Focal and generalized seizure activity after local hippocampal or cortical ablation of Na(V)1.1 channels in mice

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BRIEF COMMUNICATION

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Focal and generalized seizure activity after local hippocampal or cortical ablation of $Na_V1.1$ channels in mice

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Abstract

Early onset seizures are a hallmark of Dravet syndrome. Previous studies in rodent models have shown that the epileptic phenotype is caused by loss-of-function of voltage-gated $Na_V1.1$ sodium channels, which are chiefly expressed in γ-aminobutyric acid (GABA)ergic neurons. Recently, a possibly critical role has been attributed to the hippocampus in the seizure phenotype, as local hippocampal ablation of $Na_V1.1$ channels decreased the threshold for hyperthermia-induced seizures. However, the effect of ablation of $Na_V1.1$ channels restricted to cortical sites has not been tested. Here we studied local field potential (LFP) and behavior in mice following local hippocampal and cortical ablation of *Scn1a*, a gene encoding the α1 subunit of $Na_V1.1$ channels, and we compared seizure characteristics with those of heterozygous global knockout $Scn1^{-/+}$ mice. We found a high incidence of spontaneous seizures following either local hippocampal or cortical ablation, notably during a transient time window, similar to $Scn1a^{-/+}$ mice. Nonconvulsive seizure activity in the injected area was common and preceded generalized seizures. Moreover, mice were susceptible to hyperthermia-induced seizures. In conclusion, local ablation of $Na_V1.1$ channels in the hippocampus and cortex results in focal seizure activity that can generalize. These data indicate that spontaneous epileptic activity may initiate in multiple brain regions in Dravet syndrome.

KEYWORDS

cortex, Dravet syndrome, epilepsy, hippocampus, mouse model, sodium channels

1 | INTRODUCTION

Dravet syndrome is an epilepsy syndrome characterized by early onset seizures, developmental delays, behavioral disorders, and severe cognitive deficits.[1,2] In the majority of patients, a de novo heterozygous loss-of-function mutation in the *SCN1A* gene is found, encoding the pore-forming α1 subunit of voltage-gated $Na_V1.1$ sodium channels. Symptoms including spontaneous seizures, cognitive deficits, autism-related behaviour, and premature death are also observed in mice with *Scn1a* loss-of-function.[3-5] In *Scn1a* knockout mice, voltage-dependent sodium currents

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are reduced in hippocampal γ-aminobutyric acid (GABA) ergic neurons, whereas they are unaffected in hippocampal pyramidal neurons.[3] In hippocampus and cortex, $Na_V1.1$ is mostly expressed in GABAergic neurons[6] and loss of $Na_V1.1$ expression in forebrain inhibitory interneurons is sufficient to reproduce the epileptic phenotype of heterozygous *Scn1a* knockout (*Scn1a*$^{-/+}$) mice.[7]

The role of different brain regions in epilepsy networks in Dravet syndrome, however, remains unclear. The hippocampus has been suggested as a primary driver of epileptiform activity in a mouse model of Dravet syndrome.[8] In addition, Stein et al[9] recently demonstrated that local ablation of $Na_V1.1$ channels restricted to hippocampus results in an increased sensitivity to thermally evoked seizures. Because patients with *SCN1A* mutations may manifest with focal (cortical) epilepsy,[10,11] the relevance of various brain regions is of interest. We therefore studied the effects of local $Na_V1.1$ ablation in hippocampus and cortex on local field potential (LFP) and behavior, and we compared seizure characteristics with those of *Scn1a*$^{-/+}$ mutants.

