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RESEARCH

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Altered trial-to-trial responses to reward outcomes in *KCNMA1* knockout mice during probabilistic learning tasks

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Abstract

The large-conductance calcium- and voltage-activated potassium (BK) channels, encoded by the *KCNMA1* gene, play important roles in neuronal function. Mutations in *KCNMA1* have been found in patients with various neurodevelopmental features, including intellectual disability, autism spectrum disorder (ASD), or attention deficit hyperactivity disorder (ADHD). Previous studies of *KCNMA1* knockout mice have suggested altered activity patterns and behavioral flexibility, but it remained unclear whether these changes primarily affect immediate behavioral adaptation or longer-term learning processes. Using a 5-armed bandit task (5-ABT) and a novel Δrepeat rate analysis method that considers individual baseline choice tendencies, we investigated immediate trial-by-trial Win-Stay-Lose-Shift (WSLS) strategies and learning rates across multiple trials in *KCNMA1* knockout (*KCNMA1*$^{-/-}$) mice. Three key findings emerged: (1) Unlike wildtype mice, which showed increased Δrepeat rates after rewards and decreased rates after losses, *KCNMA1*$^{-/-}$ mice exhibited impaired WSLS behavior, (2) *KCNMA1*$^{-/-}$ mice displayed shortened response intervals after unrewarded trials, and (3) despite these short-term behavioral impairments, their learning rates and task accuracy remained comparable to wildtype mice, with significantly shorter task completion times. These results suggest that BK channel dysfunction primarily alters immediate behavioral responses to outcomes in the next trial rather than affecting long-term learning capabilities. These findings and our analytical method may help identify behavioral phenotypes in animal models of both BK channel-related and other neurodevelopmental disorders.

Keywords BK channel, *KCNMA1*, Reinforcement learning, Win-stay-lose-shift, Learning rate, 5-ABT

Introduction

The large-conductance calcium- and voltage-activated potassium (BK) channels, encoded by the *KCNMA1* gene, play a crucial role in regulating neuronal excitability through negative feedback mechanisms. These channels are located in both pre- and post-synaptic compartments, where they respond to membrane depolarization and increases in intracellular calcium by generating large outward potassium currents [24]. At the presynaptic terminal, BK channels limit calcium influx and neurotransmitter release by promoting rapid repolarization. Postsynaptically, they contribute to spike repolarization and afterhyperpolarization, thereby controlling neuronal

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firing patterns and excitability. This precise regulation of neuronal activity by BK channels is essential for normal brain function, and its disruption through mutations in *KCNMA1* has been linked to various neurological and psychiatric conditions, including motor deficits, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual disability [3, 11, 31, 38, 41, 43–45, 58, 74]. A substantial number of patients with *KCNMA1* mutations, encompassing both loss-of-function and gain-of-function variants, have been reported to exhibit neurodevelopmental disorders, with a subset displaying autistic features [37, 38, 41, 43, 44].

Notably, reduced BK channel expression has been implicated in other neurodevelopmental disorders that present with autistic features. In Fragile X syndrome (FXS), a disorder characterized by intellectual disability and autism-like behaviors, the fragile X mental retardation protein (FMRP) in the central nervous system directly modulates BK channel function to regulate action potential duration [16, 23]. Indeed, BK channels have emerged as a promising therapeutic target for FXS, with channel openers showing behavioral improvements in animal models [26, 27, 33, 75]. Similarly, Williams-Beuren syndrome, another neurodevelopmental disorder with autistic features, exhibits decreased *KCNMA1* expression [36]. Additionally, Angelman syndrome, which is characterized by hyperactivity, has been shown to involve degradation of BK channels [63].

Studies of *KCNMA1* knockout mice have revealed complex behavioral phenotypes. While these mice exhibit moderate ataxia and motor deficits [39, 50, 68, 69] and reduced wheel running [40], their open field locomotor activity remains normal [68, 69]. Intriguingly, they show increased home cage activity and Y-maze exploration [40, 68, 69], along with marked alterations in acoustic response and habituation [68, 69]. In comparison, *Fmr1* knockout mice modeling FXS display hyperactivity, sensory hyperexcitability, and impaired short-term spatial memory-deficits that can be ameliorated by BK channel openers [8, 27, 33, 75]. While these findings demonstrate the broad impact of BK channels on behavior, they do not fully characterize how BK channel dysfunction might relate to the impaired behavioral adaptation to changing environments—a hallmark feature of ASD and ADHD in human individuals.

Our recent study using the 3-choice serial reaction time task (3-CSRTT), found that, while *KCNMA1* knockout did not severely impair task acquisition, it did increase premature responses when cue waiting times are randomized [4]. This suggests that BK channels play a critical role in modulating the timing control of actions, in response to unpredictable stimulus patterns. Additionally, perseverative responses (repeating the choice behavior even after receiving a reward) decreased significantly in *KCNMA1*$^{-/-}$ mice compared to the wild type [4], indicating that their outcome recognition or in action-chain executions are altered. While the 3-CSRTT was used to examine the ability to adapt to tasks that require attention, further research using other tasks might clarify adaptation in highly uncertain environments and responses to outcomes.

Impaired behavioral flexibility, a characteristic of neurodevelopmental disorders, is often studied using reversal learning tasks [59, 66]. These tasks, which require remapping stimulus-action-outcome associations, are negatively affected by various neurological and mental disorders [51–53, 59]. Win-Stay-Lose-Shift (WSLS) strategies are used to analyze trial-by-trial decisions in reversal learning tasks [7, 12, 18, 19, 34, 35]. Win-Stay repeats rewarded choices, while Lose-Shift changes after no reward [25, 72]. Probabilistic reward-related outcomes increase task difficulty by the requiring integration of information from multiple trials. These designs, known as "probabilistic reversal learning" or "bandit tasks", represent a reinforcement learning paradigm [13, 34, 47, 48, 65].

Alterations in WSLS behaviors are common in neurodevelopmental disorders [6, 62]. Individuals with ASD often exhibit reduced cognitive flexibility and difficulty in coping with uncertainty [55]. In probabilistic reversal learning tasks, ASD patients tend to persist with the same choices, instead of adjusting responses according to the outcomes [17, 21, 57]. However, few studies reported that adults with ASD exhibited extensive choice switching and a lack of Win-Stay, during repeated experiential tasks [73] and probabilistic learning tasks [62]. This pattern is also characteristic of ADHD, where task adaptation is hindered by a tendency to switch choices regardless of the outcome [6].

