham treated or received MGE^{WT} or MGE$^{Nav1.1}$ cell transplants bilaterally into the hippocampus and cortex at P3–5. Mice were tested in a fear-conditioning test at 4–7 months of age.

(**A**) Training and testing protocols.

(**B**) Change in freezing behavior (*n* = 9–13 mice per group).

(**C**) MGE$^{Nav1.1}$, but not MGE^{WT}, cell transplants prevented excessive freezing in J20 mice during training. PSI, post-shock interval.

(**D**) Average freezing in the 5-min 24-h context test. Values are mean ± SEM. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 by repeated-measures ANOVA and Bonferroni *post hoc* test. n.s., not significant. (B) or one-way ANOVA and Bonferroni *post hoc* test (C and D).

Values are means ± SEM.

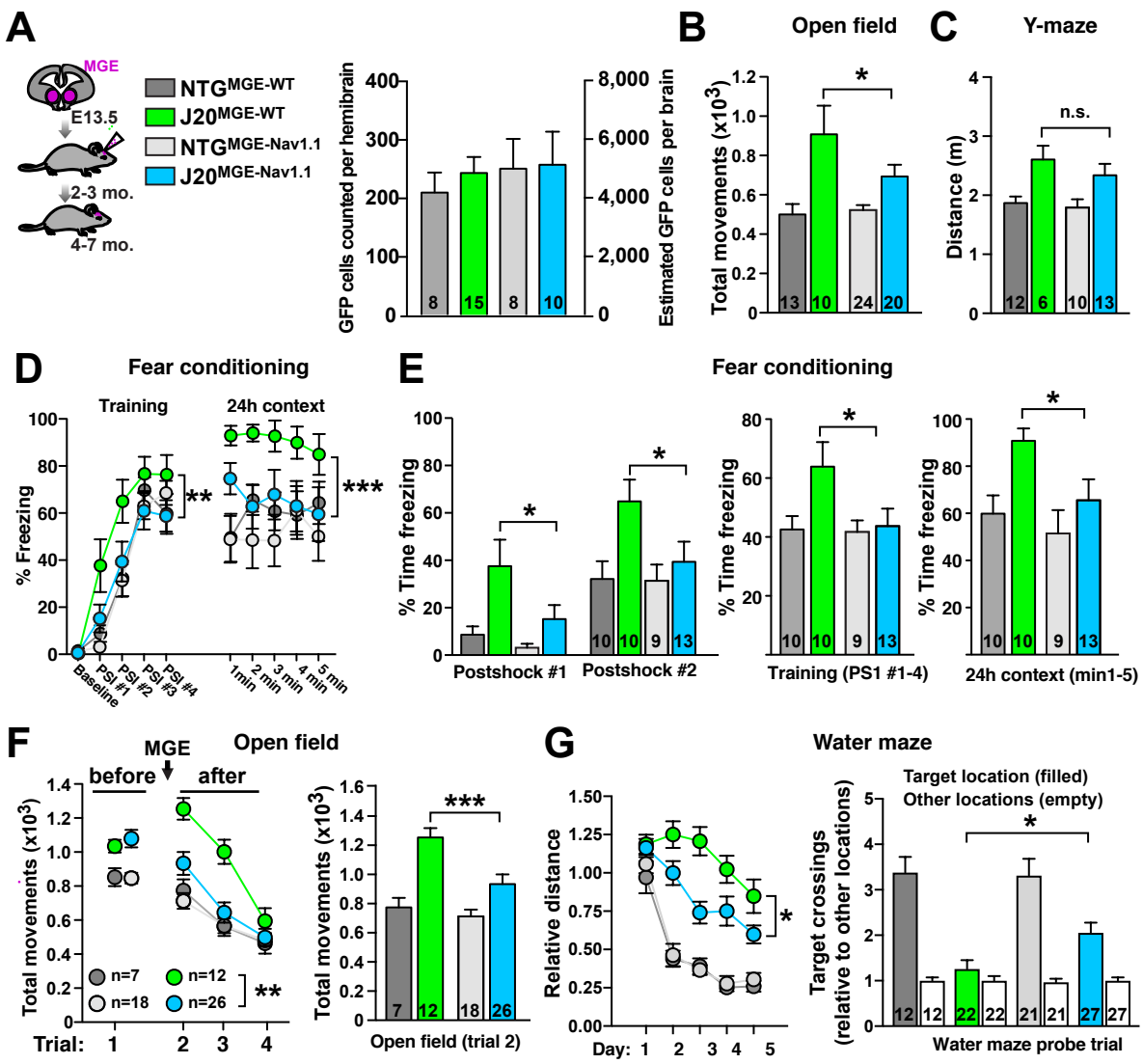
A
MGE
E13.5
2-3 mo.
4-7 mo.
NTGMGE-WT
J20MGE-WT
NTGMGE-Nav1.1
J20MGE-Nav1.1
GFP cells counted per hemibrain
Estimated GFP cells per brain
B
Open field
Total movements (x10³)
C
Y-maze
Distance (m)
n.s.
D
Fear conditioning
Training
24h context
% Freezing
Baseline
PSI #1
PSI #2
PSI #3
PSI #4
1min
2 min
3 min
4 min
5 min
E
Fear conditioning
% Time freezing
Postshock #1
Postshock #2
Training (PS1 #1-4)
24h context (min1-5)
F
MGE
before
after
Open field
Total movements (x10³)
n=7
n=18
n=12
n=26
Trial:
Open field (trial 2)
G
Water maze
Relative distance
Day:
Target location (filled)
Other locations (empty)
Target crossings (relative to other locations)
Water maze probe trial

