

Research article

Initial characterization of behavior and ketamine response in a mouse knockout of the post-synaptic effector gene *Anks1b*

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HIGHLIGHTS

- Human *ANKS1B* was associated with psychiatric phenotypes in genome-wide studies.
- Here we behaviorally characterize a knockout (KO) for the murine ortholog *Anks1b*.
- *Anks1b* KOs exhibit PPI deficits, elevated stereotypies and hyperlocomotor activity.
- *Anks1b* KOs exhibit altered response to ketamine, an NMDA receptor antagonist.
- *Anks1b* plays a role in mediating behaviors linked to glutamatergic signaling.

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ABSTRACT

The human *ANKS1B* gene encodes an activity-dependent effector of post-synaptic signaling. It was recently associated with neuropsychiatric phenotypes in genome-wide studies. While the biological function of *ANKS1B* has been partly elucidated, its role in behavior is poorly understood. Here, we breed and characterize a full knockout (KO) for murine *Anks1b*. We found that the homozygous KO genotype was partially lethal, showing significant deviation from expected segregation ratios at weaning. Behaviorally, KOs exhibited no difference in baseline acoustic startle response, but showed deficits in prepulse inhibition (PPI). KOs also exhibited locomotor hyperactivity and increased stereotypy at baseline. Administration of ketamine, a non-competitive NMDA-receptor antagonist, greatly exacerbated locomotor activity in the KOs at lower doses, but genotype groups were almost indistinguishable as dose increased. Stereotypy showed a complex response to ketamine in the KOs, with elevated stereotypy at lower doses and markedly less at high doses, compared to wild type. Our study is the first to probe the behavioral phenotypes associated with ablation of *Anks1b*. Deficits in PPI, locomotor hyperactivity, elevated stereotypy and altered response to NMDA receptor antagonism are murine behavioral outcomes with translational relevance for psychiatric disorders. These findings are also consistent with the role of *Anks1b* as an effector of glutamatergic signaling. As an intermediary between post-synaptic receptor stimulation and long-term changes to neuronal protein expression, further investigation of *Anks1b* is warranted.

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1. Introduction

The Ankyrin Repeat and Sterile Alpha Motif Domain-containing 1B (*ANKS1B*) gene is highly expressed in the CNS [1]. *ANKS1B* pro-

tein, also known as EB-1 and AIDA-1, plays a role in tyrosine kinase signal transduction [2] and is a scaffold of the post-synaptic density (PSD) [3], where it interacts with post-synaptic density protein 95 (PSD-95) and several classes of glutamate receptor. Stimulation of NMDA receptors (NMDAR) leads to translocation of the *ANKS1B* protein to the nucleus where it regulates neuronal protein expression [4]. This places *ANKS1B* at the interface between post-synaptic receptor stimulation and downstream changes to neuronal biology.

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Interest in *ANKK1B* has developed following its association with psychiatric phenotypes in human studies. Genetic variants at *ANKK1B* were among the top findings in two genome-wide association studies (GWAS) of antipsychotic response in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [5,6]. *ANKK1B* was also among the top findings in a GWAS of citalopram response [7] and a GWAS of monoamine metabolite levels in cerebrospinal fluid [8]. These findings suggest further characterization of *ANKK1B* is warranted.

The biological function of *ANKK1B* has been partly elucidated, but little is known about its effects on behavior. Here we present an initial behavioral characterization of a mouse knockout (KO) for the murine ortholog, *Anks1b*. We focus on the paradigms of prepulse inhibition (PPI) and locomotor activity (LA). PPI of the startle response is a widely-studied sensorimotor gating measure and pharmacological modulation of PPI in rodents is considered a translational model for deficits observed in schizophrenia [9]. LA is considered to tap neurological substrates such as dopaminergic neurotransmission in the limbic system and NMDAR function [10]. Disruptions to both PPI and LA have been previously observed in mouse knockouts for scaffolding proteins of the PSD [11]. Our study shows that elimination of *Anks1b* leads to effects on these behaviors and altered response the NMDAR antagonist, ketamine.

2. Methods

2.1. Ethics statement

All procedures were conducted in accordance with the “Guide for the Care and Use of Laboratory Animals” (Institute of Laboratory Animal Resources, National Academy Press, 2011) and were approved by the Institutional Animal Care and Use Committee of Virginia Commonwealth University.