Alterations in the temporal aspects of behavior, such as post-error slowing (where reaction time is prolonged after an unrewarded trial), are also often reported in neurodevelopmental disorders. For instance, children with ADHD show shortened post-error slowing in challenging tasks, which is considered to indicate reduced error recognition [5].

The k-armed bandit task (k-ABT, k = number of choices) has been a valuable tool to investigate these behavioral characteristics in animal models, as it allows to examine several quantitative behavioral indicators, such as accuracy, behavioral flexibility, WSLS strategies, and temporal response characteristics in uncertain environments [13, 30, 34, 59]. While previous studies using the 2-ABT (k = 2) have revealed abnormalities in mouse models of neurodevelopmental disorders [1, 2, 56], the potential role of BK channels in these behaviors has

not been explored using this paradigm. Therefore, we hypothesized that examining the WSLS strategies and temporal response characteristics of *KCNMA1*$^{-/-}$ mice in probabilistic learning tasks may reveal some kind of abnormalities or indication of these phenotypes. This study is expected to contribute to a deeper understanding of the behavioral characteristics of neurodevelopmental disorders originating from *KCNMA1* mutations. Additionally, it may potentially be useful to classify subtypes of clinical symptoms, thereby enhancing our ability to identify and assess these neurodevelopmental disorders.

This study uses the 5-ABT, as described by Ohta et al. [48], to explore the behavioral responses of *KCNMA1*$^{-/-}$ mice to unexpected events. In this task, the mice are required to nose-poke into one of five holes, each associated with a predefined probability of delivering food, thereby forcing the mice to learn from binary outcomes—reward or no reward. This experimental setup allows the quantitative evaluation of WSLS behaviors observed in subsequent trials. In particular, we propose a method to calculate the difference between the repeat probability and the baseline probability of selecting the same choice in WSLS analysis, based on our previous work [48], which was considered useful to detect behavioral differences in WSLS strategy. By reversing the reward probabilities, behavioral flexibility can also be assessed. While the 2-ABT has been successfully used in many studies [56, 61, 65], its design inherently limits shifting choices to a single alternative option, making it difficult to distinguish between learned alternation behavior and true choice flexibility. In contrast, the 5-ABT allows the animals to choose among four remaining options, enabling a broader evaluation of choice variation characteristics with reduced influence of simple alternation tendencies. The positive and negative learning rates and exploration tendency indexes can also be calculated by fitting a Q-learning model to the behavioral data. This provides insights into the long-term learning efficacy and choice policy [48, 49].

This study addresses three key aspects: (1) the nature of WSLS behavior in *KCNMA1*$^{-/-}$ mice, (2) their performance in a reversal learning task, and (3) the temporal characteristics of their responses. Through this comprehensive approach, we aim to elucidate the role of BK channels on the immediate behavioral adaptation and temporal aspects of operant learning, which carries implications for the understanding of *KCNMA1*-related neurodevelopmental disorders.

Materials and methods

Animals

The *KCNMA1* knockout strain was originally provided by Dr. Andrea L. Meredith at Department of Physiology, University of Maryland School of Medicine [39]. *KCNMA1*$^{+/-}$ mutant mice were backcrossed with C57BL/6 J mice for more than 10 generations and maintained at National Defense Medical College. Male BK channel-deficient mice (*KCNMA1*$^{-/-}$, n = 16) and their male wild-type (*KCNMA1*$^{+/+}$, WT) littermates (n = 16) were used for the behavioral experiments. Genotyping was conducted at 2–3 weeks of age using primers: (F) ATAGCCTGAAGAACGAGATCAGC; (R) CCTCAA GAAGGGGACTCTAAAC for detecting *KCNMA1*$^{-/-}$ and (F) TTCATCATCTTGCTCTGGCGGACG; (R) CCA TAGTCACCAATAGCCC for WT. After genotyping, mice were housed in groups of 2 or 3 per cage, with each cage containing both WT and *KCNMA1*$^{-/-}$ littermates. Animals were maintained in a temperature-controlled room (22–25 °C) with a 12-h light/dark cycle. Mice were tested in the 5-ABT from 11 to 28 weeks of age, and were food-restricted for the 24 h hours preceding the test. Average group weights were as follows: WT, 27.6 ± 1.6 g (mean ± SD) at baseline and 24.7 ± 1.9 g (89.5% of baseline) after food restriction; *KCNMA1*$^{-/-}$, 22.3 ± 2.2 g at baseline and 19.6 ± 2.1 g (87.9%) post-restriction. Throughout the experiment, mice could obtain food reward pellets (Dustless Precision Pellets, 20 mg, Bio-Serve, Frenchtown, NJ, USA) by performing the 5-ABT.

Apparatus

The 5-ABT was conducted individually in an operant chamber measuring 18.8 × 23.0 × 17.5 cm (MED-NP9M-B1, Med Associates Inc., VT, USA). This chamber featured a curved rear panel fitted with a horizontal array of nine round holes (diameter: 1.2 cm), each equipped with an infrared photocell beam sensor for nose-poke detection and an LED light. From the nine holes, five were used for the test and four were covered with plastic plates for the duration of the task. The front panel included a food magazine outfitted with an infrared sensor and an LED light. An acrylic nest box measuring 13.6 × 20.8 × 11.5 cm (SN-798; AS ONE Corp., Japan) was connected to the operant box by a 3-cm diameter passage linking the two box walls. This setup allows the continuous monitoring of the mice's choices in response to changes in reward probabilities, across several days [28, 48, 54]. Water was freely available from a bottle mounted on the nest box.

Experimental procedures

The experiment comprised two stages, training and testing, as previously described by Ohta et al. [48]. Initially, during the training stage, the process was divided into four progressive phases (i.e., Phase 0 to Phase 3). In Phase 0, magazine training, mice were trained to nose-poke the magazine to receive a pellet, with the phase ending after 50 pellets were dispensed. In Phase 1, mice were allowed

to nose-poke any of five available holes to receive a pellet, and this phase also concluded after 50 pellets. Phase 2 began with the first nose-poke to the magazine (task call), and the mice received a pellet with every nose-poke, ending once 25 pellets were dispensed. In Phase 3, the reward probability at each of the five holes was set to 70%, and this phase was completed once another 25 pellets were delivered.