Figure S4

Supplemental Figure S4. Related to Figure 2. Nav1.1 Expression in MGE cells is Required to Reduce Behavioral and Cognitive Abnormalities in J20 Mice. Direct statistical comparisons between $J20^{MGE\text{-}WT}$ and $J20^{MGE\text{-}Nav1.1}$ mice by one-way ANOVA and Bonferroni *post hoc* test (B, C, E, F right, and G right) or by repeated-measures one-way ANOVA and Bonferroni *post hoc* test (D, F left, G left) for the behavioral tests described in Figure 2.

(**A**) J20 and NTG mice received MGE^{WT} or $MGE^{Nav1.1}$ cell transplants bilaterally into the hippocampus and cortex at 2–3 months of age. Number of GFP-positive cells per hemibrain (*left*) and estimated number of GFP-positive cells per brain (*right*). Cells were counted in every 10th serial section in one hemibrain per mouse at 7–8 months of age (n = 8–15 mice per group). Values are mean ± SEM. Numbers in bars are the numbers of mice.

(**B**–**E**) J20 and NTG mice received MGE^{WT} or $MGE^{Nav1.1}$ cell transplants bilaterally into the hippocampus and cortex at P3–5. Mice were tested in the open filed (**B**), Y-maze (**C**), and fear-conditioning tests (**D** and **E**) at 4–7 months of age.

(**F**–**G**) J20 and NTG mice received MGE^{WT} or $MGE^{Nav1.1}$ cell transplants into the hippocampus and cortex at 2–3 months of age. Mice were tested in the open filed (**F**) and Morris water maze tests (**G**) at 4–7 months of age.

Values are mean ± SEM. Numbers in bars indicate numbers of mice.