2.2. Development of the *Anks1b* knockout mouse and breeding program

Progenitor mice heterozygous for the *Anks1b^{tm1a(KOMP)Wtsi}* allele on a C57BL/6N-Atm1Brd background were generated by Knockout Mouse Project (KOMP) CSD 79332, and obtained from the Wellcome Trust Sanger Institute (Cambridge, UK). *Anks1b^{tm1a(KOMP)Wtsi}* is a “knockout-first” allele [12,13] in which an *En2*:IRES:*lacZ* reporter cassette was inserted into intron 16, and efficient splicing to the *En2* splice acceptor site results in the truncation of the *Anks1b* transcript. Exon 17 (Ensembl accession number: ENSMUSE00001274863), which encodes amino acid residues 871–921, is also floxed in the *Anks1b^{tm1a(KOMP)Wtsi}* allele, and was targeted for deletion because it overlaps with the second Sterile Alpha Motif (SAM) domain (residues 877–938). Helix 5 of this domain contains the *Anks1b* nuclear localization signal [14]. *Anks1b^{tm1a}* mice were bred to a transgenic line expressing Cre recombinase in the germline (B6.FVB-Tg(Ella-cre)C5379Lmgd/J—Jackson Laboratory stock #003724), generating the *Anks1b^{tm1b}* KO line in which the *En2*:IRES:*lacZ* cassette is retained, but in which exon 17 is deleted (Fig. 1). The Ella-cre mice used donor strain FVB/N bred to C57BL/6N for 11 generations. Thus both the KOMP *Anks1b^{tm1a(KOMP)Wtsi}* allele and the Ella-cre gene were on C57BL/6N backgrounds. Genotyping methods to screen for conversion of the *Anks1b^{tm1a}* allele to the *Anks1b^{tm1b}* allele via Cre-mediated deletion of exon 17 (Supplementary Fig. S1) and to screen for the Ella-cre transgene are provided in the Supplementary material.

Subjects for behavioral analysis were generated by matings of Ella-cre negative *Anks1b^{tm1b}* heterozygous pairs. Pups were genotyped at three weeks of age using DNA extracted from tail snips and a three-primer PCR protocol (Supplementary Fig. S2). We aimed

for approximately equal numbers of wild-type (WT), heterozygous (Het), and KO mice of both sexes in our experiments. Mice were tested in cohorts as they became available, with testing staggered so that each cohort received tests around the same age. Baseline behavioral testing was conducted at approximately 10 weeks of age with inter-test intervals ranging from 1 to 5 days. PPI ketamine testing was completed at approximately 15 weeks, while ketamine LA assays were completed at approximately 20 weeks. When not in testing, mice were allowed *ad libitum* access to standard diet (7012 Teklad LM-485, Harlan Labs Inc., Indianapolis, IN) and water, and were housed at a maximum of five mice per cage in a temperature-controlled (22°C) facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Mice were kept under a 12-h/12-h light/dark cycle (lights on from 0600-h to 1800-h), with all testing occurring during the light segment.

2.3. Validation of the knockout allele via western blotting

Drug-naïve mice of each genotype were euthanized by CO₂ asphyxiation, the whole brain excised and immediately frozen. Cortical tissue samples were lysed in Pierce® RIPA buffer (Thermo Scientific, Rockford, IL) and homogenized. Samples were resolved on polyacrylamide gels and transferred to a PVDF membrane (Bio-Rad, Hercules, CA), which was then treated with either mouse anti-AIDA-1/*Anks1b* antibody (C-10, Santa Cruz Biotechnology, Dallas, TX), or mouse anti-GAPDH antibody (Thermo Scientific), followed by anti-mouse IgG secondary antibody (Cell Signaling Technology, Danvers, MA). A ChemiDoc system (Bio-Rad) was used to capture and process blot images. Protein band intensity was quantified by normalizing the chemiluminescent image to the stain-free blot image captured before antibody treatment. All experiments were repeated at least three times.

2.4. Drugs

Ketamine (KetaVed, Vedco, Inc., St. Joseph, MO) was prepared in 0.9% saline. Intraperitoneal (i.p.) injections were given in a volume equivalent to 10 ml/kg body weight.

2.5. Prepulse inhibition of the startle reflex (PPI)

Commercially-supplied startle chambers (San Diego Instruments, San Diego, CA) were used to record startle following acoustic stimuli. Beginning with the onset of the startle pulse (STIM) for each trial, 1000 readings were taken at 1-ms intervals. A test session consisted of 75, 200-ms trials, with five trial types: STIM alone, 73pp (i.e., “73dB prepulse”) + STIM, 77pp + STIM, 85pp + STIM, and NO STIM. Both prepulse and pulse stimuli were 20-ms in duration, with an interstimulus interval of 100-ms between the onset of their presentations, and an intertrial interval average of ~15-s across the session (range: 10–20-s). STIM intensity was set at 119dB, while prepulses were set at 4, 8, and 16dB above the background level of 69dB (i.e., 73, 77, and 85dB). A test session was initiated with a 10-min acclimation period to the background level of noise before presentation of five STIM alone trials. Following this, 12–14 replicates of each trial type were presented in a mixed sequence to prevent habituation. Test sessions ended with five STIM alone trials. Total session time was approximately 30 min.

