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Altered cognitive processes shape tactile perception in autism

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eLife Assessment

This study provides **valuable** insights with **convincing** evidence detailing altered tactile perception in a mouse model of ASD (*Fmr1* mice), paralleling sensory abnormalities in Fragile X and autism. Its main strength lies in the use of a novel and quantitative tactile categorization task and the careful dissection of behavioral performance across training and difficulty levels, suggesting that deficits may stem from an interaction between sensory and cognitive processes. The behavioral experiments are well executed and set the stage for subsequent mechanistic, causal, and computational approaches. The work is relevant to those interested in autism, cognition, and/or sensory processing.

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Abstract

Altered sensory perception is a hallmark of autism and shapes how individuals engage with their environment, with tactile perception playing a critical role in daily functioning and for social interactions. While sensory alterations are thought to contribute to cognitive differences in autism, the impact of cognition on sensory perception remains unclear. Here, we investigated how cognitive processes modulate tactile perception in the *Fmr1*-KO genetic mouse model of autism through a translational perceptual decision-making task. Our results revealed salience-dependent cognitive alterations that influenced sensory performance. During training, *Fmr1*^{-/-} male mice distinguishing between a high- and a low-salience stimulus exhibited an increased choice consistency bias in low-salience trials. When tested across a continuum of intermediate stimulus intensities, these mice demonstrated enhanced tactile discrimination of low-salience stimuli but reduced discrimination facilitation for stimuli crossing category boundaries. These effects were accompanied by diminished integration of sensory history and were dissociable from the attention deficits that emerged under high cognitive load. Together, our findings reveal that tactile perceptual alterations reflect context-dependent weighting and integration of sensory information during decision-making rather than uniform sensory deficits or enhancements, supporting a shift beyond traditional sensory–cognitive dichotomies.

Introduction

Autism is a neurodevelopmental condition that affects approximately 1 in 31 children (Shaw et al., 2025 [↗](#)). Autistic individuals display differences in social interaction and communication, repetitive behaviors, intense or special interests, and altered sensory experience as core symptoms (American Psychiatric Association, 2022 [↗](#)). Sensory alterations strongly affect the way autistic individuals interact with their environment. According to the DSM-5-TR, these are broadly expressed as “*hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment*” and are reported in 90% of autistic individuals, spanning all sensory modalities (Robertson and Baron-Cohen, 2017 [↗](#)).

Amongst sensory modalities, touch is the first sense to develop and plays a fundamental role in the exploration of the environment, the definition of “self”, and early social bonding (Bremner and Spence, 2017 [↗](#)). Tactile processing alterations have a significant impact on daily functioning and

are thought to contribute to repetitive behaviors and social interaction difficulties in autism (Foss-Feig et al., 2012 [↗](#); Green et al., 2018 [↗](#); Thye et al., 2018 [↗](#); He et al., 2021a [↗](#); Zhai et al., 2023 [↗](#); Carati et al., 2024 [↗](#)). However, clinical studies focusing on tactile discrimination have yielded controversial results (Zetler et al., 2019 [↗](#)), likely due to the substantial heterogeneity of tactile processing alterations in autism (Mikkelsen et al., 2018 [↗](#)) and inconsistent terminology across studies (He et al., 2023 [↗](#)). In contrast, numerous studies in the visual and auditory domains (Plaisted et al., 1998a [↗](#); O’Riordan and Plaisted, 2001 [↗](#); O’Riordan et al., 2001 [↗](#); Bonnel et al., 2003 [↗](#); O’Riordan and Passetti, 2006 [↗](#); Samson et al., 2006 [↗](#); Rotschafer, 2021 [↗](#)) have supported enhanced sensory processing in autism, as proposed by several influential models of the condition (Plaisted, 2001 [↗](#); Frith, 2003 [↗](#); Mottron et al., 2006 [↗](#)).

Although clinical studies highlight the heterogeneity of tactile responses in autism, variability in experimental protocols and stimulus types has made it difficult to draw cohesive conclusions. Tactile discrimination of vibrotactile stimuli delivered to the glabrous skin of the fingers was reported reduced (Puts et al., 2014 [↗](#); Espenhahn et al., 2023 [↗](#)), or intact (He et al., 2021a [↗](#); Asaridou et al., 2022 [↗](#)) in autistic individuals. Similarly, studies of sharp-dull discrimination have reported both reduced (Abu-Dahab et al., 2013 [↗](#)) and typical performance (Minshew et al., 1997 [↗](#); Minshew and Hobson, 2008 [↗](#)), as have studies of form discrimination (Minshew and Hobson, 2008 [↗](#); Demopoulos et al., 2015 [↗](#); Failla et al., 2017 [↗](#)). Translational approaches employing mouse models of autism in combination with psychometric measures from well-controlled behavioral tasks may help clarify whether these inconsistencies reflect genuine inter-individual variability or arise from methodological differences.