After completing all training phases, mice performed the testing stage, which involved three distinct tasks: ALL, BIT and REV (Reversal). In the ALL task, each hole had a 30% chance of receiving a pellet; in the BIT task, only the third hole offered a 50% chance of a pellet, with all other holes having zero probability; and in the REV task, every hole except the third offered a 30% chance of receiving a pellet. Each task continued until 151 pellets were collected. If mice failed to collect at least 75 pellets within 24 h, they were manually fed 75 pellets. The allotted time from task call to nose-poke was 15 s, and failures to act within this window were recorded as timeouts. The inter-trial interval (ITI) was consistently maintained at 4 s.

All mice successfully progressed through the training phases and completed the experimental protocol, with no exclusions necessary due to training failures or incomplete task performance.

Indexes

The outcomes measured in the study were as follows: Accuracy, which corresponded to the number of times a mouse selected the correct hole (i.e., the option with a non-zero reward probability), divided by the number of selection attempts for each task (BIT, REV). Timeout, which corresponded to the number of trials in which a mouse failed to nose-poke a hole within the 15-s time limit following a task call. Repeat rate, which represented the rate at which a mouse chose the same hole after obtaining (repeat rate after Win) or not obtaining (repeat rate after Lose) a reward, across all subtasks. Δrepeat rate, which represented the rate of change in the repeat rate after win (Δrepeat rate after Win) or repeat rate after lose (Δrepeat rate after Lose) across all subtasks. Reaction time, which corresponded to the median time elapsed between a task call after a rewarded (i.e., reaction time after Win) or an unrewarded (i.e., reaction time after Lose) trial, and a nose-poke. Reward latency, which corresponded to the median time elapsed from the correct nose-poke to the magazine nose-poke. Task call latency after Lose, which indicated the median time taken between an unrewarded nose-poke and the start of a new task with a magazine nose-poke. Inter-response interval (IRI), which corresponded to the median time elapsed between a rewarded (i.e., IRI after Win) or an unrewarded (i.e., IRI after Lose) nose-poke, and the next nose-poke. The IRI was calculated across the trials of each subtask. Entropy, was calculated based on the probability distribution of nose-pokes for each hole i for the first 300 trials of each task, using the definition by Shannon [60]: $H = -\Sigma p_i log_2 p_i$.

Q-learning-based analysis

Behavioral data were analyzed in the assumption that each mouse continuously attributed an action value to each hole, as previously described [13, 34, 48]. Action values were determined according to the Differential Learning Rate Q-learning model (DLR-Q) [9, 14, 29, 48], which can be summarized as follows:

Let A be the set actions, where $A = \{1, 2, 3, 4, 5\}$, with each number corresponding to choosing a specific hole. On each trial t, where an action $a \in A$ was selected and an outcome $r \in \{0,1\}$ was obtained, the action value Q_t of choosing action a was calculated/updated as:

$$Q_{t+1}(a) = Q_t(a) + \begin{cases} \alpha^+(r - Q_t(a)) \; if \; r = 1 \\ \alpha^-(r - Q_t(a)) \; if \; r = 0 \end{cases}$$

where α^+ and α^- are free parameters that control the magnitude of value updates based on the presence or absence of reward. They are referred to as the positive and negative learning rates, respectively. The probability of selecting action a on trial t was predicted using the soft-max policy function:

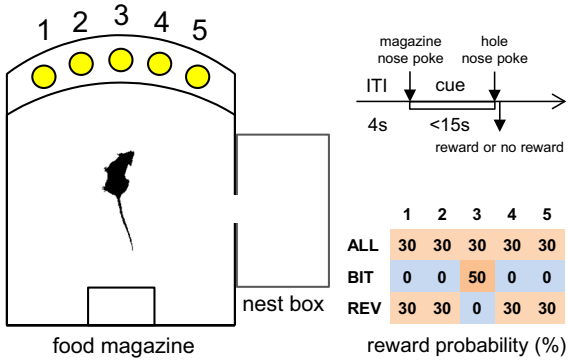
$$P(a) = \frac{exp(Q_t(a)\beta)}{\sum_{b \in A} exp(Q_t(b)\beta)}$$

where β is a free parameter called the inverse temperature, which governs the exploration–exploitation trade-off [64]. These three free parameters ($\alpha^+, \alpha^-$and β) were estimated using the importance sampling method [29].

Statistical analysis

Duration was compared between both groups across all seven phases (training phases 0–3 and test phases ALL, BIT, and REV) using a two-way repeated measures ANOVA, with Sidak's post-hoc test for multiple comparisons. For other measures, comparisons were made as follows: Accuracy was compared between both groups and two tasks (BIT, REV) using a two-way repeated measures ANOVA with Sidak's post-hoc test. Entropy, timeout, IRIs after Win and Lose, reward latency, task call latency after Lose, and reaction times after Win and Lose were compared between both groups across three test tasks (ALL, BIT, REV) using a two-way repeated ANOVA with Sidak's test for post-hoc multiple comparisons. Repeat rates after Win and Lose, Δrepeat rates after Win and Lose, positive and

negative learning rates and inverse temperature were analysed using the two-tailed *t*-test with Welch's correction. All statistical analysis were performed with GraphPad Prism 10 (GraphPad Software, USA).



	1	2	3	4	5
ALL	30	30	30	30	30
BIT	0	0	50	0	0
REV	30	30	0	30	30

Fig. 1 The five-armed bandit task (5-ABT). A nose-poke into the magazine initiated a trial (task-call), after which the mouse was required to nose-poke into one of the five holes within 15 s. Each hole was associated with a preset probability of food pellet delivery. The experiment consisted of three consecutive tasks—ALL, BIT (only one choice yields reward), and REV (reverse)—each featuring distinct reward probabilities for each hole. Each task ended after 151 food pellets had been dispensed

Results

We investigated the reinforcement learning abilities of WT and *KCNMA1*$^{-/-}$ mice using the 5-ABT (Fig. 1). Figure 2A, B show choice rate changes of individual representative mice (one WT, and another *KCNMA1*$^{-/-}$ mouse, respectively) for the five-hole options in the subtasks ALL, BIT, and REV. In BIT, hole 3 had a 50% reward probability while others were 0%; both WT (Fig. 2A) and *KCNMA1*$^{-/-}$ (Fig. 2B) mice gradually increased their selection of the hole 3. In REV, all holes except hole 3 had 30% reward probability, and both genotypes correspondingly decreased their selection of hole 3. The average choice rates for each group are presented separately for BIT (Fig. 2C, D) and REV (Fig. 2E, F), aligned to the start of each subtask to account for individual differences in task completion times. Both groups successfully identified the correct hole choice in BIT and its reversal in REV.