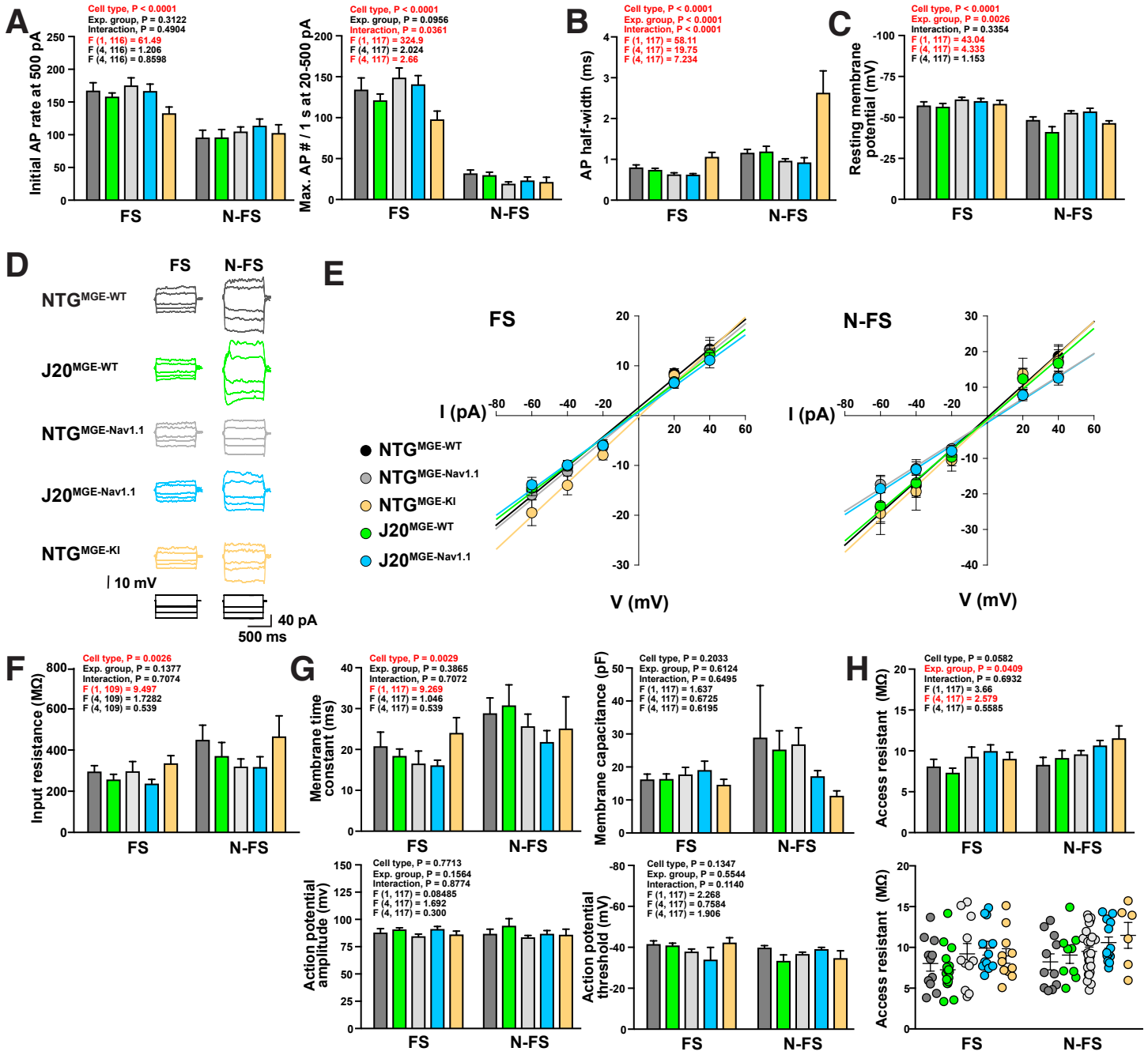
A
Initial AP rate at 500 pA
Cell type, P < 0.0001
Exp. group, P = 0.3122
Interaction, P = 0.4904
F (1, 116) = 61.49
F (4, 116) = 1.206
F (4, 116) = 0.8598
FS
N-FS
Max. AP # / 1 s at 20-500 pA
Cell type, P < 0.0001
Exp. group, P = 0.0956
Interaction, P = 0.0361
F (1, 117) = 324.9
F (4, 117) = 2.024
F (4, 117) = 2.66
B
AP half-width (ms)
Cell type, P < 0.0001
Exp. group, P < 0.0001
Interaction, P < 0.0001
F (1, 117) = 58.11
F (4, 117) = 19.75
F (4, 117) = 7.234
C
Resting membrane potential (mV)
Cell type, P < 0.0001
Exp. group, P = 0.0026
Interaction, P = 0.3354
F (1, 117) = 43.04
F (4, 117) = 4.335
F (4, 117) = 1.153
D
FS
N-FS
NTGMGE-WT
J20MGE-WT
NTGMGE-Nav1.1
J20MGE-Nav1.1
NTGMGE-KI
10 mV
40 pA
500 ms
E
FS
N-FS
I (pA)
V (mV)
NTGMGE-WT
NTGMGE-Nav1.1
NTGMGE-KI
J20MGE-WT
J20MGE-Nav1.1
F
Input resistance (MΩ)
Cell type, P = 0.0026
Exp. group, P = 0.1377
Interaction, P = 0.7074
F (1, 109) = 9.497
F (4, 109) = 1.7282
F (4, 109) = 0.539
G
Membrane time constant (ms)
Cell type, P = 0.0029
Exp. group, P = 0.3865
Interaction, P = 0.7072
F (1, 117) = 9.269
F (4, 117) = 1.046
F (4, 117) = 0.539
Membrane capacitance (pF)
Cell type, P = 0.2033
Exp. group, P = 0.6124
Interaction, P = 0.6495
F (1, 117) = 1.637
F (4, 117) = 0.6725
F (4, 117) = 0.6195
Action potential amplitude (mv)
Cell type, P = 0.7713
Exp. group, P = 0.1564
Interaction, P = 0.8774
F (1, 117) = 0.08485
F (4, 117) = 1.692
F (4, 117) = 0.300
Action potential threshold (mV)
Cell type, P = 0.1347
Exp. group, P = 0.5544
Interaction, P = 0.1140
F (1, 117) = 2.268
F (4, 117) = 0.7584
F (4, 117) = 1.906
H
Access resistant (MΩ)
Cell type, P = 0.0582
Exp. group, P = 0.0409
Interaction, P = 0.6932
F (1, 117) = 3.66
F (4, 117) = 2.579
F (4, 117) = 0.5585
Access resistant (MΩ)