2.6. Locomotor activity (LA)

For LA studies, mice were placed in automated activity monitoring chambers that were sound- and light-attenuating (AccuScan Instruments, Columbus OH). Each arena was 20 × 20 × 30 cm, with photobeam sensors spaced 2.5 cm apart along each axis to detect

movement. For baseline measurements, mice were placed in chambers for a 2-h test session with distance traveled recorded in 10-min bins. For the LA ketamine challenge, each subject received a cumulative dosing regimen. In this procedure, mice were habituated to chambers for 30-min before the trial, then removed and administered an i.p. injection of saline before being returned to the chamber for a 6-min recording period. Mice were then removed, administered an i.p. injection of ketamine, and placed back into the chamber for the next 6-min recording period. This process was repeated three more times to obtain the complete dose-effect curve. Subjects were administered acute injections of 0, 10, 20, 26, and 44 mg/kg ketamine, to generate cumulative doses of 0, 10, 30, 56, and 100 mg/kg.

2.7. Behavioral data analysis

For both PPI and LA, electronically captured data files from test days were combined and processed using scripts written in R (www.r-project.org). Percentage PPI (% PPI) was calculated using the mean peak startle amplitude (vmax) of STIM alone trials or prepulse + STIM trials, according to standard methods [15].

LA used the “total distance traveled” variable. For stereotypy, we used the “stereotypy count” variable as defined by the software that records the number of times the mouse breaks the same beam in succession without breaking an adjacent beam [16].

Analysis of behavioral outcomes by genotype used linear regression implemented via the linear model (lm) function in R. Genotypes were coded 0 = KO homozygote; 1 = heterozygote and 2 = wild type. Degrees of freedom and P values were output for regression coefficients. Data were visualized using the ggplot2 package.

3. Results

3.1. Biological validation of the KO and lethality

The knockout-first (KO-first) targeting strategy used by KOMP [12,13] produces a KO at the transcript level due to a splice acceptor in the cassette. KO-first (tm1a) homozygotes are typically null, but hypomorphic expression may occur if the RNA processing module is bypassed [17]. Western blotting of cortical tissue lysate (Fig. 1) revealed 5–6% Anks1b protein expression in *Anks1b^{tm1a}*