2 | METHODS

2.1 | Animals

To enable (local) ablation of $Na_V1.1$ channels in mice, a novel conditional *Scn1a* mouse model was generated. To this end, homologous recombination was used to replace exon 8 of the *Scn1a* gene, by using a targeting vector that contained the same exon but flanked by loxP sites in addition to a neomycin selection cassette flanked by *flippase* recognition target sites, introduced in strain IB10 mouse embryonic stem cells (a subclone of line E14 that is derived from 129/Ola mice). Clones were injected in C57BL/6J blastocysts to generate chimeras, which were then bred with C57BL/6J mice to achieve germline transmission, followed by breeding with a *flippase*-expressing mouse (C57BL/6-Tg(CAG-flpe)36Ito/ItoRbrc, stock #RBRC01834, RIKEN BioResource Center) to delete the neomycin cassette and backcrossing to C57BL/6J mice for at least five generations. No alterations in behavior or survival were noted in heterozygous or homozygous floxed (*Scn1a*$^{fl/+}$ or *Scn1a*$^{fl/fl}$, respectively) mice, when compared to wild-type (WT) littermates. To create *Scn1a*$^{-/+}$ mice, *Scn1a*$^{fl/+}$ males were crossed with EIIA-Cre deleter mice (B6.FVB-Tg(EIIa-cre)C5379Lmgd/J, stock #003 724, Jackson Laboratory). Offspring were bred with C57BL/6J mice to achieve germline transmission. Interbreeding of *Scn1a*$^{-/+}$ mice was used to obtain homozygous (*Scn1a*$^{-/-}$) and heterozygous (*Scn1a*$^{-/+}$) *Scn1a* global knockout mice, as well as WT littermates.

Experiments were approved by local and national ethical committees in accordance with the recommendations of the European Communities Council Directive (2010/63/EU) and carried out in accordance with "Animal Research: Reporting of In Vivo Experiments" guidelines.

2.2 | Viral infection and electrode implantation

AAV vectors expressing eGFP-Cre (AAV-GFP-Cre; Addgene viral prep #105545-AAV8) or eGFP only (AAV-GFP; Addgene viral prep #105530-AAV8) were used for viral infection (both gifts from James M. Wilson). For ablation of $Na_V1.1$ channels in the hippocampus, AAV-GFP-Cre was injected bilaterally (500 nL per injection, 50 nL/min) in the dorsal (−2.2 anteroposterior [AP], ±1.4 mediolateral [ML], −1.7 dorsoventral [DV]; coordinates in mm relative to bregma) and ventral (−3.0 AP, ±2.9 ML, −2.8 DV) hippocampus of P21 *Scn1a*$^{fl/fl}$ mice, followed by implantation of LFP electrodes (75 µm platinum/iridium, PT6718; Advent Research Materials) at all four sites, and in the right occipital cortex (−3.5 AP, 2.4 ML, −0.5 DV). For cortical ablation of $Na_V1.1$ channels, 500 nL of AAV-GFP-Cre was bilaterally injected into the occipital cortex, followed by implantation of LFP electrodes at both sites, as well as bilaterally in the frontal cortex (+1.5 AP, ±1.8 ML, −0.5 DV). Reference and ground electrodes were implanted above the cerebellum. Electrodes were attached to a 7-channel pedestal (MS373 pedestal; Plastics One). For control experiments, P21 *Scn1a*$^{fl/fl}$ littermates received injections of AAV-GFP preceding implantation of the electrodes.

For recordings in *Scn1a*$^{-/+}$ mice, LFP electrodes were implanted at P21 at the same location as for mice receiving hippocampal or cortical injections.

2.3 | Hyperthermia-induced seizures

In a separate set of *Scn1a*$^{-/+}$ mice and injected *Scn1a*$^{fl/fl}$ mice, the threshold for hyperthermia-induced seizures was tested as described previously,[12] adapted for freely behaving animals as follows: following implantation of electrodes, a thermistor (MEAS-G22K7MCD419, Measurement Specialties) was placed in the peritoneal cavity. In weeks 4-5 after surgery (ie, P43-49), a heat lamp was positioned above the mouse during video-EEG recording. Core temperature was gradually increased (0.5°C every 2 minutes) until a seizure occurred, or 42.0°C was reached.

2.4 | Data acquisition and analyses

Naive (ie, not implanted) *Scn1a*$^{-/+}$ mice were videotaped from P21-49 for detection of spontaneous seizures. For video-EEG recordings, *Scn1a*$^{fl/fl}$ mice were connected to

a commutator in a Faraday cage for 24 hours of video-EEG recordings at days 7, 14, and 21 following surgery. For *Scn1a*$^{-/+}$ mice, recordings used for comparison with *Scn1a*$^{fl/fl}$ mice were performed at P25-28 for 24 hours, as spontaneous seizures are prevalent at this developmental window in another Dravet mouse model.[5] LFP signals were pre-amplified (3X), band-pass filtered (0.05-500 Hz), amplified (400X; custom-built recording hardware), and digitized (Power1401 with Spike2 software; Cambridge Electronic Design) at 5000 Hz.