Figure S5

Supplemental Figure S5. Related to Figures 4 and 5. Electrophysiological Properties of Transplanted MGE^{WT}, MGE$^{Nav1.1}$ or MGE$^{Nav1.1–KI}$-Derived Fast-Spiking (FS) and Non-Fast-Spiking (N-FS) Interneurons in NTG and J20 Mice. Mice received MGE^{WT}, MGE$^{Nav1.1}$ or MGE$^{Nav1.1–KI}$ cell transplants into the hippocampus and cortex at P3–5. Whole-cell patch-clamp recordings from acute coronal brain slices were performed at 6–11 months of age. FS: *n* = 11, 17, 11, 12, and 11 cells from 5 NTG^{MGE-WT}, 7 J20^{MGE-WT}, 4 NTG$^{MGE-Nav1.1}$, 4 J20 $^{MGE-Nav1.1}$, and 3 NTG$^{MGE-Nav1.1-KI}$ mice, respectively. N-FS: *n* = 11, 9, 26, 13, and 6 cells from 4 NTG^{MGE-WT}, 6 J20^{MGE-WT}, 8 NTG$^{MGE-Nav1.1}$, 4 J20 $^{MGE-Nav1.1}$, and 3 NTG$^{MGE-Nav1.1-KI}$ mice, respectively.

(**A**–**C**) The intrinsic properties used to classify the FS and N-FS interneurons included the initial firing rate of APs at 500 pA (**A**, left) and the maximum number of APs that fired in response to a 1-s current injection at any current intensity (20–500 pA) (**A**, right), the AP half-width (**B**) and the resting membrane potential (**C**).