No significant group differences were found for accuracy in the BIT and REV tasks (task × group: $p = 0.274$, $F\ [1, 30] = 1.24$; task: $p < 0.001$, $F\ [1, 30] = 44.7$; group: $p = 0.638$, $F\ [1, 30] = 0.227$; Fig. 3A). Analysis of choice entropy showed only a significant main effect of task (Fig. 3B; task × group: $p = 0.142$, $F\ [2, 60] = 2.02$; task: $p < 0.001$, $F\ [1.741, 52.22] = 9.99$; group: $p = 0.440$, $F\ [1, 30] = 0.612$), indicating that all mice altered their

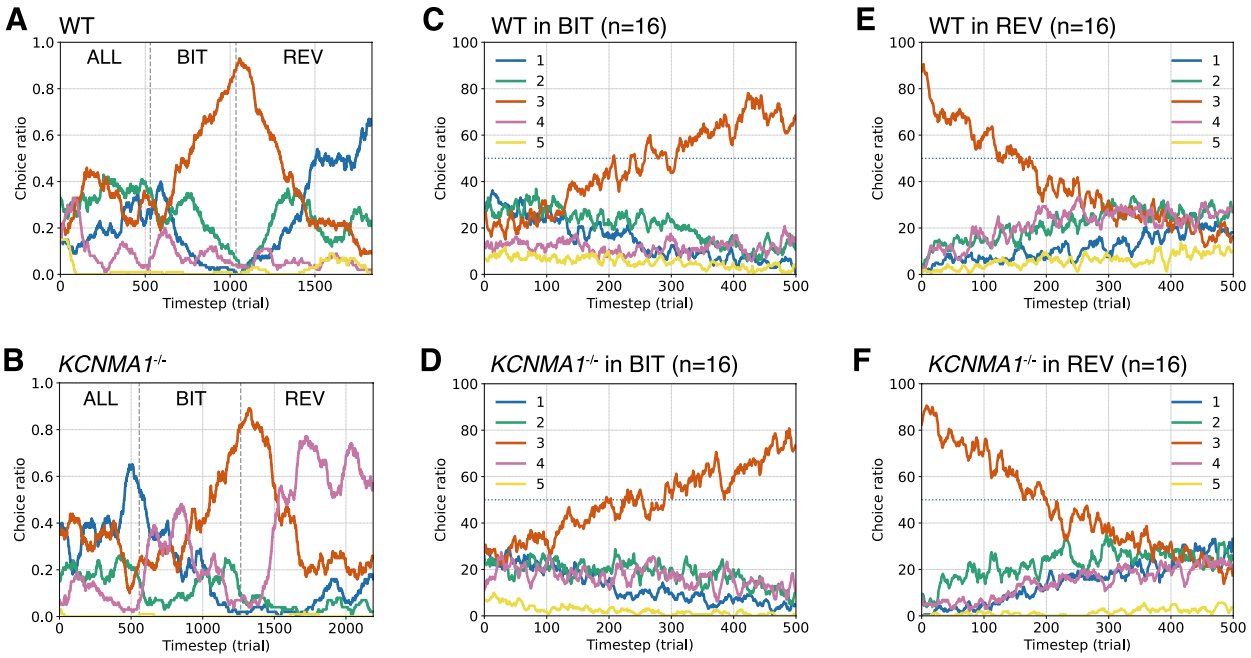


Fig. 2 5-ABT responses of WT and *KCNMA1*$^{-/-}$ mice. **A** and **B** A representative choice history of WT and *KCNMA1*$^{-/-}$ mice in subtasks ALL, BIT and REV. Blue, green, orange, magenta, and yellow lines represent selection rates for holes 1, 2, 3, 4, and 5, respectively, plotted as 20-step moving averages of choice ratios. Vertical dotted lines indicate task switching. **C** and **D** Group average of 20-step moving averages of hole selection for each mouse in the subtask BIT. Since mice completed BIT in different numbers of trials, averages are shown for the first 500 steps. **E** and **F** Group average in REV. The horizontal, blue, dotted lines indicate a 50% choice ratio

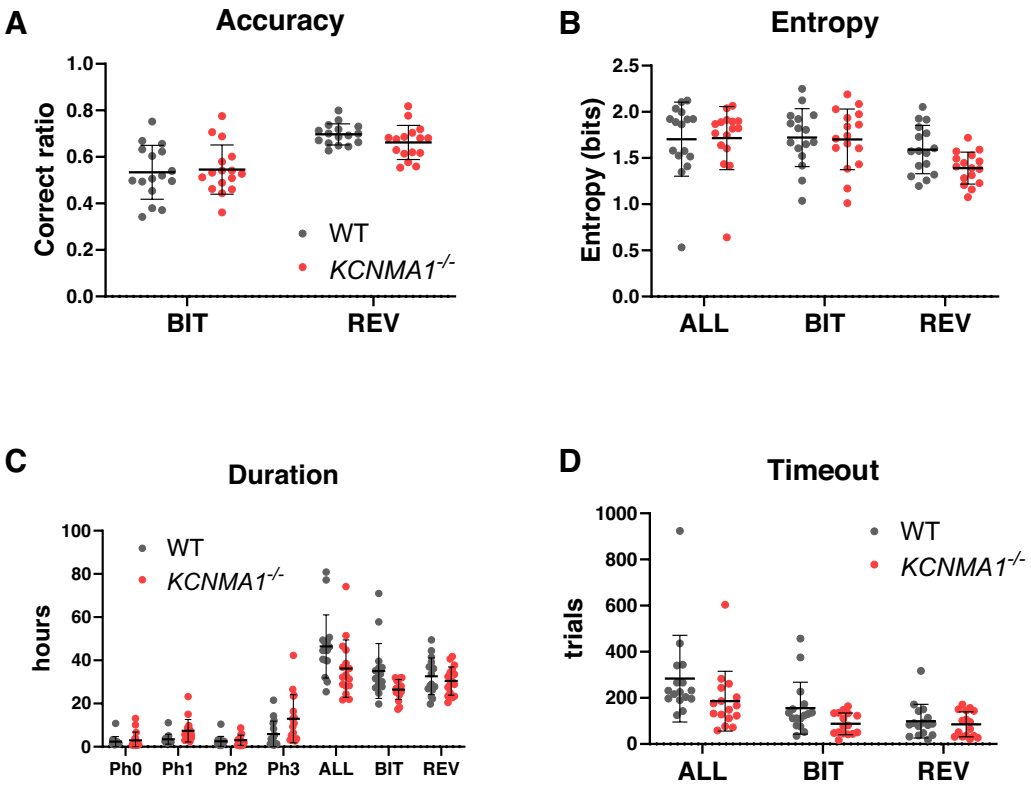


Fig. 3 Behavioral characteristics exhibited in the 5-ABT. **A** Accuracy, the ratio of correct choices in BIT and REV. **B** Choice entropy. **C** Duration, time required to complete each task. **D** Number of timeout trials per task. No significant differences were found between groups