While tactile discrimination has been explored in several clinical studies, it remains underexplored in mouse models of autism. Rodent studies leveraging innate responses have reported atypical whisker-dependent texture discrimination (Balasco et al., 2021 [↗](#), 2022 [↗](#); Mattioni et al., 2024 [↗](#)) and forepaw-dependent roughness discrimination (Orefice et al., 2016 [↗](#)). However, these studies have not employed psychophysical methods to quantify tactile discrimination, restricting the translatability of their findings. Implementing psychophysics in animal models might clarify previous inconsistencies between studies in mice (Orefice et al., 2016 [↗](#)) and humans (O’Riordan and Passetti, 2006 [↗](#)).

Sensory alterations are thought to impact cognition in autism (Haigh, 2018 [↗](#)). However, sensory perception is shaped not only by the physical properties of stimuli but also by higher-order cognitive processes such as attention and categorization—both of which are altered in autism (Allen and Courchesne, 2001 [↗](#); Church et al., 2010 [↗](#); Gastgeb and Strauss, 2012 [↗](#); Cascio et al., 2015 [↗](#); Barbot et al., 2018 [↗](#); Rong et al., 2021a [↗](#)). Moreover, autistic individuals demonstrate differences in how prior beliefs and expectations (priors) are integrated with sensory input during perceptual decision-making. They tend to rely less on contextual priors (Amoruso et al., 2019 [↗](#)) and more heavily on prior choices (Feigin et al., 2021 [↗](#)), and often form priors that are imprecise or inflexible (Zaidel et al., 2015 [↗](#); Sapey-Triomphe et al., 2021b [↗](#)). Notably, variability in the use of priors has also been linked to individual differences in sensory responsivity (Sapey-Triomphe et al., 2021a [↗](#)). Thus, cognitive differences may compound or interact with primary sensory processing alterations, contributing to the distinct perceptual experiences observed in autism.

In this study, we investigated the interplay between tactile discrimination and cognitive processes during perceptual decision-making. To enhance translational relevance and address questions of inter-individual heterogeneity, we developed a forepaw-based 2-Alternative Choice task for mice, using vibrotactile stimuli analogous to those used in human psychophysical protocols. Leveraging this task, we explored how stimuli of varying salience are discriminated in the *Fmr1*^{-/-} mouse model of autism and disentangled stimulus-driven from cognitively modulated-tactile responses.

Our results revealed salience-dependent alterations in both tactile processing and cognitive modulation in *Fmr1*^{-/-} mice, with a decreased influence of cognitive processes on tactile perception. During training, *Fmr1*^{-/-} mice exhibited heightened choice consistency bias during low-salience trials, which contributed to reduced performance during perceptual learning. In contrast, trained *Fmr1*^{-/-} mice displayed enhanced discrimination of low-salience stimuli, but a diminished facilitatory effect of categorization on across-category discrimination. Despite their

increased discrimination sensitivity at the low-salience range, *Fmr1*^{-/-} mice showed attention deficits specifically for these stimuli under high cognitive load conditions. While a strong choice consistency bias was observed during the testing phase for both WT and *Fmr1*^{-/-} mice, integration of recent sensory history was selectively disrupted in *Fmr1*^{-/-} mice, such that past sensory information no longer informed ongoing decisions.

These findings uncover distinct, salience-dependent cognitive alterations that shape tactile perception in the *Fmr1*^{-/-} model, advancing our understanding of tactile perception in autism. Importantly, our results indicate that the variability observed in clinical studies may arise not solely from primary sensory alterations but also from differences in cognitive context, attentional demands, or task complexity—offering a potential framework to reconcile prior inconsistencies in the field.

Results

Fmr1^{-/-} mice show intact learning rate and trajectory during perceptual learning

To investigate perceptual and cognitive alterations in a highly translational approach, we developed a forepaw-based 2-Alternative Choice perceptual decision-making task in the *Fmr1*-KO mouse model of autism. In this task, mice learn to discriminate between vibrotactile stimuli that differ in perceptual salience, which we define as the prominence of a stimulus based on its physical amplitude. To ensure that all mice could reliably detect the applied stimuli, we selected amplitudes above the perceptual thresholds previously established for both wild-type (WT) and *Fmr1*^{-/-} male mice (Semelidou et al., 2024 [↗](#)). Accordingly, all stimuli used in the present study (40 Hz, ≥12 μm) were well above the detection threshold (10 Hz, 4.46 μm for WT; 10Hz, 7.29 μm for *Fmr1*^{-/-} mice), allowing us to specifically probe discrimination, categorization, and decision-making rather than sensory detection.

During each trial, head-fixed, water-controlled mice received a 500 ms vibrotactile stimulus to the forepaw at 40 Hz with either high amplitude (26 μm) or low amplitude (12 μm). Stimulus salience was defined in a relative manner: across animals, the lower-amplitude stimulus elicited consistently higher miss rates, indicating reduced perceptual strength and attentional engagement within the suprathreshold range. We therefore refer to the 12 μm stimulus as “low salience” and the 26 μm stimulus as “high salience.” Mice were trained to report high-salience stimuli by licking the right lick-port, and low-salience stimuli by licking the left port within a 2-s response window following stimulus delivery. Incorrect choices resulted in a 5-s timeout (Fig. 1A [↗](#)).