(**D**–**F**) In current clamp mode, the membrane potential was maintained at -60 mV and 1-s current injections were applied to generate the current-voltage relationship of the MGE-derived FS and N-FS interneurons. (**D**) Representative traces of the membrane potential shifts elicited by incremental current injections in the FS and N-FS interneurons. (**E, F**) The slope of the current-voltage relationship in MGE-derived FS and N-FS interneurons was calculated to determine their input resistance.

(**G**) Quantification of the mean membrane time constant, membrane capacitance, AP amplitude and AP threshold.

(**H**) Bar (*top*) and scatter (*bottom*) graphs of the access resistance for all recorded MGE-derived interneurons. Access resistance was <16MΩ for all recorded cells.

Values are mean ± SEM. *P* values by two-way ANOVA assessing cell type, experimental group, and interaction. Significant *P* values are indicated in red.

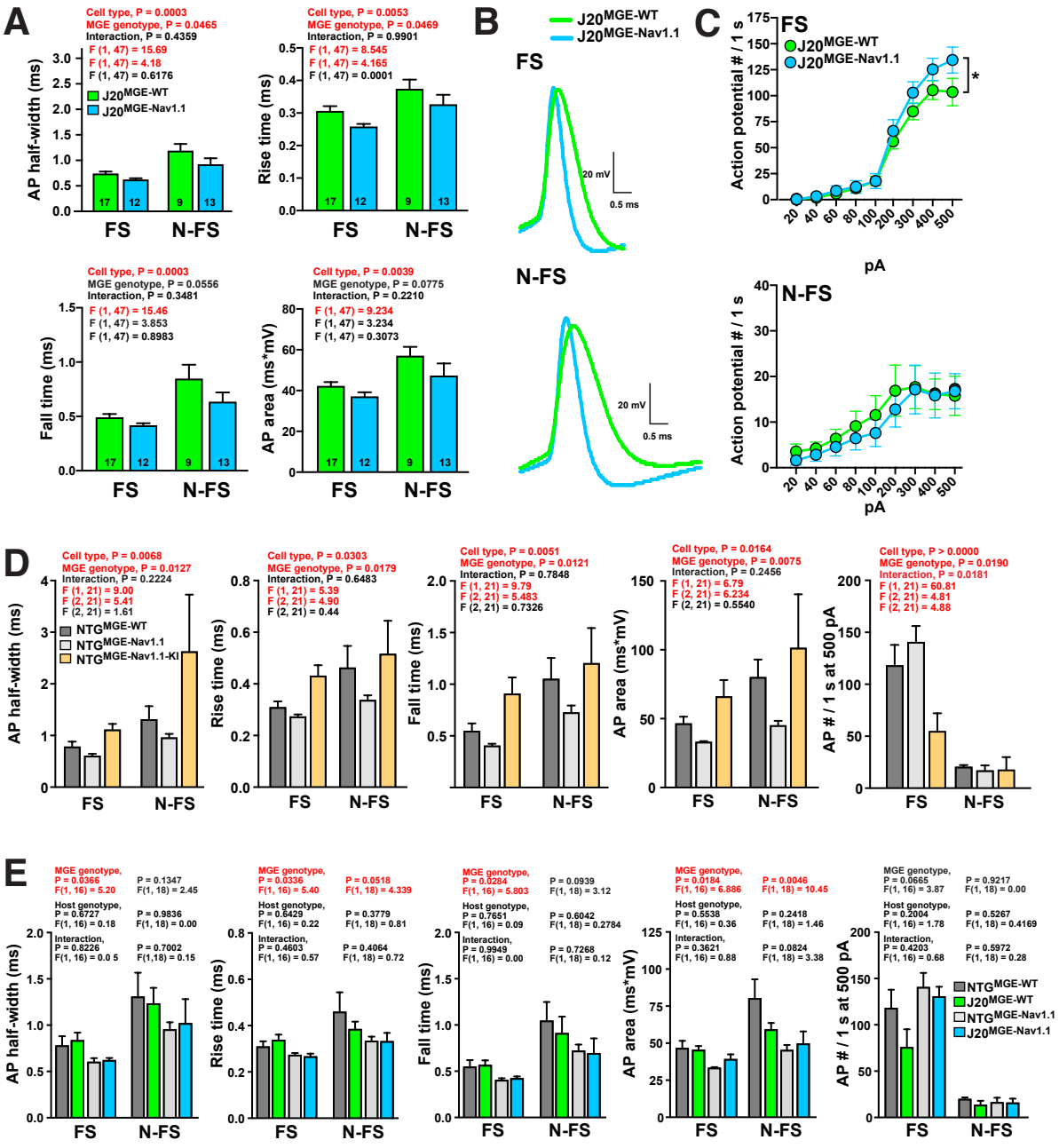
A
Cell type, P = 0.0003
MGE genotype, P = 0.0465
Interaction, P = 0.4359
F (1, 47) = 15.69
F (1, 47) = 4.18
F (1, 47) = 0.6176
J20MGE-WT
J20MGE-Nav1.1
AP half-width (ms)
Cell type, P = 0.0053
MGE genotype, P = 0.0469
Interaction, P = 0.9901
F (1, 47) = 8.545
F (1, 47) = 4.165
F (1, 47) = 0.0001
Rise time (ms)
Cell type, P = 0.0003
MGE genotype, P = 0.0556
Interaction, P = 0.3481
F (1, 47) = 15.46
F (1, 47) = 3.853
F (1, 47) = 0.8983
Fall time (ms)
Cell type, P = 0.0039
MGE genotype, P = 0.0775
Interaction, P = 0.2210
F (1, 47) = 9.234
F (1, 47) = 3.234
F (1, 47) = 0.3073
AP area (ms*mV)
17
12
9
13
FS
N-FS
B
J20MGE-WT
J20MGE-Nav1.1
FS
20 mV
0.5 ms
N-FS
20 mV
0.5 ms
C
FS
J20MGE-WT
J20MGE-Nav1.1
Action potential # / 1 s
*
pA
N-FS
Action potential # / 1 s
pA
D
Cell type, P = 0.0068
MGE genotype, P = 0.0127
Interaction, P = 0.2224
F (1, 21) = 9.00