exploration patterns across different task phases, regardless of genotype. A significant interaction between task and genotype was found in the duration to complete all task phases, including training phases 0–3 and the three test phases (Fig. 3C; task × group: $p < 0.001$, F [6, 180] = 5.58; task: $p < 0.001$, F [3.52, 106] = 149; group: $p = 0.377$, F [1, 30] = 0.80). Post-hoc analyses did not show significant difference in each task phase (Phase 0: WT 2.36 h vs *KCNMA1*$^{-/-}$ 2.96 h, $p = 0.998$; Phase 1: 3.49 vs 7.38, $p = 0.085$; Phase 2: 2.51 vs 3.01, $p = 0.996$; Phase 3: 5.91 vs 13.0, $p = 0.225$; ALL: 46.4 vs 36.2, $p = 0.284$; BIT: 35.1 vs 26.5, $p = 0.131$; REV: 32.7 vs 30.4, $p = 0.976$). The groups did not differ significantly in the number of timeouts (Fig. 3D; task × group: $p = 0.108$, F [2, 60] = 2.31; task: $p < 0.001$, F [1.477, 44.32] = 28.9; group: $p = 0.075$, F [1, 30] = 3.39; WT: mean = 179.2; *KCNMA1*$^{-/-}$: mean = 119.6).

We examined group differences in the Win-Stay-Lose-Shift (WSLS) strategy. We calculated the probability of both a rewarded (Fig. 4A, Win-Stay) and an unrewarded (Fig. 4D, Lose-Shift) choice being re-selected after n trials (repeat rate). Our previous research showed that, after a rewarded trial, the probability of selecting the same option was higher only for the immediately subsequent trial [48]. Based on this, we used the mean probability of the same-option selection from the 6th to the 10th trial, following either Win or Lose as a baseline. We then established the Δrepeat ratio by computing the difference between this baseline and the repetition rate in the immediately subsequent trial for each individual mouse (Fig. 4B, E). The Δrepeat ratio after Win differed significantly between groups ($p < 0.001$, t [27.18] = 4.51; Fig. 4B), with an average of 0.0490 ± 0.034 (SD) for WT mice and 0.0020 ± 0.024 for *KCNMA1*$^{-/-}$ mice. Similarly, a significant difference was found for Δrepeat ratio after Lose ($p < 0.001$, t [28.05] = 5.65; Fig. 4E), with an average of -0.050 ± 0.025 for WT mice and -0.0050 ± 0.019 for *KCNMA1*$^{-/-}$ mice. For comparison with previous studies using other ASD mouse models [1, 56], the repeat rates for the trial that followed a rewarded and an unrewarded trial, were also calculated and compared between groups (Fig. 4C, F). In contrast to our findings using the Δrepeat rates analysis, conventional repeat rate calculations showed that *KCNMA1*$^{-/-}$ mice had significantly higher repeat rates after Lose ($p = 0.047$, t [27.19] = 2.08) but not after Win ($p = 0.053$, t [29.91] = 2.02).

To explore the temporal characteristics of the behavior that followed the outcome of each choice, we evaluated