Electrophysiological recordings were inspected for epileptiform activity. For epileptiform discharges lasting >5 seconds, video recordings were scored using the Racine scale.[15] Stage 4 and 5 seizures were used for comparison of seizure duration and power analyses, and seizure onset was defined as time of onset of motor symptoms, that is, facial movements and/or forelimb clonus. Total LFP power (frequency range: 1-100 Hz) was calculated by a fast Fourier transform and normalized to baseline (60 seconds pre-ictal) using a custom-written MATLAB (Mathworks) script.

2.5 | Immunohistochemistry

Following euthanasia by CO_2 and transcardial perfusion with phosphate-buffered saline (PBS) and 4% paraformaldehyde, brains were post-fixed, cryoprotected, and coronally sectioned (20 μm). Antigen retrieval was done for 10 minutes at 80°C in 10 mmol/L sodium citrate buffer with 0.05% Tween. Sections from *Scn1a*$^{fl/fl}$ mice (P43-49) were blocked with 10% normal goat serum and incubated in rabbit anti-$Na_v1.1$ (1:200; Alomone Labs), followed by incubation in goat anti-rabbit Cy2 or anti-rabbit Cy3 (both 1:200; Jackson Immunoresearch). For *Scn1a*$^{-/+}$ mice (P14 and P21), sections were additionally incubated in mouse anti-GAD67 (1:200; Millipore Sigma), followed by goat anti-mouse Cy3 (1:200; Jackson Immunoresearch). Sections were mounted in glycerol/PBS (1:1) containing 12.5 mg/mL sodium azide and 1 μL/mL Hoechst-33258 and examined using confocal microscopy.

3 | RESULTS

3.1 | Generation of conditional *Scn1a*$^{fl/fl}$ and global *Scn1a* knockout mice

Conditional *Scn1a*$^{fl/fl}$ mice were generated using homologous recombination, replacing exon 8 of the *Scn1a* gene by the same exon flanked by loxP sites (Figure S1A,B). Breeding with EIIA-Cre deleter mice resulted in global knockout *Scn1a*$^{-/+}$ and *Scn1a*$^{-/-}$ mice, with absence of $Na_V1.1$ expression in the latter (Figure S1D). Survival of *Scn1a*$^{-/+}$ was decreased and *Scn1a*$^{-/-}$ mice did not survive past P15 (Figure S1E), in line with findings from a similar *Scn1a* knockout model.[3] Generalized seizures were observed in the fourth postnatal week in both naive and implanted *Scn1a*$^{-/+}$ mice (example in Figure S1F). Of the recorded naive *Scn1a*$^{-/+}$ mice (n = 21), five died during recording, in all cases immediately following a stage 5 seizure.

3.2 | Local hippocampal ablation of $Na_V1.1$ results in spontaneous seizures

Hippocampal injection of AAV-GFP-Cre in P21 *Scn1a*$^{fl/fl}$ mice (Figure 1A-C) resulted in reduced $Na_V1.1$ staining in GFP-positive cells, indicating successful ablation of $Na_V1.1$ by AAV-GFP-Cre, whereas $Na_V1.1$ staining was still present following control AAV-GFP injections (Figure 1D). Spontaneous generalized seizures were recorded in six of seven mice injected with AAV-GFP-Cre, compared to zero of six mice injected with control AAV-GFP ($P = .005$, Fisher's exact test). Stage 4/5 seizures represented 54% (13/24) of seizures and had a duration of 29.5 ± 2.2 seconds (mean ± SEM), which was significantly shorter compared to stage 4/5 seizures in *Scn1a*$^{-/+}$ mice (38.5 ± 6.6 seconds, 16 seizures in 6/15 mice; $P = .01$, Mann-Whitney test). All behavioral seizures in *Scn1a*$^{fl/fl}$ mice injected with AAV-GFP-Cre were preceded by high-amplitude epileptiform discharges in the hippocampus, usually first detected in the ventral hippocampus (Figure 1E), whereas these local discharges were not observed in *Scn1a*$^{-/+}$ mice or *Scn1a*$^{fl/fl}$ mice injected with control AAV-GFP. These localized discharges were also observed in isolation (Figure 1F) at days 14 and 21 after injection. However, generalized seizures were rarer at 21 days after injection (Figure 1G). Similarly, 24-hour recordings in *Scn1a*$^{-/+}$ mice at P36-39 showed a decrease in seizure frequency over time (1 seizure at P36-39 vs 16 seizures at P25-28, in 360 hours of recording per age window; n = 15 mice; $P < .001$, Fisher's exact test).