F (2, 21) = 5.41
F (2, 21) = 1.61
NTGMGE-WT
NTGMGE-Nav1.1
NTGMGE-Nav1.1-KI
AP half-width (ms)
Cell type, P = 0.0303
MGE genotype, P = 0.0179
Interaction, P = 0.6483
F (1, 21) = 5.39
F (2, 21) = 4.90
F (2, 21) = 0.44
Rise time (ms)
Cell type, P = 0.0051
MGE genotype, P = 0.0121
Interaction, P = 0.7848
F (1, 21) = 9.79
F (2, 21) = 5.483
F (2, 21) = 0.7326
Fall time (ms)
Cell type, P = 0.0164
MGE genotype, P = 0.0075
Interaction, P = 0.2456
F (1, 21) = 6.79
F (2, 21) = 6.234
F (2, 21) = 0.5540
AP area (ms*mV)
Cell type, P > 0.0000
MGE genotype, P = 0.0190
Interaction, P = 0.0181
F (1, 21) = 60.81
F (2, 21) = 4.81
F (2, 21) = 4.88
AP # / 1 s at 500 pA
FS
N-FS
E
MGE genotype, P = 0.0366 F(1, 16) = 5.20
P = 0.1347 F(1, 18) = 2.45
Host genotype, P = 0.6727 F(1, 16) = 0.18
P = 0.9836 F(1, 18) = 0.00
Interaction, P = 0.8226 F(1, 16) = 0.0 5
P = 0.7002 F(1,18) = 0.15
AP half-width (ms)
MGE genotype, P = 0.0336 F(1, 16) = 5.40
P = 0.0518 F(1, 18) = 4.339
Host genotype, P = 0.6429 F(1, 16) = 0.22
P = 0.3779 F(1, 18) = 0.81
Interaction, P = 0.4603 F(1, 16) = 0.57
P = 0.4064 F(1, 18) = 0.72
Rise time (ms)
MGE genotype, P = 0.0284 F(1, 16) = 5.803
P = 0.0939 F(1, 18) = 3.12
Host genotype, P = 0.7651 F(1, 16) = 0.09
P = 0.6042 F(1, 18) = 0.2784
Interaction, P = 0.9949 F(1, 16) = 0.00
P = 0.7268 F(1, 18) = 0.12
Fall time (ms)
MGE genotype, P = 0.0184 F(1, 16) = 6.886
P = 0.0046 F(1, 18) = 10.45
Host genotype, P = 0.5538 F(1, 16) = 0.36
P = 0.2418 F(1, 18) = 1.46
Interaction, P = 0.3621 F(1, 16) = 0.88
P = 0.0824 F(1, 18) = 3.38
AP area (ms*mV)
MGE genotype, P = 0.0665 F(1, 16) = 3.87
P = 0.9217 F(1, 18) = 0.00
Host genotype, P = 0.2004 F(1, 16) = 1.78
P = 0.5267 F(1, 18) = 0.4169
Interaction, P = 0.4203 F(1, 16) = 0.68
P = 0.5972 F(1, 18) = 0.28
AP # / 1 s at 500 pA
NTGMGE-WT
J20MGE-WT
NTGMGE-Nav1.1
J20MGE-Nav1.1
FS
N-FS