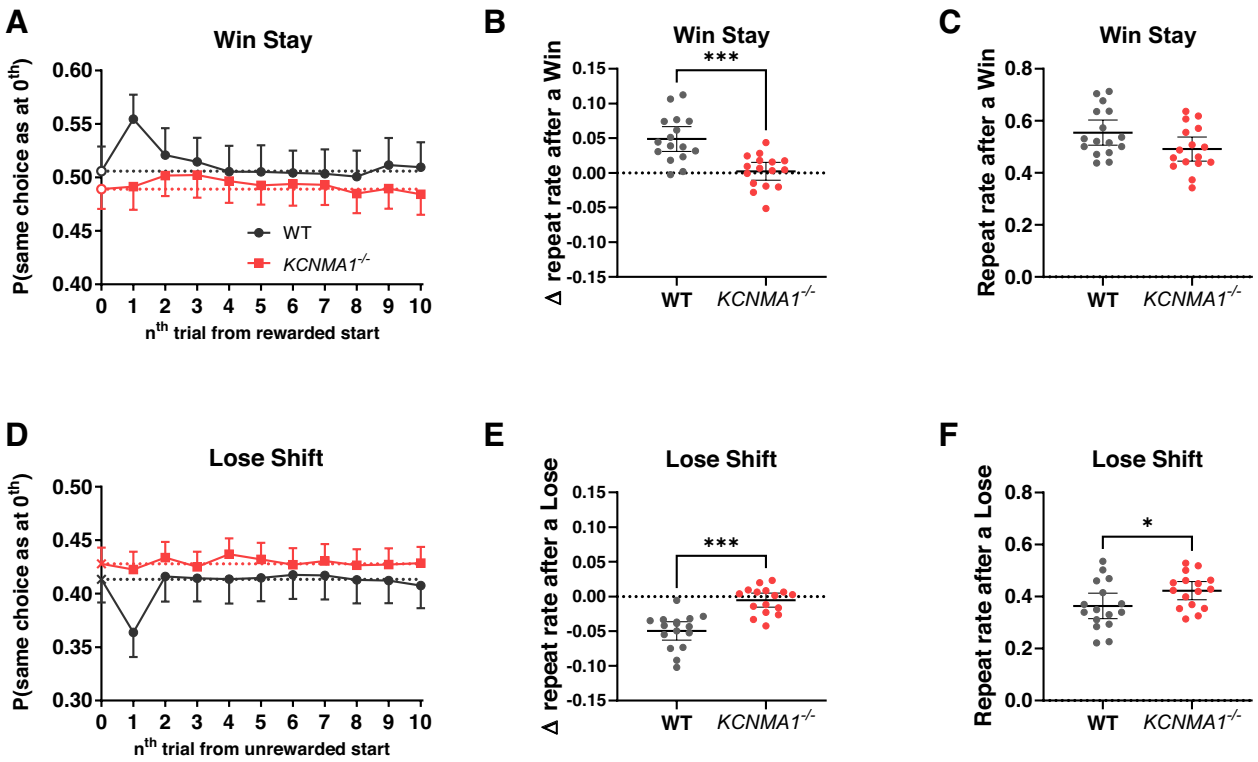


Fig. 4 Win-Stay-Lose-Shift behaviors in WT and *KCNMA1*$^{-/-}$ mice. **A** and **D** Probability of repeating choices. Black (WT) and red (*KCNMA1*$^{-/-}$) lines show the probability (0–1.0) of selecting the same hole in subsequent trials after a rewarded (**A**) or unrewarded (**D**) choice at trial 0. Dotted lines represent the baseline probability, calculated as the mean probability of selecting the same hole across trials 6–10. Error bars represent the standard error of the mean. **B** and **E** Change in repeat probability (Δrepeat rate). The difference between immediate repeat probability (trial 1) and baseline probability (trials 6–10 average) after Win (**B**) or Lose (**E**). Positive values indicate increased tendency to repeat choices compared to baseline, while negative values indicate decreased tendency. **C** and **F** Absolute repeat probability. The probability (0–1.0) of selecting the same hole in the immediately following trial after a rewarded choice (**C**) or unrewarded choice (**F**). Asterisks indicate statistical significance at $p < 0.05$ (*) and $p < 0.001$ (***)

the inter-response interval (IRI), which measured the time elapsed between two-hole choices. No significant difference was found between groups for IRI after a Win (Fig. 5A; task × group: $p = 0.796$, $F\ [2, 60] = 0.229$; task: $p < 0.011$, $F\ [1.188, 35.63] = 6.63$; group: $p = 0.056$, $F\ [1, 30] = 3.96$; WT: mean = 62.8; *KCNMA1*$^{-/-}$: mean = 46.2). However, the groups differed significantly in the IRI after a Lose (Fig. 5B; task × group: $p = 0.505$, $F\ [2, 60] = 0.691$; task: $p < 0.001$, $F\ [1.346, 40.39] = 22.0$; group: $p = 0.002$, $F\ [1, 30] = 11.4$; WT: mean = 20.0; *KCNMA1*$^{-/-}$: mean = 14.5). These findings suggest a temporal response alteration, specific to trials in which no reward is obtained, which prompts a detailed breakdown of the IRI components.

We measured the time from the rewarded hole nose-poke to the magazine nose-poke to obtain a reward, known as reward latency, and the time from the hole nose-poke to the magazine nose-poke to task call when no reward was given. No significant difference was found in the reward latency of the two groups (Fig. 5C; task × group: $p = 0.214$, $F\ [2, 60] = 1.58$; task: $p < 0.001$, $F\ [1.856, 55.67] = 18.6$; group: $p = 0.258$, $F\ [1, 30] = 1.33$; WT: mean = 2.28 s; *KCNMA1*$^{-/-}$: mean = 2.12 s). However, the groups differed significantly on the latency to a new task call following a Lose (Fig. 5D; task × group: $p = 0.127$, $F\ [2, 60] = 2.14$; task: $p < 0.001$, $F\ [1.481, 4.44] = 23.3$; group: $p = 0.005$, $F\ [1, 30] = 9.46$; WT: mean = 12.8 s; *KCNMA1*$^{-/-}$: mean = 9.1 s). Regarding the reaction time after initiating the task, no significant difference was found between the groups in the trial that followed a Win (Fig. 5E; task × group: $p = 0.216$, $F\ [2, 60] = 1.58$; task: $p < 0.001$, $F\ [1.960, 58.79] = 21.8$; group: $p = 0.875$, $F\ [1, 30] = 0.0251$; WT: mean = 6.79 s; *KCNMA1*$^{-/-}$: mean = 6.69 s), while the groups differed significantly in the trial that followed a Lose (Fig. 5F; task × group: $p = 0.190$, $F\ [2, 60] = 1.71$; task: $p < 0.001$, $F\ [1.435, 43.04] = 59.1$; group: $p = 0.018$, $F\ [1, 30] = 6.22$; WT: mean = 5.50 s; *KCNMA1*$^{-/-}$: mean = 4.63 s).

Taken together, our results indicate that *KCNMA1* knockout leads to altered choices and temporal control