During early training sessions, performance was low, characterized by a low proportion of correct and a high proportion of incorrect choices, which either remained stable or gradually improved over the course of the session (Fig. S1A-left [↗](#)). Licking patterns were also inconsistent during these early sessions and poorly time-locked to the response window (Fig. S1A-right [↗](#)). In contrast, late training sessions showed consistently high correct choice rates and low incorrect choice rates (Fig. S1B-left [↗](#)), along with stable licking patterns during the response window for both high- and low-salience trials (Fig. S1B-right [↗](#)).

Learning difficulties and altered learning trajectories have been reported in autistic individuals and replicated in several mouse models of autism, including *Fmr1*^{-/-} mice (Arnett et al., 2014a [↗](#); Goel et al., 2018 [↗](#); Mercado et al., 2020 [↗](#); Khachadourian et al., 2023 [↗](#); Shenouda et al., 2023 [↗](#); Mol et al., 2024 [↗](#)). To assess whether *Fmr1*^{-/-} mice exhibit alterations in learning rate in our task, we compared the number of days required to reach the predefined learning criterion (>70% correct choices for each stimulus salience across three consecutive training days). Our results showed no significant differences between *Fmr1*^{-/-} mice and their WT littermates in the total number of training days to reach criterion (Fig. 1B [↗](#); T test: $t = 0.438$, $p = 0.667$) or in the duration spent at each stage of the training protocol (Fig. S1C-D [↗](#), see Methods; Blocks: T test: $t = 1.259$, $p = 0.224$; Mixed: T test: $t = -0.185$, $p = 0.855$). Similarly, both genotypes required a comparable number

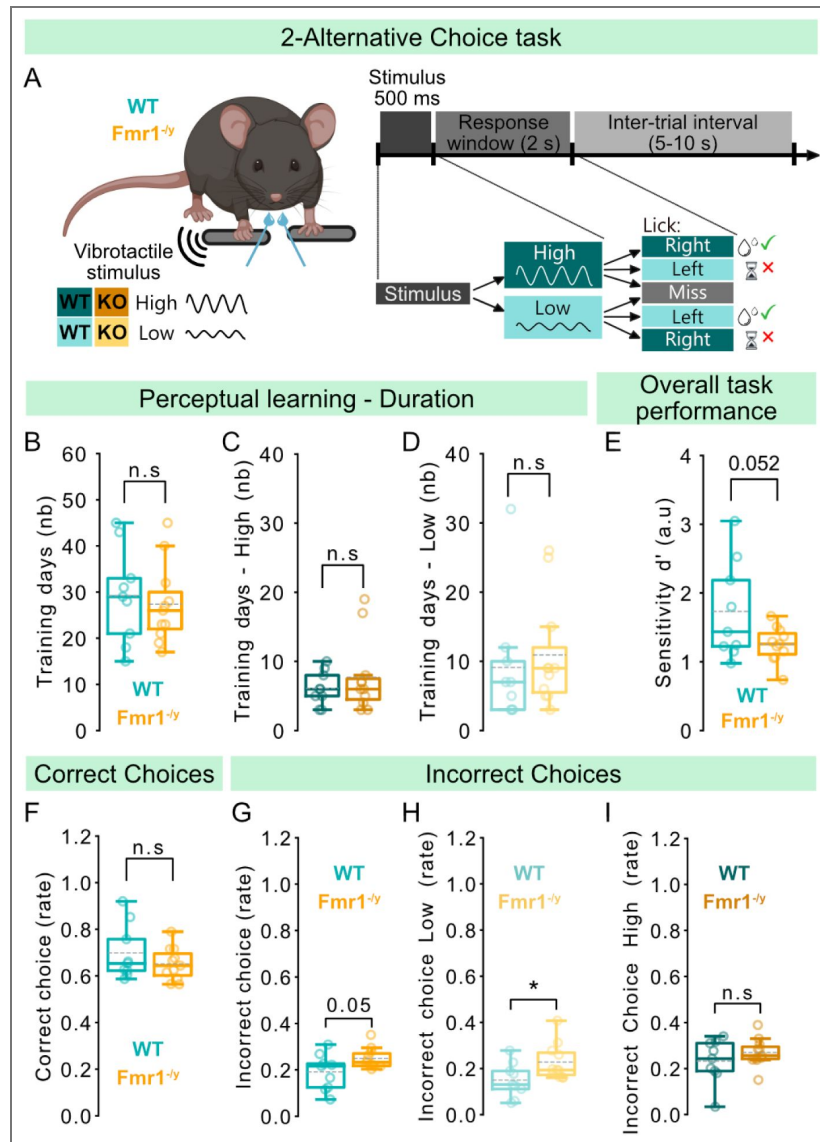


Figure 1. Perceptual learning performance in a forepaw-based decision-making task.