Figure S6

Supplemental Figure S6. Related to Figures 4 and 5. Transplanted $MGE^{Nav1.1}$-Derived Interneurons Exhibit Faster AP Kinetics and Increased AP Firing Rates in J20 Mice. Mice received MGE^{WT}, $MGE^{Nav1.1}$ or $MGE^{Nav1.1–KI}$ cell transplants into the hippocampus and cortex at P3–5. Whole-cell patch-clamp recordings from acute coronal brain slices were performed at 6–11 months of age. FS: *n* = 11, 17, 11, 12, and 11 cells from 5 NTG^{MGE-WT}, 7 $J20^{MGE-WT}$, 4 $NTG^{MGE-Nav1.1}$, 4 J20 $^{MGE-Nav1.1}$, and 3 $NTG^{MGE-Nav1.1-KI}$ mice, respectively. N-FS: *n* = 11, 9, 26, 13, and 6 cells from 4 NTG^{MGE-WT}, 6 $J20^{MGE-WT}$, 8 $NTG^{MGE-Nav1.1}$, 4 J20 $^{MGE-Nav1.1}$, and 3 $NTG^{MGE-Nav1.1-KI}$ mice, respectively.

(**A**–**C**) Direct statistical comparisons between transplanted MGE^{WT}- and $MGE^{Nav1.1}$-derived FS and N-FS interneurons in J20 mice for the cells described in Figure 5. J20 mice received MGE^{WT} or $MGE^{Nav1.1}$ cell transplants into the hippocampus and cortex at P3–5. Whole-cell patch-clamp recordings from interneurons in the cortex of acute coronal brain slices were done at 6–11 months of age**.** (**A**) Quantification of AP waveform properties of MGE^{WT}- and $MGE^{Nav1.1}$-derived FS and N-FS interneurons in J20 mice. Numbers in bars indicate numbers of cells. *P* values by two-way ANOVA assessing MGE genotype (WT and Nav1.1), host brain genotype (NTG and J20), and interaction. *P* values by two-way ANOVA assessing MGE genotype (WT and Nav1.1), host brain genotype (NTG and J20), and interaction. Significant *P* values are in red. (**B**) Representative traces of AP waveforms recorded from MGE^{WT}- and $MGE^{Nav1.1}$-derived FS and N-FS interneurons in J20 mice. (**C**) Mean number of APs evoked by the indicated incremental current intensities in MGE^{WT}- and $MGE^{Nav1.1}$-derived FS (*top*) and N-FS (*bottom*) interneurons transplanted into J20 mice. $^{*}P < 0.05$ by repeated-measures ANOVA and Bonferroni test for 200–500 pA.