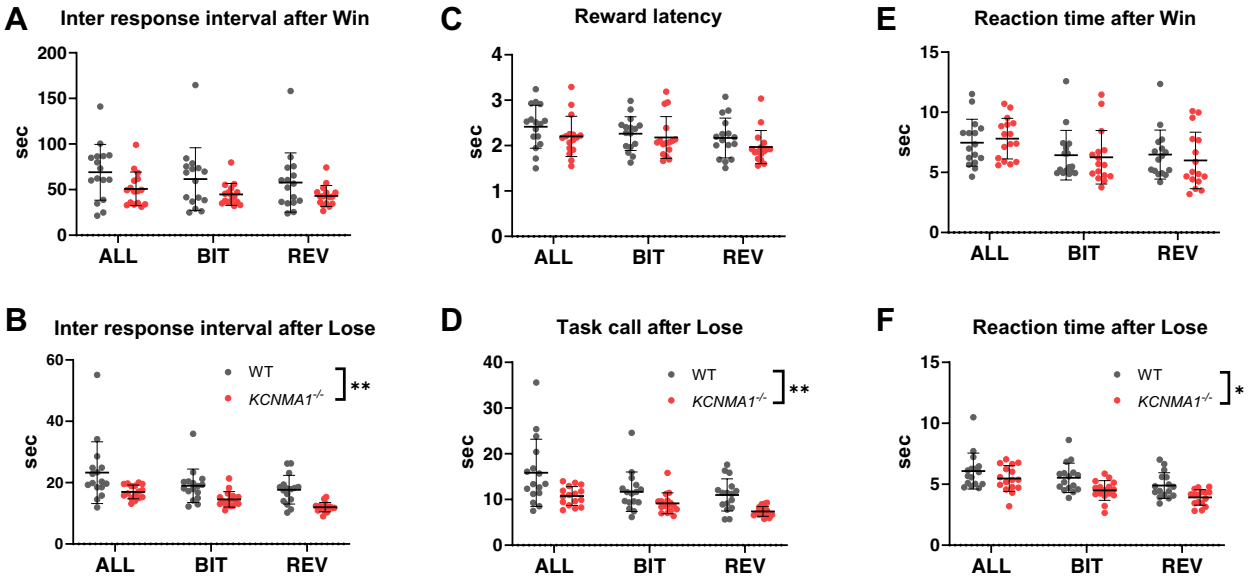


Fig. 5 Temporal characteristics of 5-ABT responses. **A** and **B** Inter response interval (IRI) after a Win (**A**) or a Lose (**B**), representing the time between consecutive hole nose-pokes. Significant genotype differences were observed in IRI after Lose. **C** Reward latency, time elapsed from successful hole selection to magazine nose-poke to obtain a pellet. **D** Task call latency after Lose, time elapsed from unsuccessful hole selection to magazine nose-poke to initiate the next trial, showing significant differences between genotypes. **E** and **F** Reaction time after a Win (**E**) and a Lose (**F**), representing the time elapsed from a task call to the next hole selection, with significant genotype differences in reaction time after Lose (F). Asterisks indicate statistical significance between genotypes, $p < 0.05$ (*) and $p < 0.005$ (**)

of behavior, on a scale from seconds to tens of seconds for the next trial. However, since the overall learning of the task was still achieved (Fig. 2 and 3A), we further investigated long-term reinforcement learning capabilities across multiple trials using Q-learning model-based analysis. We found no significant differences between the groups in both positive (Fig. 6A; $p = 0.779$, $t\ [27.14] = 0.284$) and negative learning rates (Fig. 6B; $p = 0.223$, $t\ [28.00] = 1.25$). Additionally, no significant differences were found for inverse temperature, a parameter related to exploratory behavior (Fig. 6C; $p = 0.932$, $t\ [25.88] = 0.0867$).

Discussion

This study demonstrates three key characteristics of BK channel dysfunction of mice, in the context of the 5-ABT: (1) it abolishes the WSLS strategy, (2) it shortens the time to retry after an unrewarded trial, and (3) despite these short-term behavioral impairments, their learning rates and task accuracy remained comparable to wild type mice.

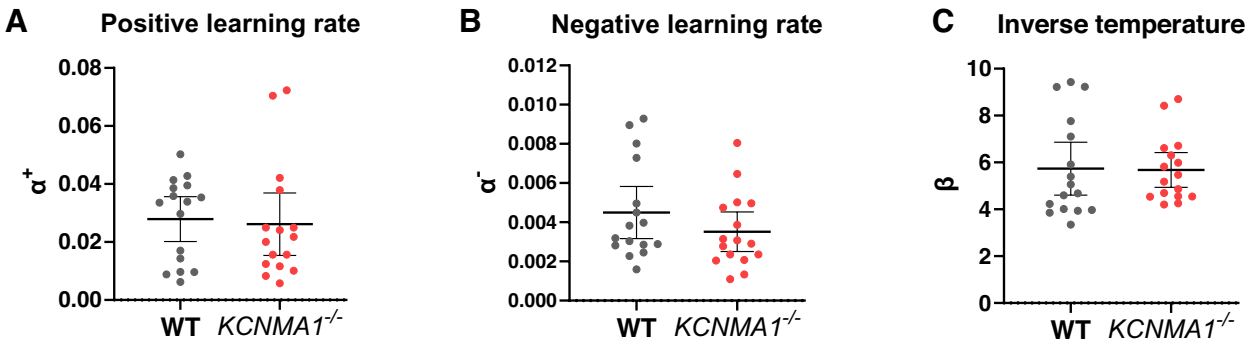


Fig. 6 Estimated reinforcement learning meta-parameters. **A** Positive learning rate estimated from the action-selection data of each mouse. **B** Negative learning rate. C Inverse temperature. No significant group differences were found for any of these parameters

Widely used analyses of WSLS behavior in other studies have investigated the probability of repeating the same choice in the trial that follows a Win or a Lose outcome [56, 61, 65]. In the present study, using the same method, we initially hypothesized that, similar to other ASD models such as *Fmr1*-KO and BTBR mice [1, 56], *KCNMA1*$^{-/-}$ mice would increase Lose-Shift behavior (Fig. 4F). However, acknowledging the possibility of individual variations in the baseline probability of repeating the same choice, we refined the analysis method, based on our previous work [48]. In this refined approach, we calculated the difference between an individual's average repeat probability and the repeat rate immediately after a Win/Lose outcome. Intriguingly, this new analysis revealed that *KCNMA1*$^{-/-}$ mice actually showed a decrease in both Lose-Shift (Fig. 4E) and Win-Stay behaviors (Fig. 4B), thus contradicting the previous conclusions that *KCNMA1*$^{-/-}$ mice increased Lose-Shift behavior (Fig. 4F) and did not change in Win-Stay behavior (Fig. 4C). By pooling up to 10 subsequent trials, instead of considering only the first trial after a Win or a Lose, and assuming the number of trials after which the effects of Win or Lose would disappear, the expected value could be calculated based on the average repeat rate of each individual mouse. This, in turn, allowed to calculate the Δrepeat rate. This analytical method can potentially be useful to identify short-term behavioral characteristics in probabilistic learning task, both for animal models of various neurodevelopmental disorders and for patients with those disorders.

Human studies use multi-choice tasks like Iowa Gambling Task [46], while animal studies often use two-choice paradigms (2-ABT). In the case of 2-ABT, after animals are trained in alternating behavior, the probability patterns are changed or reversed. However, this makes it difficult to distinguish between WSLS strategies and the learned alternating behavior. To enhance translational studies between human neurodevelopmental/mental disorders and animal models, it is crucial to investigate using Δrepeat rate how the number of available choices influences the sensitivity in detecting WSLS strategy differences.

Despite the significant loss of WSLS strategy observed in *KCNMA1*$^{-/-}$ mice, only partial changes were found in their long-term learning ability. Since the positive and negative learning rates did not differ significantly between groups (Fig. 6A, B), it is concluded that their ability to update the action value of each choice over the long term was not significantly impaired. This indicates the lack of a direct correlation between the short-term WSLS strategy and the update of the long-term action value, which suggests that they function through independent mechanisms.

In terms of reversal learning, *KCNMA1*$^{-/-}$ mice did not show severely impaired behavioral flexibility, as evidenced by similar accuracy to WT mice in both BIT and REV tasks (Fig. 3A). The inverse temperature parameter indicates the balance between exploration and exploitation: lower values suggest a stronger tendency to explore regardless of past outcomes, while higher values indicate a preference for choices that previously yielded rewards [15, 20, 65]. The absence of significant differences in inverse temperature and choice entropy between groups (Figs. 6C, 3B) suggests that their overall exploration tendencies were similar.