For panels **B, C, D, E, F, G, H, I, J, K**: n=9 WT, 11 *Fmr1^{-ly}* male mice. **A**, Left: schema showing the behavioral setup. Right: Trial protocol and behavioral outcomes depending on the type of trial and the animal's response. **B**, Total number of days spent in training for WT and *Fmr1^{-ly}* mice. **C**, Total number of days spent in training until the criterion was met for high-salience stimuli for WT and *Fmr1^{-ly}* mice. **D**, Total number of days spent in training until the criterion was met for low-salience stimuli for WT and *Fmr1^{-ly}* mice. **E**, Sensitivity d' throughout the training period for WT and *Fmr1^{-ly}* mice. **F**, Correct choice rate for both high- and low-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. **G**, Incorrect choice rate for both high- and low-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. **H**, Incorrect choice rate for low-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. **I**, Incorrect choice rate for high-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. P values were computed using two-sided t-test for panels **B, E, F, G, I**; Mann-Whitney test for panels **C, D, H**; * $P < 0.05$ or n.s, not significant. Created with *BioRender.com*.

of days to learn the association between stimulus salience and the correct lick-port (Fig. 1C-D; High salience: Mann-Whitney U test: $U=45.5$, $p = 0.788$; Low salience: Mann-Whitney U test: $U = 38.5$, $p = 0.422$).

To capture potential genotype differences in the learning dynamics during training, we analyzed the performance of all mice that reached the learning criterion during the training phase with mixed low- and high-salience trials. Both WT and *Fmr1*^{-/-} mice showed similar learning dynamics, with a slow, gradual improvement across days (main effect of day: $\beta = 0.007$, $SE = 0.004$, $z = 1.882$, $p = 0.060$, 95% CI [0.00, 0.01]) (Fig. S2A-top). Consistent with the extended training duration required for the task, learning slopes were shallow and comparable between genotypes (Fig. S2B; Mann-Whitney U test: $U=38.0$, $p=0.536$). Importantly, the Genotype \times Day interaction was small ($\beta = 0.002$), indicating no detectable genotype differences in learning rate across animals.

These similar learning trajectories were accompanied by comparable baseline performance on the first day of training across genotypes (Fig. S2A-top, S2C; genotype effect: $\beta = -0.087$, $SE = 0.066$, $z = -1.328$, $p = 0.184$, 95% CI [-0.22, 0.04]) and similar within-animal day-to-day performance variability (Fig. S2A-bottom; Fig. S2D; T test: $t=-0.302$, $p=0.767$).

We next assessed whether performance differed during an intermediate stage of learning, defined for each animal as the middle three days of its training period. Here, both genotypes again showed comparable performance (Fig. S2E, slope; T-test: $t = 0.801$, $p = 0.437$) with similar correct-choice rates (Fig. S2F; T-test: $t=1.240$, $p=0.228$), indicating no genotype-specific differences during intermediate learning.

Together, these results show that *Fmr1*^{-/-} mice display an intact learning rate and trajectories in this 2-AFC perceptual decision-making task.

***Fmr1*^{-/-} mice display impaired performance on low-salience trials during perceptual learning**

Given that comparable learning trajectories and training duration to reach the criterion do not exclude the presence of performance alterations, we next evaluated additional behavioral metrics during training with mixed high- and low-salience trials. Specifically, we analyzed overall discrimination sensitivity (d') as well as correct and incorrect choice rates throughout training to determine whether *Fmr1*^{-/-} mice exhibited altered task performance despite intact learning progression.

To quantify mice's sensitivity in discriminating high-versus low-salience stimuli throughout training, we used the signal detection theory and computed the sensitivity index d' . This measure captures stimulus discriminability by comparing normalized hit rates (rightward licks on high salience trials) and false alarm rates (rightward licks on low salience trials). *Fmr1*^{-/-} mice showed a strong trend with a large effect size toward reduced overall task sensitivity compared to WT littermates (Fig. 1E; T-test: $t=-2.083$, $p=0.052$, Hedges' $g=0.90$), indicating diminished perceptual performance during training. These results demonstrate that, despite acquiring the task at a comparable rate (Fig. 1B-D) and with similar learning trajectories (Fig. S2), *Fmr1*^{-/-} mice display a trend for diminished performance during salience discrimination training.