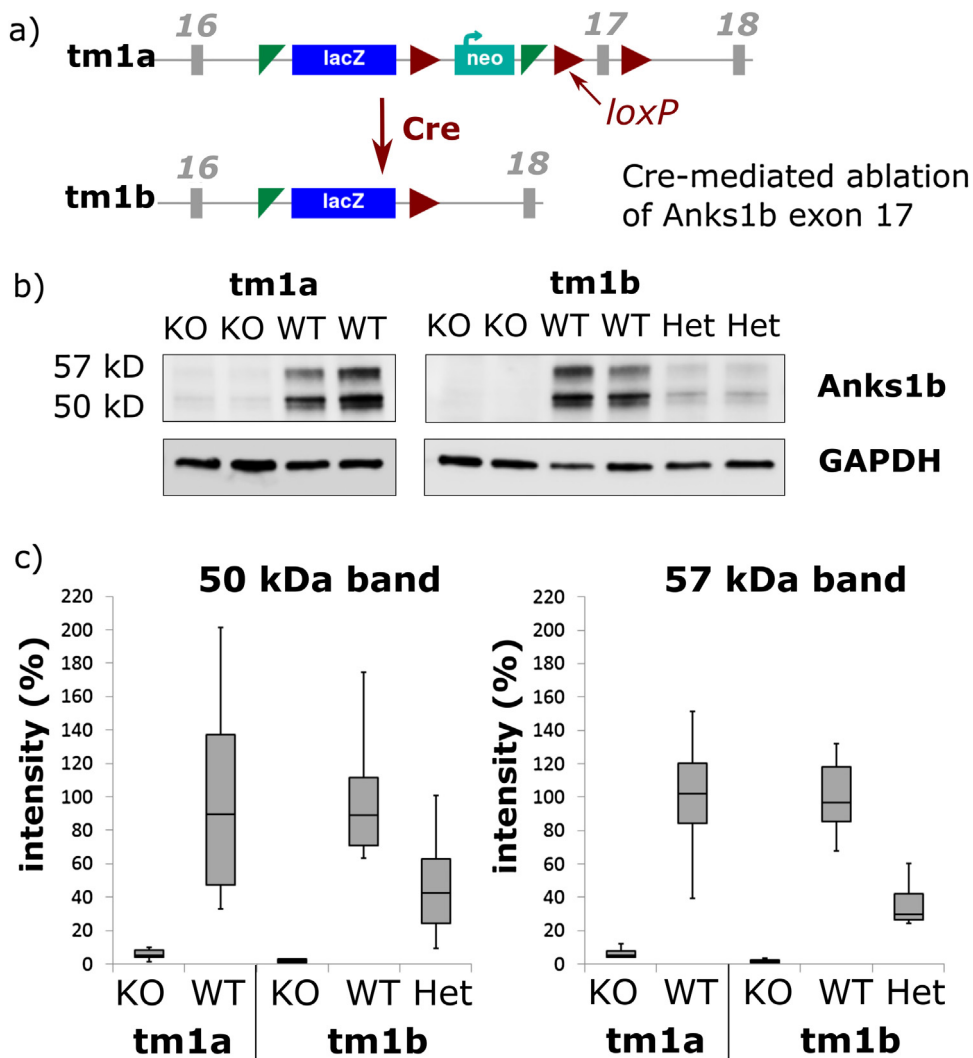
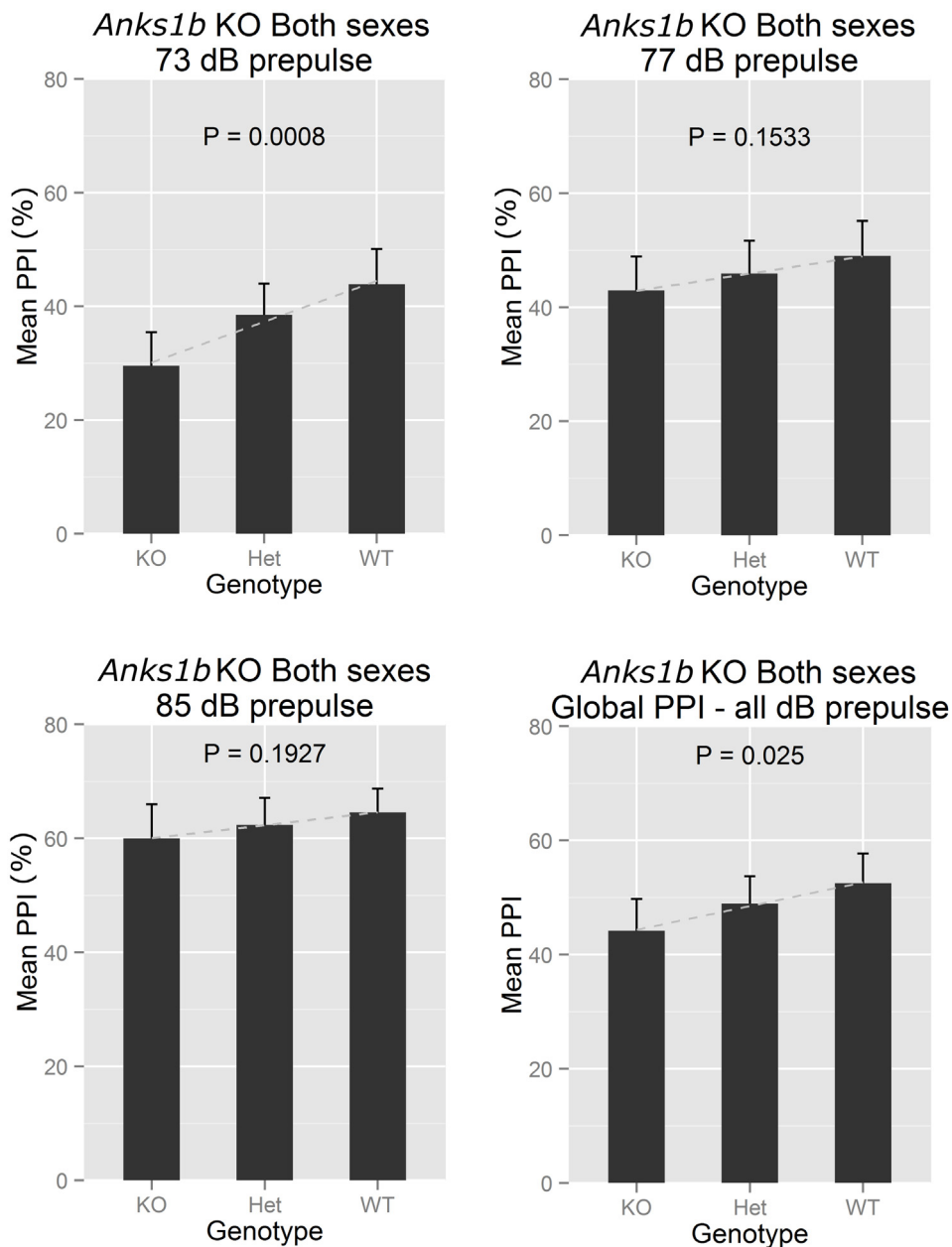