(**D**) Quantification of AP waveform properties of transplanted MGE^{WT}-, $MGE^{Nav1.1}$-, and $MGE^{Nav1.1–KI}$-derived FS and N-FS interneurons in NTG mice from Figure 4 analyzed using mice as the biological unit to calculate averages. FS: *n* = 5 NTG^{MGE-WT}, 4 $NTG^{MGE-Nav1.1}$, and 3 $NTG^{MGE-Nav1.1-KI}$ mice with 11, 11, and 11 cells analyzed, respectively. N-FS: *n* = 4 NTG^{MGE-WT}, 8 $NTG^{MGE-Nav1.1}$, and 3 $NTG^{MGE-Nav1.1-KI}$ mice with 11, 26, and 6 cells analyzed, respectively. *P* values by two-way ANOVA assessing cell type (FS and N-FS), MGE genotype (WT, Nav1.1, and Nav1.1-KI), and interaction. Significant *P* values are indicated in red.

(**E**) Quantification of AP waveform properties of MGE^{WT}- and $MGE^{Nav1.1}$-derived FS and N-FS interneurons in NTG and J20 mice from Figure 5 analyzed using mice as the biological unit to calculate averages. FS: *n* = 5 NTG^{MGE-WT}, 7 $J20^{MGE-WT}$, 4 $NTG^{MGE-Nav1.1}$, and 4 $J20^{MGE-Nav1.1}$ with 11, 17, 11, and 12 cells analyzed, respectively. N-FS: *n* = 4 NTG^{MGE-WT}, 6 $J20^{MGE-WT}$, 8 $NTG^{MGE-Nav1.1}$, and 4 $J20^{MGE-Nav1.1}$ mice with 11, 9, 26, and 13 cells analyzed, respectively. *P* values by two-way ANOVA assessing MGE genotype (WT and Nav1.1), host brain genotype (NTG and J20), and interaction.

Values are mean ± SEM.

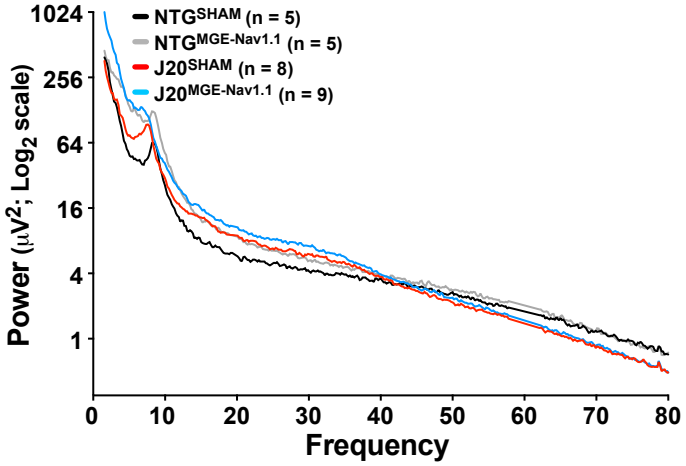
NTG^SHAM (n = 5)
NTG^MGE-Nav1.1 (n = 5)
J20^SHAM (n = 8)
J20^MGE-Nav1.1 (n = 9)
Power (μV²; Log2 scale)
1024
256
64
16
4
1
0
10
20
30
40
50
60
70
80
Frequency

Figure S7

Supplemental Figure S7. Related to Figure 7. Power Spectrum Analysis of NTG and J20 Mice Sham-Treated or Transplanted with MGE$^{Nav1.1}$ Cells. Mice were sham-treated or transplanted bilaterally with MGE$^{Nav1.1}$ cells at 2–3 months of age. EEGs were recorded at 7–8 months during the first 10 min of novel environment exploration (See Figure 6A). Please note that these dada represent raw power values without normalization to resting locomotor activity and experimental groups may differ in locomotor activity. Power spectrum data was extracted using Spike2 software version 8 with FFT size 1024 (resolution 0.1953) and Hanning window function.