3.3 | Local cortical ablation of $Na_V1.1$ results in spontaneous seizures

To test whether spontaneous seizure activity is specific for ablation of $Na_V1.1$ in hippocampus, we injected AAV-GFP-Cre locally in the occipital cortex of *Scn1a*$^{fl/fl}$ mice (Figure 2A,B; n = 6), yielding reduced $Na_V1.1$ staining in GFP-positive cells (Figure 2C). Local cortical ablation of $Na_V1.1$ resulted in spontaneous generalized seizures in all mice, whereas no seizures were observed in mice receiving cortical control AAV-GFP (n = 6; $P = .002$, Fisher's exact test). Of all spontaneous seizures, 36% (12/33) were classified as stage 4/5 seizures. Seizure duration was significantly shorter when compared to seizures in *Scn1a*$^{-/+}$ mice (27.1 ± 4.1 seconds and

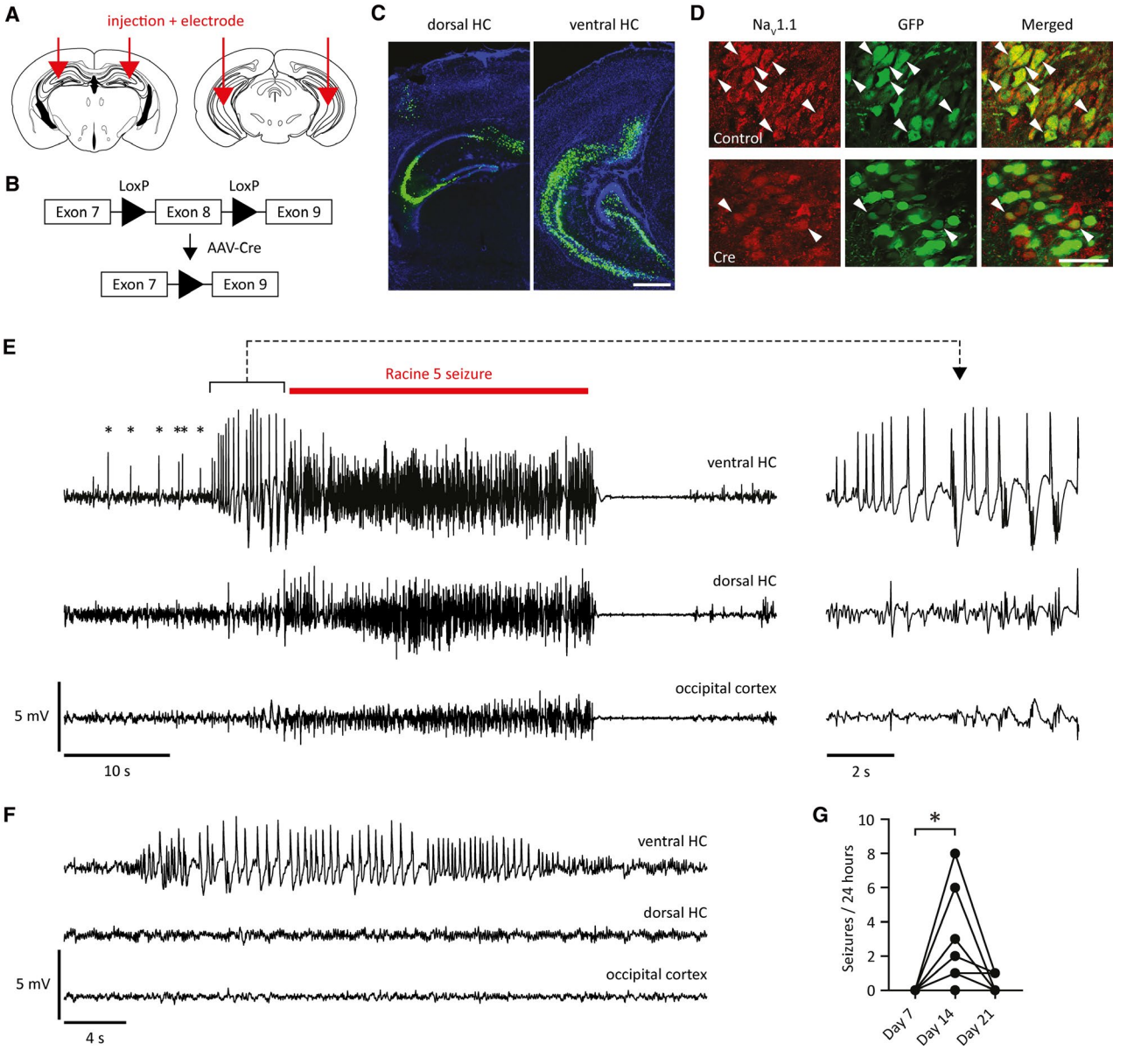

FIGURE 1 Local ablation of Na$_V$1.1 channels in the hippocampus of mice results in spontaneous seizures that are preceded by local discharges. A,B, Bilateral AAV-GFP-Cre or control AAV-GFP injections (A) in dorsal (left) and ventral (right) hippocampus (HC) were followed by electrode implantation, in P21 mice with loxP-flanked exon 8 of *Scn1a* (B). C,D, Hippocampal cells infected by AAV-GFP-Cre, as evidenced by GFP labeling (C), showed reduced Na$_V$1.1 staining (D, detail of CA2 region), whereas cells infected by AAV-GFP did