Fig. 1. (a) Schematic of the *Anks1b* KOMP project allele variants. The ‘knockout-first’ allele (*tm1a*) contains an *En2:IRES:lacZ* reporter cassette inserted into intron 16, disrupting gene function. Cre deletes the promoter driven selection cassette and floxed (loxP-flanked) exon 17 to generate a *lacZ* tagged allele (*tm1b*) [12]. (b) Western blots showing the approximately 50 and 57 kD isoforms of Anks1b (AIDA-1e and AIDA-1d respectively) in mice of different genotypes for the *tm1a* and *tm1b* alleles. WT = wild type, KO = homozygous *tm1a* or *tm1b*, Het = heterozygote. (d) Quantitative analysis of 3 technical replicates of Western blots showing results grouped by genotype, where quantities are normalized relative to WT, where mean (WT) = 100%. Box and whisker plots show median and interquartile ranges.



n(KO) = 18 M, 9 F ; n(Het) = 17 M, 15 F ; n(WT) = 17 M, 13 F

Fig. 2. Baseline percentage (%) PPI at three different prepulse intensities and global PPI by genotype for the *Anks1b^{tm1b}* allele. Means are plotted for each group and error bars show 95% confidence intervals.

(KO-first) animals compared to WT for both the ~50 and ~57 kD isoforms (AIDA-1e and AIDA-1d respectively). In contrast, ablation of exon 17 (*Anks1b^{tm1b}*) resulted in no detectable protein above background (Fig. 1) confirming the validity of this KO. Protein levels in *Anks1b^{tm1b}* heterozygotes were intermediate between KOs and WT (approximately 40–50%), indicating the use of an additive statistical model would be valid in our phenotypic analysis.

We established heterozygous breeding pairs for the *Anks1b^{tm1b}* line and noticed that many pups did not survive to maturity. Over the 9 month breeding period, we recorded 221 live births, of which 202 survived to weaning. We genotyped some early losses and found them to all be homozygous KOs. Genotyping of all surviving mice at weaning revealed a significant deviation from expected segregation ratios (Chi square = 8.257, 2df, P = 0.016) due to mor-

talidity in the *Anks1b^{tm1b}* KO homozygotes. Therefore, the *Anks1b^{tm1b}* allele is partially lethal. Conversely, neither we nor KOMP observed any deviation from expected ratios in the *Anks1b^{tm1a}* KO-first line (www.mousephenotype.org/data/genes/MGI:1924781).

3.2. Baseline PPI in the *Anks1b* KO

Baseline acoustic startle responses revealed no significant differences across *Anks1b^{tm1b}* genotypes, indicating that these mice startled normally. Furthermore, startle diminished in proportion to increasing prepulse intensities (Supplementary Fig. S3). Together, these data indicated that hearing was normal in the KOs. Male mice (all genotypes combined) exhibited a greater startle amplitude than females ($t(87) = 3.51$, $P = 0.0007$), but this sex difference