The *KCNMA1*$^{-/-}$ mice exhibit a unique form of hyperactivity that becomes apparent under specific circumstances. While these knockout mice demonstrated comparable task performance metrics (accuracy, duration, and timeouts) to WT mice (Fig. 3A, C, D), they showed distinctive temporal patterns in their inter-trial behavior. Analysis of inter-response intervals (IRI) revealed that *KCNMA1*$^{-/-}$ mice had shorter retry times following unrewarded trials (Fig. 5B). They also demonstrated reduced task call times after non-reward (Fig. 5D) and decreased reaction times, specifically after Lose (Fig. 5F). These findings point to a distinctive tendency in *KCNMA1*$^{-/-}$ mice to rapidly engage in subsequent actions, particularly following negative outcomes. This behavioral pattern is further corroborated by Y-maze experiments, where *KCNMA1*$^{-/-}$ mice exhibited twice the number of explorations compared to WT mice, while maintaining similar alternation rates [68, 69]. This suggests a propensity for quick exploration of alternative paths without perseveration. Additionally, in the 3-CSRTT, *KCNMA1*$^{-/-}$ mice showed significantly fewer perseverative responses [4], contrasting with other ASD model mice. The hyperactivity observed in *KCNMA1*$^{-/-}$ mice is characterized by increased actions per unit time, especially after unsuccessful experiences. This behavior is distinct from simple repetitive actions and is not marked by a fixation on specific choices, as evidenced by their diminished Win-Stay strategy (Fig. 4B). Instead, it reflects a rapid transition to new actions, particularly in response to negative outcomes, similar to the hyperactivity observed after stress induction in *KCNMA1*$^{-/-}$ mice [50]. However, while these behavioral changes might appear to reflect cognitive alterations, they could potentially arise from more fundamental sensory processing deficits. Given that BK channels play crucial roles in both locomotor function and auditory and visual systems [26, 67–69] abnormalities in sensory processing might secondarily lead to these apparent changes in trial-to-trial behavior.

Our findings have significant implications for the understanding of various neurodevelopmental disorders.

Recent studies in humans using probabilistic reversal learning, have revealed distinct behavioral patterns in patients with different neurodevelopmental issues. For example, ASD patients aged 8–44 years old have exhibited Lose-Shift errors following reversal of task probability conditions, maintaining the choice for the previously learned option, which lead to deteriorated performance [21]. Additionally, adolescents with ASD were found to have significantly lower Win-Stay probabilities and positive learning rates compared to typically developing subjects [17]. Adults with ASD have also been reported to show lower Win-Stay probabilities, while maintaining intact Lose-Shift probabilities [62]. Fragile X syndrome (FXS) patients exhibiting ASD symptoms presented slower task learning and significant deficits in Lose-Shift learning [56]. In contrast, young adults with ADHD tended to switch choices after both Win and Lose outcomes and displayed a decreased negative learning rate [6]. While the exact relationship between BK channels and these disorders remains to be clarified [22, 37, 38, 74] it is noteworthy that both *KCNMA1*$^{-/-}$ mice and patients with BK channel-related disorders [38] share at least one common behavioral/phenotypic feature: altered WSLS strategy.

Post-error slowing is typically observed in probabilistic learning tasks where reaction time increases after a Lose, and differs among distinct cohorts. Notably, children with ADHD exhibit shorter post-error slowing in more challenging tasks [5], which indicates diminished error recognition. This feature may share common underlying factors with the decreased reaction time after Lose and the absence of the WSLS strategy observed in *KCNMA1*$^{-/-}$ mice.

The impaired WSLS strategy observed in *KCNMA1*$^{-/-}$ mice indicates a significant dysfunction in the neural circuits responsible for rapid behavioral adaptation to positive and negative outcomes. Previous animal and human studies have identified the specific brain regions associated with WSLS behavior [42, 61], Van Den [70, 71]. However, since our study was based on a non-selective, whole-body *KCNMA1*$^{-/-}$ model, it was not possible to pinpoint the exact brain regions involved, which highlights important directions for future research. Given that BK channels play a critical role in suppressing neuronal hyperexcitability [24], the loss of this regulatory mechanism in *KCNMA1*$^{-/-}$ mice may lead to excessive neural activity, ultimately resulting in impaired behavioral adjustments following outcome recognition. Subsequent studies are needed to identify specific brain regions and neuronal cell types that contribute for a non-zero Δrepeat ratio, which quantifies WSLS behavior.

A limitation of this study is the inclusion of only male mice, as sex differences in WSLS strategies have been reported [10]. Our decision to focus on male mice was driven by two key considerations. First, we aimed to establish and validate our novel Δrepeat ratio analysis method as a sensitive tool for detecting subtle or uncharacterized behavioral alterations in various types of knockout mouse models. Second, we sought to minimize potential confounding variables related to food restriction required for operant conditioning. Female BK KO mice are known to show different metabolic responses compared to males, including distinct patterns of body composition and weight regulation [32], suggesting they may be more sensitive to food restriction protocols. While this approach allowed us to demonstrate the utility of our analytical method and identify specific behavioral phenotypes, we acknowledge that extending this investigation to include female mice is crucial for future research. Such studies would not only provide a more comprehensive understanding of BK channel function across sexes but would also better align with the current emphasis on sex-inclusive research in pre-clinical studies for neurodevelopmental disorders.

Conclusion

This study demonstrates that *KCNMA1*$^{-/-}$ mice present lower Win-Stay-Lose-Shift (WSLS) behavior and shorter retry time after unrewarded trials than WT mice, indicating that BK channels are crucial for short-term behavioral adjustment and temporal control. This study therefore shows a strong correlation between *KCNMA1* gene mutations and specific indications or symptoms of neurodevelopmental disorders.

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Author contributions

H.O., T.N., and K.H. wrote the main manuscript text. H.O. acquired all data and prepared all figures. H.O. and K.H. analyzed the data. H.O., Y.S., Y.M., and T.I. designed the work. A.M. and Y.S. provided research tools and methodology and edited the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All animal procedures were performed in accordance with the institutional ethical guidelines for animal experiments of National Defense Medical College. The Animal Research Committee of National Defense Medical College approved the experimental procedures.

Competing interests

The authors declare no competing interests.

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