To complement our sensitivity (d') analysis, we also quantified correct and incorrect choice rates, allowing us to assess both rightward and leftward lick responses. Correct choice rates were comparable between *Fmr1*^{-/-} and WT mice (Fig. 1F, T-test: $t=1.064$, $p=0.307$) with similar Hit rates for both high- and low-salience stimuli (Fig. S1E-F, High salience-T-test: $t=0.721$, $p=0.480$; Low salience-T-test: $t=1.060$, $p=0.303$). In contrast, *Fmr1*^{-/-} mice exhibited a significantly higher rate of incorrect choices (Fig. 1G; T-test: $t=-2.099$, $p=0.050$; Hedge's $g=0.90$), an effect that was specific to low-salience trials (Fig. 1H; Mann-Whitney $U = 23.0$, $p = 0.048$; Hedge's $g = 0.97$), while high-salience error rates were similar across genotypes (Fig. 1I; T-test: $t=-1.072$; $p=0.298$). After outlier analysis and exclusion of one *Fmr1*^{-/-} mouse, the genotype difference was reduced to a trend,

though with a large effect size, for incorrect choices (T-test: $t=-1.803$; $p=0.089$, Hedge's $g = 0.79$) and for incorrect choices during low-salience trials (Mann–Whitney $U = 23.0$, $p = 0.079$; Hedge's $g = 0.89$).

These results suggest a modest reduction in task performance in *Fmr1*^{-/-} mice, primarily driven by increased errors on low-salience trials.

***Fmr1*^{-/-} mice show higher choice consistency bias during training**

Perceptual learning can further reveal potential alterations in decision strategy, manifested as changes in response bias (decision criterion c) or expectation bias (priors). To examine whether mice exhibited stereotyped licking toward one of the two lickports—a potential indicator of response bias—we calculated the decision criterion. This analysis revealed no significant differences between *Fmr1*^{-/-} mice and WT littermates (Fig. 2A [↗](#); Mann–Whitney U : $U=65.000$, $p=0.254$), with both groups showing a bias toward the left lickport (WT: Wilcoxon signed-rank test $W=5.000$, $p=0.039$; *Fmr1*^{-/-}: Wilcoxon signed-rank test $W=10.000$, $p=0.042$).

Since mice did not exhibit differences in stereotyped licking, we could rule out simple response biases and further assess whether their decisions are influenced not only by the sensory features of stimuli but also by previous experiences that shape expectations (i.e., priors). To investigate the impact of prior experience on current choices, we analyzed behavioral responses on a trial-by-trial basis. We first examined how a rewarded choice in the previous trial influenced the performance in the current trial (Fig. 2B [↗](#)). *Fmr1*^{-/-} mice exhibited an increased rate of incorrect responses to low-salience stimuli when these were preceded by a rewarded high-salience stimulus (Fig. 2C [↗](#); T-test: $t=-2.352$, $p=0.030$). In contrast, no genotype difference was observed when a high-salience stimulus followed a rewarded low-salience trial (Fig. 2D [↗](#); T-test: $t=0.603$, $p=0.554$).

We next tested whether *Fmr1*^{-/-} mice were more influenced by their prior choices. To assess this, we compared the rates of repeated prior choices in current low- and high-salience trials, controlling for the total number of correct and incorrect responses. Our analysis revealed higher previous choice repetition during low-salience trials in *Fmr1*^{-/-} compared to WT mice (Fig. 2E [↗](#); T-test: $t=-2.618$, $p=0.017$), but a comparable impact of prior choices during high-salience trials (Fig. 2F [↗](#); T-test: $t=1.215$, $p=0.240$).

To verify that the observed differences in performance between WT and *Fmr1*^{-/-} mice reflected differential reliance on priors rather than differences in prior strength per se, we quantified the strength of the priors induced by high- and low-salience stimuli. Specifically, we calculated the rate of choices that were repeated following a low- or high-salience trial, correcting for the overall rate of correct and incorrect responses. Our results showed similar prior strength between groups, both for high-salience (Fig. S3A [↗](#); T-test: $t=-1.705$, $p=0.105$) and for low-salience stimuli (Fig. S3B [↗](#); Mann–Whitney U : $U=38.500$, $p=0.425$).

Together, these results indicate an increased choice consistency bias during low-salience trials, which contributes to performance differences during perceptual learning in *Fmr1*^{-/-} mice.

***Fmr1*^{-/-} mice do not show attention deficits during perceptual learning**

Stimulus salience is closely linked to attentional processes (Kerzel and Schönhammer, 2013 [↗](#); Forschack et al., 2022 [↗](#); Bouvier et al., 2023 [↗](#)), and attentional alterations are well-documented in autistic individuals (Allen and Courchesne, 2001 [↗](#); Grubb et al., 2013 [↗](#); Barbot et al., 2018 [↗](#); Licznarski et al., 2020 [↗](#); Rong et al., 2021b [↗](#)). Given that *Fmr1*^{-/-} mice exhibit salience-dependent performance differences during training (Fig. 1 [↗](#)–2 [↗](#)), we asked whether their reduced task performance might also reflect underlying attention deficits. To assess attention, we analyzed the trials in which the animal failed to respond to the stimulus (Miss trials) (Fig. 1A [↗](#)). Within-genotype analysis confirmed studies linking salience and attention in humans (Kerzel and Schönhammer, 2013 [↗](#)), and validated that low amplitude stimuli are less salient, yielding significantly higher Miss rates in both groups (Fig. S3C [↗](#); WT: Wilcoxon signed-rank: $W=0.000$,