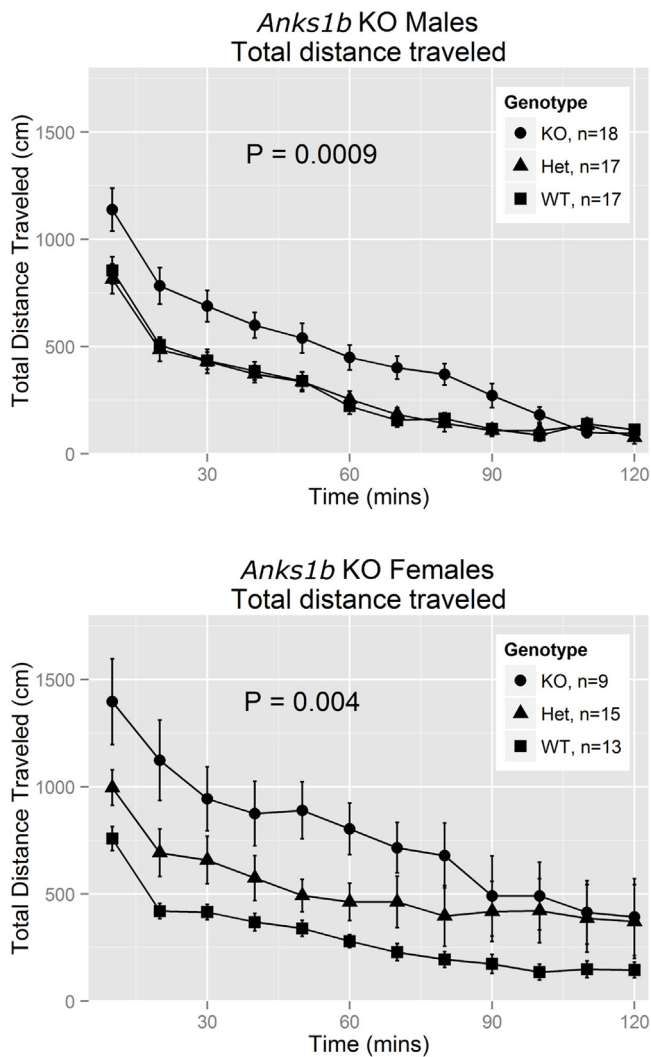


Fig. 3. Baseline locomotor activity (total distance traveled in cm) in *Anks1b^{tm1b}* mice over a 2-h observation period, displayed in 12, consecutive 10 min periods. Means are plotted for each group for each 10 min period and error bars show 95% confidence intervals. We observed a significant sex difference and so have plotted both sexes independently. The reported P-values are for tests of total distance traveled by genotype over the entire 2-h period.

did not extend to PPI and was not observed at any of the prepulse intensities used. This pattern of sexual dimorphism in startle but not PPI is in agreement with previous studies of C57s [18]. Therefore, we present baseline PPI for both sexes combined in Fig. 2, with results for each sex provided separately in Supplementary Figs. S4–S5. Our analysis showed that mice carrying the *Anks1b^{tm1b}* allele had significant PPI deficits using a 73 dB prepulse ($t(87) = 3.46$, $P = 0.0008$), with nonsignificant deficits at higher prepulse intensities. Global PPI, or the average effect across all prepulse intensities, was significant ($t(87) = 2.28$, $P = 0.025$).

3.3. Baseline LA and stereotypy

Female mice (all genotypes combined) exhibited elevated baseline LA (Fig. 3) relative to males ($t(87) = -2.56$, $P = 0.012$). Therefore, in Fig. 3, we show results separately by sex. A test of the summed total distance traveled across all time periods showed significant differences between genotypes for males ($t(50) = -3.54$, $P = 0.0009$) and females ($t(35) = -3.08$, $P = 0.004$), with KOs showing the highest activity levels.

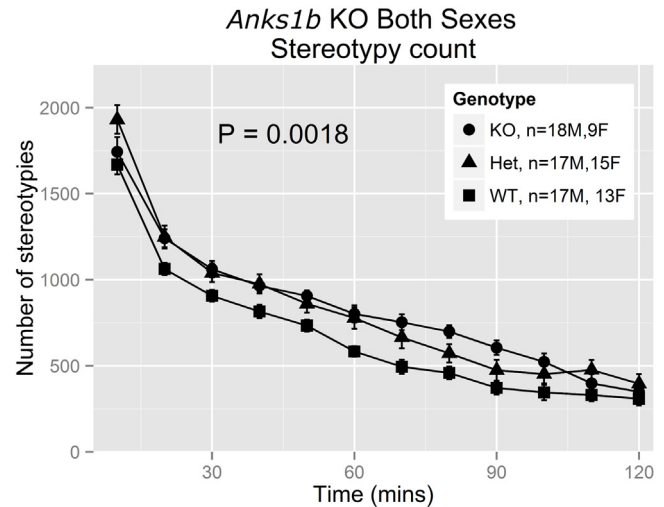


Fig. 4. Baseline stereotypies in *Anks1b^{tm1b}* mice over a 2-h observation period, displayed as 12, consecutive 10 min periods. Means are plotted for each group for each 10 min period and error bars show 95% confidence intervals. The reported P-value is for total stereotypies by genotype over the entire 2-h period.