not (double-labelled cells indicated by white arrowheads). Scale bars: 500 μm in C, 50 μm in D. E, Spontaneous generalized seizure preceded by spikes (asterisks) and discharges (inset) in the ventral HC. F, Local discharge in the ventral HC at day 21 following injection. G, Behavioral seizures occurred frequently at day 14 following injection, but were rare at day 21 (*P = .02, Friedman test)

38.5 ± 6.6 seconds, respectively, P = .007, Mann-Whitney test) but of similar duration as observed after hippocampal ablation of Na$_V$1.1 channels (P = .35, Mann-Whitney test). Also similar to hippocampal injections, generalized seizures occurred most frequently at day 14 after injection (Figure 2E) and were preceded by local discharges (Figure 2D). Local discharges that did not generalize were also observed (Figure S2). Pre-ictal LFP showed increased power in the occipital cortex preceding seizure behavior, which was not observed in the frontal cortex or in *Scn1a*$^{-/+}$ mice (Figure 2F,G). Local seizure activity was not observed following cortical control AAV-GFP injections (n = 6 mice).

3.4 | Both hippocampal and cortical ablation of Na$_V$1.1 lower the threshold for hyperthermia-induced seizures

An increase in core temperature causes generalized seizures in *Scn1a*$^{-/+}$ mice[12] and in mice with local hippocampal