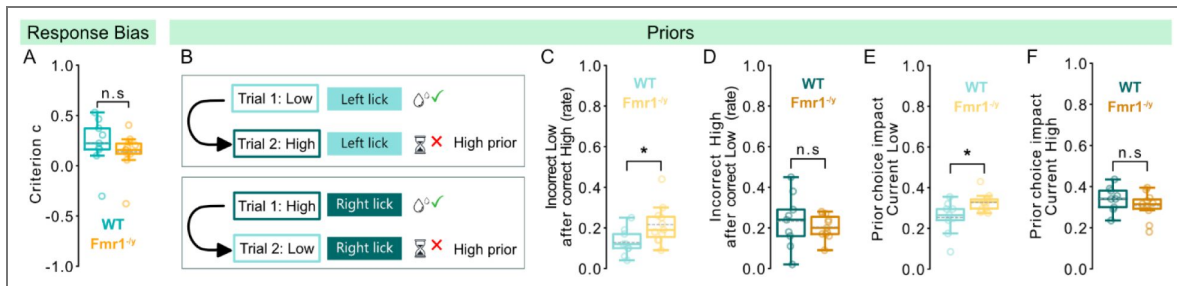


Figure 2. Overall strategy and impact of prior choice during perceptual learning.

For panels **A**, **C**, **D**, **E**, **F**: $n=9$ WT, 11 $Fmr1^{-/-}$ male mice. **A**, Criterion depicting the licking strategy of the animals. **B**, Schema showing an example of how high impact of prior choice on the current trial affects the response during a high-salience trial (top) or low-salience trial (bottom). **C**, Proportion of incorrect responses in low-salience trials immediately following a correctly rewarded high-salience trial. **D**, Proportion of incorrect responses in high-salience trials immediately following a correctly rewarded low-salience trial. **E**, Proportion of correct responses in low-salience trials immediately following a correctly rewarded high-salience trial and incorrect responses in low-salience trials immediately following a correctly rewarded high-salience trial. Rates are corrected over the total number of correct and incorrect choices in low-salience trials. **F**, Proportion of correct responses in high-salience trials immediately following a correctly rewarded high-salience trial and incorrect responses in high-salience trials immediately following a correctly rewarded low-salience trial. Rates are corrected over the total number of correct and incorrect choices in high-salience trials. P values were computed using Mann-Whitney test for panel **A**; two-sided t-test for panels **C**, **D**, **E**, **F**; * $P < 0.05$ or n.s, not significant.

$p=0.004$; $Fmr1^{-/y}$: Paired T-test: $t=-4.113$, $p=0.002$). However, there were no genotype differences in Miss rates for either high- or low-salience stimuli (Fig. S3D-E [↗](#); Miss rate High: Mann–Whitney U: $U=51.000$, $p=0.939$; Miss rate Low: Mann–Whitney U: $U=50.000$, $p=1.000$). These data demonstrate that low-salience stimuli are less effective at capturing attention in both $Fmr1^{-/y}$ and WT mice, and that the reduced task performance of $Fmr1^{-/y}$ mice during perceptual training cannot be attributed to an attentional deficit during low-salience trials.

Trained $Fmr1^{-/y}$ mice show enhanced discrimination of low-salience stimuli

Altered tactile discrimination has been reported in clinical studies, though findings are inconsistent (reviewed in (Zetler et al., 2019 [↗](#))), and has also been observed in mouse models of autism (Orefice et al., 2016 [↗](#); Balasco et al., 2021 [↗](#), 2022 [↗](#); Mattioni et al., 2024 [↗](#)). To assess tactile discrimination in our study, we incorporated the original training stimuli along with 6 intermediate amplitudes, spaced 2 μm apart. Stimuli ranging from 20 to 26 μm (20, 22, 24, 26 μm) were categorized and rewarded as high-salience stimuli, while those from 12 to 18 μm (12, 14, 16, 18 μm) were treated as low-salience stimuli (Fig. 3A [↗](#)). Only animals that successfully acquired the task during the training phase were included in the tactile discrimination test. $Fmr1^{-/y}$ and WT mice showed similar performance during the last three days of training, with no significant differences in task sensitivity (d' ; T-test: $t=0.800$, $p=0.438$; Fig. S4A [↗](#)), rates of correct (Fig. S4B-C [↗](#); High: T-test: $t=0.442$, $p=0.666$; Low: T-test: $t=0.697$, $p=0.498$) and incorrect responses (Fig. S4D-E [↗](#); High: T-test: $t=-0.680$, $p=0.509$; Low: T-test: $t=-1.069$, $p=0.305$), decision bias (Fig. S3F [↗](#); criterion c ; Mann–Whitney U: $U=28.000$, $p=0.955$), use of priors (Fig. S4G-L [↗](#); Fig. S4G [↗](#): T-test: $t=0.485$, $p=0.636$; S4H [↗](#): T-test: $t=0.155$, $p=0.879$; S4I [↗](#): T-test: $t=-0.667$, $p=0.516$; S4J [↗](#): T-test: $t=-0.667$, $p=0.516$; S4K [↗](#): T-test: $t=-0.072$, $p=0.944$; S4L [↗](#): T-test: $t=-0.472$, $p=0.644$), or attention (Fig. S4M-N [↗](#); High: Mann–Whitney U: $U=32.500$, $p=0.555$; Low: T-test: $t=0.087$, $p=0.932$).