Elevated stereotypy is characteristic of mice with disrupted NMDAR signaling [19,20], so we hypothesized that stereotypy would differ by *Anks1b* genotype in our LA data. We observed no significant sex difference in stereotypy and present the results for both sexes combined in Fig. 4, with results for each sex separately in Supplementary Figs. S6–S7. As predicted, stereotypy count was significantly elevated in *Anks1b^{tm1b}* mice ($t(87) = -3.22$, $P = 0.0018$).

3.4. Response to ketamine in *Anks1b* KO mice

Altered response to glutamatergic psychotomimetic drugs is a psychosis-related endophenotype and a correlate of glutamatergic dysfunction [21]. We hypothesized that *Anks1b^{tm1b}* mice would exhibit altered behavioral response to the NMDAR antagonist ketamine. Our ketamine challenge experiments were conducted after baseline testing and by then too few female KOs ($n = 3$) survived to analyze. Hence the following results include males only.

We first tested ketamine's effects on PPI. Ketamine typically induces PPI deficits, so our choice of dose (56 mg/kg) was based on PPI disruption in a preliminary study of male C57BL/6Js (Supplementary Fig. S8). Analysis of all genotypes combined confirmed that 56 mg/kg ketamine had a significant effect ($t(42) = -4.16 = 1.55 \times 10^{-4}$). However, a test of interaction between ketamine exposure and genotype was not significant ($t(40) = -0.58$, $P = 0.564$), indicating no detectable difference in response across genotypes.

We evaluated the LA effects of ketamine at several doses, to characterize its dose-response curve. Subjects were administered acute injections of ketamine prior to each of five, 6-min recording periods to generate cumulative doses of 0 (vehicle), 10, 30, 56, and 100 mg/kg (Fig. 5A). Over the 30-min trial, mice carrying the *Anks1b^{tm1b}* allele showed elevated LA ($t(42) = -4.28$, $P = 0.0001$). In particular, they showed extreme sensitivity to ketamine's locomotor activating effects at lower doses. At 10 mg/kg ketamine, the lowest dose tested, KOs showed significant increases in total distance traveled relative to their own scores at baseline ($t(28) = 6.95$, $P = 1.5 \times 10^{-7}$) and relative to the other genotype groups ($t(42) = -6.94$, $P = 1.78 \times 10^{-8}$). However, at rate-decreasing doses of ketamine (i.e. ≥ 56 mg/kg) those differences diminished, such that the LA levels of the KOs were indistinguishable from the other subjects.

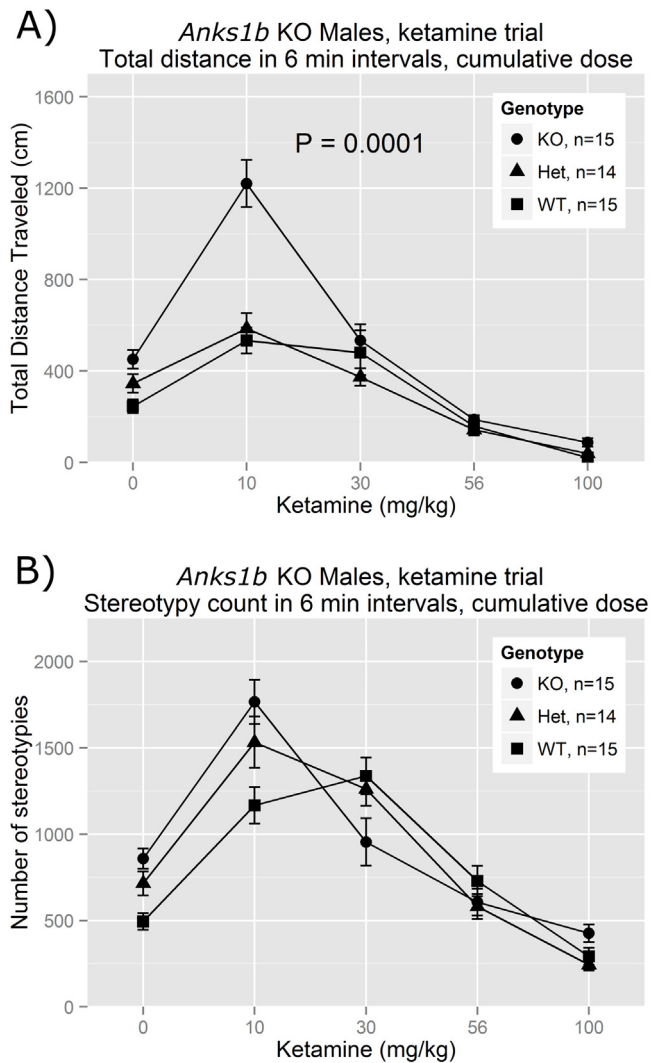


Fig. 5. Total distance traveled in cm (panel A) and stereotypy counts (panel B) as a function of cumulative ketamine dose. Dependent measures were summed within 6-min intervals following each ketamine (cumulative) dose. Reported P-values are for differences between genotype groups considered cumulatively over the entire 30-min test period.