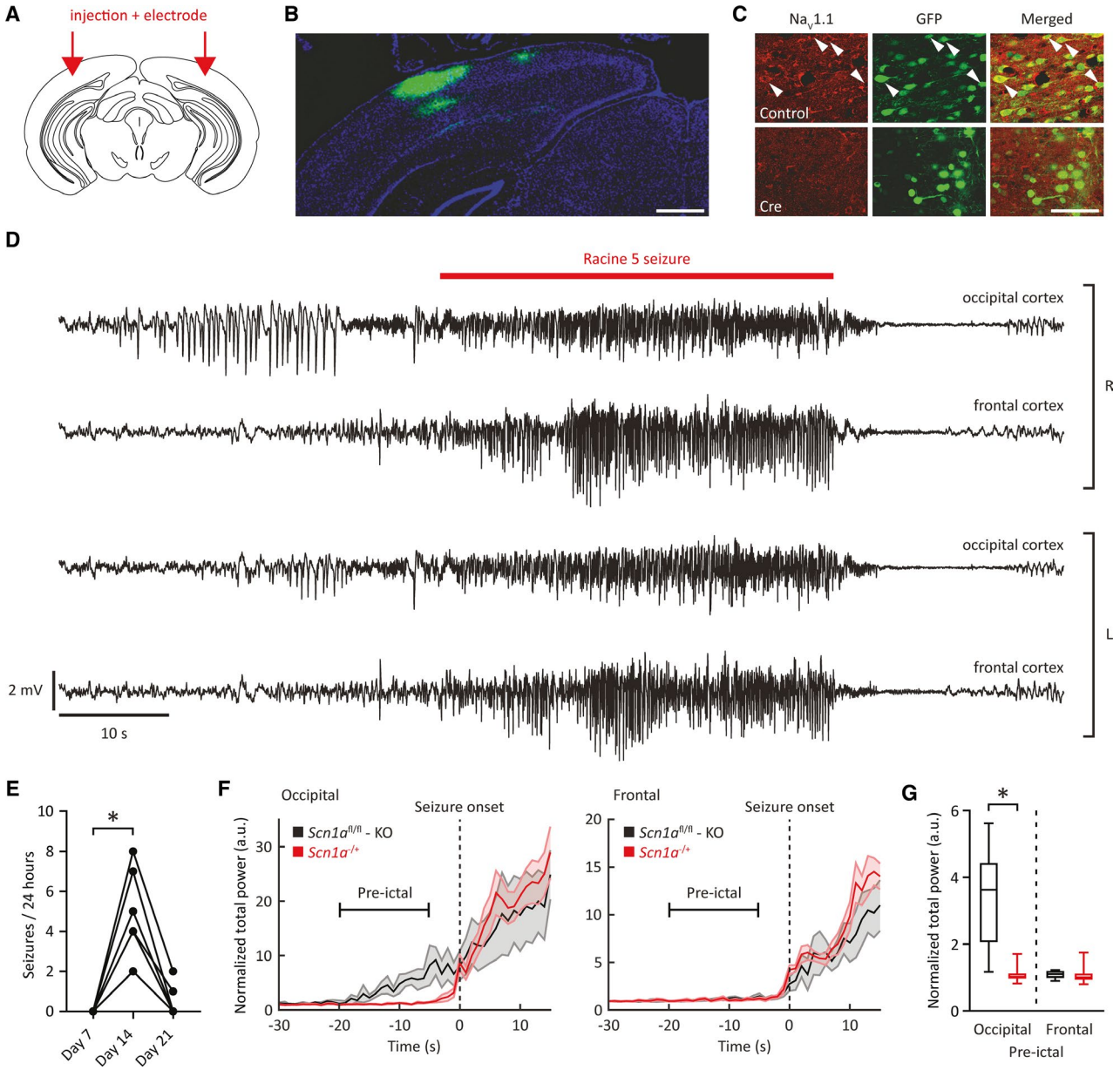

FIGURE 2 Local ablation of Na$_V$1.1 channels in the occipital cortex of mice results in spontaneous seizures that are preceded by local discharges. A, Bilateral AAV-GFP-Cre or control AAV-GFP injections in the occipital cortex, followed by electrode implantation, including in the bilateral frontal cortex, in *Scn1a*$^{fl/fl}$ mice. B,C, AAV-mediated GFP-Cre expression, limited to cortex (B), resulted in reduced Na$_V$1.1 staining (C, detail of occipital cortex), whereas this was not the case for cells infected by AAV-GFP (double-labeled cells indicated by white arrowheads). Scale bars: 500 μm in B, 50 μm in C. D, Spontaneous generalized seizure at day 14 following injection, preceded by discharges in the occipital cortex. E, Behavioral seizures occurred most frequently at day 14 following injection (*P = .008, Friedman test). F, Pre-ictal time series of LFP power (frequency range: 1-100 Hz) for occipital (left) and frontal (right) cortex in *Scn1a*$^{fl/fl}$ mice injected with AAV-GFP-Cre in occipital cortex (black; n = 12 seizures in six mice) and *Scn1a*$^{-/+}$ mice (red; n = 16 seizures in six mice; data presented as mean ± standard error of the mean [SEM]). G, Pre-ictal LFP power was increased in occipital cortex of *Scn1a*$^{fl/fl}$ mice, but not in frontal cortex, or in either of two locations in *Scn1a*$^{-/+}$ mice (*P < .001, Mann-Whitney test)

Na$_V$1.1 ablation,[9] reflecting the early febrile seizures often observed in infants with Dravet syndrome.[1,2] We therefore tested whether seizures could also be induced by hyperthermia in our *Scn1a*$^{-/+}$ (n = 7) and AAV-GFP-Cre-injected *Scn1a*$^{fl/fl}$ (hippocampus: n = 4; cortex: n = 5) mice. Both groups showed stage 4/5 seizures at temperatures <42.0°C, whereas none of the *Scn1a*$^{fl/fl}$ mice injected with control AAV-GFP (n = 6) developed seizures. *Scn1a*$^{-/+}$ mice showed lower seizure thresholds than AAV-GFP-Cre-injected *Scn1a*$^{fl/fl}$ mice, whereas no differences were noted between *Scn1a*$^{fl/fl}$ mice injected in hippocampus or cortex (Figure S3).