To evaluate task performance, we quantified the rate of right-lick responses, corresponding to reports of high-salience stimuli, and constructed psychometric curves, which increased with stimulus amplitude in both genotypes. Mixed-effects modeling revealed a strong main effect of amplitude (all amplitude coefficients $p < 0.005$) but no evidence for a genotype-dependent change across the psychometric function (amplitude \times genotype interaction coefficients $p > 0.266$), indicating comparable performance between WT and KO animals across stimulus intensities (Fig. 3A [↗](#)). A genotype-by-amplitude interaction was observed only at 18 μm amplitude ($\beta = 0.127$, SE = 0.06, $z = -2.18$, $p = 0.030$, 95% CI [-0.24, -0.01]), where responses were slightly reduced in WT mice. However, this effect did not survive post-hoc analysis (T-test: $t = 0.568$, $p = 0.580$) and did not generalize across amplitudes.

We then assessed the animals' ability to discriminate high-salience stimuli by comparing the proportion of right-lick responses to 26 μm and 24 μm stimuli. Our results showed that neither WT nor $Fmr1^{-/y}$ mice were able to reliably distinguish between these two amplitudes (Fig. 3B [↗](#); WT: Wilcoxon signed-rank: statistic=3.000, $p=0.156$; $Fmr1^{-/y}$: Paired t-test: $t = 1.447$, $p = 0.221$). However, both groups reliably discriminated between 26 μm and 22 μm stimuli (Fig. 3C [↗](#); WT: Wilcoxon signed-rank: statistic = 0.000, $p = 0.031$; $Fmr1^{-/y}$: Paired t-test: $t = -4.929$, $p = 0.001$). These results demonstrate that high-salience stimuli differing by 4 μm in amplitude can be discriminated by both genotypes.

We next investigated low-salience stimulus discrimination by comparing the rate of right-lick responses (reporting high salience) to stimuli of 12 μm and 14 μm amplitude. WT mice responded similarly to both amplitudes (Fig. 3D-left [↗](#); Paired t-test: statistic = -1.684, $p = 0.153$), consistent with their performance on high-salience stimuli differing by 2 μm (Fig. 3B-left [↗](#)). In contrast, $Fmr1^{-/y}$ mice exhibited enhanced discrimination for these low-salience stimuli, with increased high-salience report rates for the 14 μm stimuli compared to those for 12 μm (Fig. 3D-right [↗](#); Paired t-test: $t = -5.007$, $p = 0.001$). Both genotypes efficiently discriminated 12 μm from 16 μm stimuli (Fig. 3E [↗](#); WT: Paired t-test: $t = -3.274$, $p = 0.022$; $Fmr1^{-/y}$: Paired t-test: $t = -6.772$, $p < 0.001$). This enhanced discrimination in $Fmr1^{-/y}$ mice was further supported by low-salience reports that