In Fig. 5B, we show stereotypy findings for the same experiment. For all groups, stereotypy counts first increased and then decreased as ketamine dose increased. KOs exhibited significant increases in stereotypy induced by low dose (10 mg/kg) ketamine relative to their baseline levels ($t(28) = 6.46, P = 5.33 \times 10^{-7}$), as well as relative to the other genotype groups ($t(42) = -2.62, P = 0.012$). KOs also showed the greatest sensitivity to ketamine's suppressive effects on stereotypy at high doses, which were decreased relative to other genotype groups ($t(42) = 2.48, P = 0.018$) and were close to vehicle levels by 30 mg/kg. Because of these dose-induced, bimodal effects there was a net nonsignificant effect on cumulative stereotypy counts across the entire 30-min period ($t(42) = -1.39, P = 0.171$).

4. Discussion

4.1. Overview and the lethal phenotype

We bred, validated and characterized a KO for murine *Anks1b*, achieved through ablation of exon 17 (*Anks1b^{tm1b}*). We observed that the homozygous *Anks1b^{tm1b}* genotype was partially lethal.

However, hypomorphic expression in the KO-first (*Anks1b^{tm1a}*) homozygotes appeared sufficient to rescue the phenotype. A previous study of a forebrain-specific (CaMKII α) conditional KO for *Anks1b* did not report lethality [22], suggesting that the lethality is caused by deletion of *Anks1b* in another tissue.

4.2. Behavioral comparison to other KOs

Anks1b protein is activated upon stimulation of NMDARs [4] and regulates NMDAR subunit composition at synapses [22]. NMDARs are heterodimers of two obligatory NR1 subunits and two variable NR2 subunits (NR2A–D). NMDAR subunit KOs exhibit specific behavioral anomalies [23]. Hypomorphic NR1 mice exhibit increased LA and deficits in PPI [19,24], mirroring our findings here. NR2A mutant mice exhibit increased LA only, while NR2B and NR2C mutants exhibit no changes to sensory or motor behavior and NR2D exhibit reduced LA only [23]. These observations suggest that, behaviorally, ablation of *Anks1b* shows some similarities to reduced NR1 expression. However, NR1 mutant mice exhibit a broad spectrum of behavioral abnormalities and the extent to which *Anks1b* KOs would align on these additional domains remains untested.

Scaffolding proteins of the PSD, including *Anks1b* [3,25], are principal organizers of glutamatergic neurotransmission. KOs for PSD scaffolds such as homer, shank, etc. exhibit specific behavioral phenotypes [11]. However, insofar as characterizations have been carried out, no other PSD scaffold deletion exhibits diminished PPI while enhancing LA (see [11], Table 1 for review). Therefore, deletion of *Anks1b* has a different effect on behavior than other PSD scaffolds.

4.3. *Anks1b* and response to ketamine

Pharmacological blockade of NMDARs in rodents produces PPI deficits, hyperlocomotion and stereotypies [10,26], which is exactly the pattern of effects observed with knocking out *Anks1b*. Therefore, we might expect that administering ketamine to the *Anks1b* KOs should yield larger effects in the same direction. This was the case for LA, where hyperlocomotion in the KO was potentiated further. However, KOs did not differ from WT in their PPI response to ketamine, while their stereotypy response was complex and dose-dependent. Considering all these outcomes, *Anks1b* KOs exhibit altered response to ketamine but this varies across behavioral domains and will require further work to fully elucidate.

4.4. Conclusion

As an effector post-synaptic NMDA signaling, *Anks1b* operates as an intermediary between neuronal activity and downstream changes to neuronal biology [25]. Our study shows that *Anks1b* is a critical in post-natal development, exhibiting partial lethality at weaning. Furthermore, ablation of *Anks1b* has behavioral effects consistent with disruption to NMDAR-mediated glutamatergic signaling. These findings may have implications for translational studies of psychiatric disorders.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neulet.2017.01.044>.

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