4 | DISCUSSION

Here, we show that local ablation of $Na_V1.1$ channels in hippocampus or cortex is sufficient to induce spontaneous generalized seizures in mice. We found that localized discharges occurred in the infected area, which did not always generalize to distant electrodes.

Of note, recently, Stein et al[9] did not observe spontaneous seizures following hippocampal $Na_V1.1$ ablation using a similar approach. Although differences in mouse strain, AAV serotype, and variability in the affected hippocampal area may contribute to this discrepancy, seizure development was not assessed in the 21 days following injection. In their study, mice showed a reduced threshold for thermally induced seizures, measured 21 days after viral infection, similar to our findings. However, in the absence of longitudinal recordings before day 21, spontaneous seizures may have gone undetected, as *Scn1a*$^{-/+}$ mice show spontaneous seizures with a high frequency between P21 and 28,[5] approximately 10-18 days after $Na_V1.1$ expression is first detected in brain tissue.[6] After this time, seizure frequency is much lower,[5] which we confirmed in our *Scn1a*$^{-/+}$ mice. Onset of spontaneous (fatal) seizures in *Scn1a*$^{-/-}$ mice occurs already before P16.[3] Here, we observed spontaneous seizures 14 days after AAV-GFP-Cre injection in the hippocampus, whereas seizures were rare at 21 days, supporting a critical time window for spontaneous seizures following loss of *Scn1a* function. In *Scn1a*$^{-/+}$ mice, excitability of cortical GABAergic neurons normalizes to WT levels by P35,[13] which parallels the reduction in seizure frequency. Mechanisms such as upregulation of other voltage-gated sodium channel subtypes may underlie these findings, as suggested previously,[13] and may also cause the eventual decrease in seizure frequency following local ablation of $Na_V1.1$.

Notably, we found that also local cortical $Na_V1.1$ ablation was sufficient to induce spontaneous seizures and reduce the threshold for hyperthermia-evoked seizures. Similar to local hippocampal ablation, generalized seizures were preceded by discharges observed only in the injected area. Pre-ictal LFP amplitude was increased in the occipital cortex, which was not the case for *Scn1a*$^{-/+}$ mice. In patients, *SCN1A* mutations have been implicated in focal epilepsy, which could progress into a phenotype typical of Dravet syndrome.[10,11] Our study is the first to show seizure activity from a cortical focus following localized ablation of $Na_V1.1$, offering a paradigm to study focal seizures and their generalization. In addition, although the hippocampus is likely an important driver of seizures in Dravet syndrome,[8] our data challenge the (curative) potential for future region-specific gene therapy in these patients.

Scn1a$^{-/+}$ mice showed seizure-related mortality; however, no mortality was observed in mice in which $Na_V1.1$ was locally ablated in either hippocampus or cortex. This may be explained by a limited duration or severity of seizures following local $Na_V1.1$ ablation, and/or by the absence of $Na_V1.1$ ablation in other brain areas that could be critically involved in seizure-related mortality.

We observed localized seizure activity following local ablation of $Na_V1.1$ channels, but not in heterozygous global knockout *Scn1a*$^{-/+}$ mice. Although nonconvulsive seizures have been reported in a mouse model of Dravet syndrome,[14] the activity we observed following local $Na_V1.1$ ablation appears more localized and of higher amplitude. This localized seizure activity may affect behavioral outcomes such as reported by Stein et al,[9] by disrupting neuronal populations that are not affected directly by $Na_V1.1$ ablation, suggesting that recordings from injected areas are necessary for interpretation of behavioral outcomes.

In conclusion, local ablation of $Na_V1.1$ channels in hippocampus or cortex results in epileptic discharges that may generalize, indicating that localized dysfunction of $Na_V1.1$ channels is sufficient to induce generalized seizures characteristic of Dravet syndrome.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

NAJ designed and performed the research, analyzed the data, and wrote and revised the paper. AD performed immunohistochemistry and confocal microscopy. CB constructed the targeting vectors and generated the mouse models. EAT and AMJMv.d.M. supervised the research and revised the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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