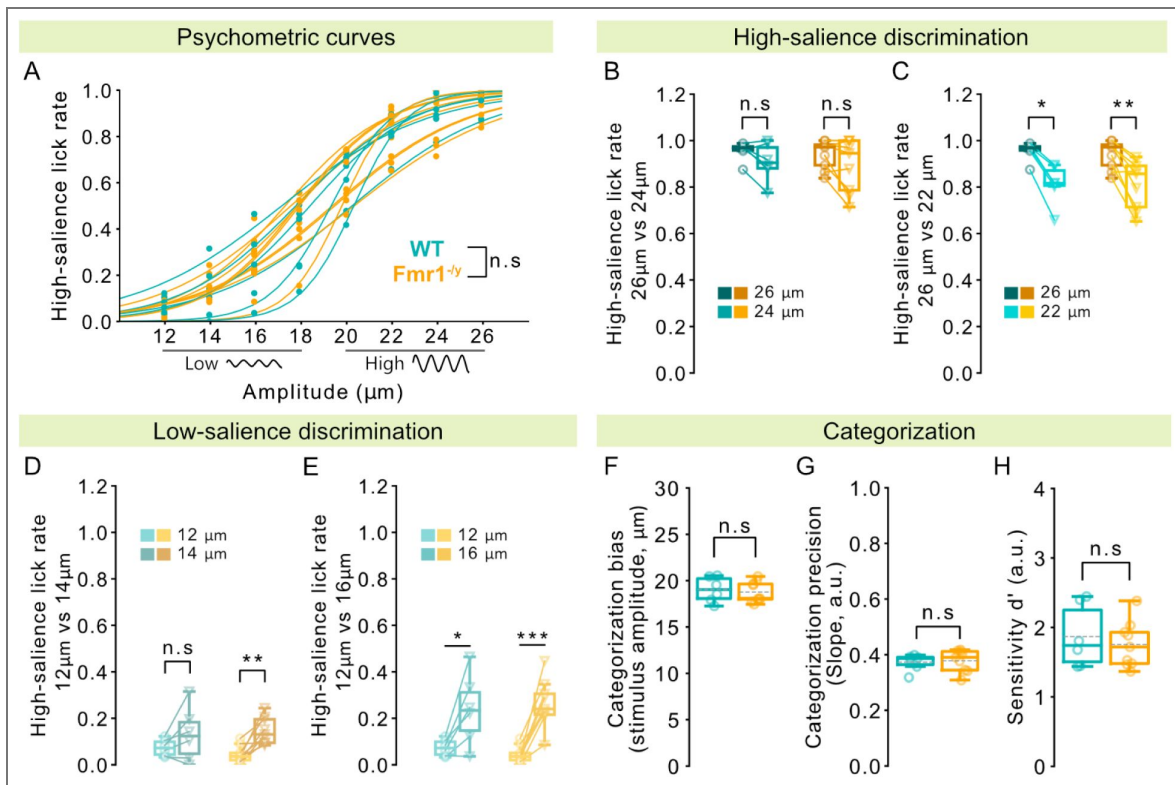


Figure 3. Tactile discrimination and categorization.

n=6 WT, 9 *Fmr1^{-/-}* male mice. **A**, Psychometric curves for WT and *Fmr1^{-/-}* mice generated based on the high-salience lick rate (rate of rightward licks) across 8 different amplitudes. Stimuli between 12–18 μm were designated as low-salience and rewarded at the left lickport, while stimuli between 20–26 μm were designated as high-salience and rewarded at the right lickport. Each amplitude was presented an average of 84 times. **B**, Comparison of high-salience (rightwards) responses for high-salience stimuli of 26 and 26 μm . **C**, Comparison of high-salience (rightwards) responses for high-salience stimuli of 26 and 22 μm . **D**, Comparison of high-salience (rightwards) responses for low-salience stimuli of 12 and 14 μm . **E**, Comparison of low-salience (leftwards) responses for low-salience stimuli of 12 and 14 μm . **F**, Categorization bias calculated based on the psychometric curves. **G**, Categorization precision computed based on the slope of the psychometric curves. **H**, Sensitivity d' of the responses in all stimulus amplitudes. P values were computed using Mixed Linear Model Regression for panel **A**; two-sided paired t-test for panels **B-right**, **C-right**, **D**, **E**; two-sided t-test for panels **F**, **G**, **H**; Wilcoxon signed-rank test for panels **B-left**, **C-left**; Bonferroni correction was applied for panels **B**, **C**, **D**, **P < 0.01, *P < 0.05, or n.s, not significant.

showed lower low-salience lick rates for 14 μm than 12 μm stimuli (Fig. S5A-right [↗](#); Paired t-test: $t = 2.394$, $p = 0.044$), whereas WT mice responded similarly (Fig. S5A-left [↗](#); Paired t-test: $t = 1.589$, $p = 0.173$), validating that improved discrimination was not driven by higher miss rates for 12 μm stimuli.

Together, these results demonstrate that *Fmr1*^{-/-} mice present enhanced tactile fine-discrimination for low-salience stimuli.

***Fmr1*^{-/-} mice exhibit intact salience categorization**

In addition to assessing stimulus discrimination, our task allowed us to evaluate whether *Fmr1*^{-/-} and WT mice form the same categories of low- and high-salience stimuli. Using the psychometric curves of the animals' high-salience responses (Fig. 3A [↗](#)), we measured the categorization bias and precision. No differences were observed between *Fmr1*^{-/-} mice and their WT littermates regarding their categorization bias (Fig. 3F [↗](#); T-test: $t = 0.432$, $p = 0.673$) or precision (slope, Fig. 3G [↗](#); T-test: $t = -0.283$, $p = 0.782$), showing comparable salience categorization between groups. These findings were further confirmed by similar overall task sensitivity (d' , Fig. 3H [↗](#); T-test: $t = 0.571$, $p = 0.578$). Furthermore, *Fmr1*^{-/-} mice showed similar rates of correct (Fig. S5B-C [↗](#); High: T-test: $t = -0.160$, $p = 0.875$; Low: T-test: $t = 1.389$, $p = 0.188$) and incorrect choices (Fig. S5D-E [↗](#); High: T-test: $t = 0.421$, $p = 0.681$; Low: T-test: $t = -0.709$, $p = 0.491$), as well as comparable overall decision strategy (Fig. S5F [↗](#), criterion c ; T-test: $t = 0.639$, $p = 0.533$) compared to their WT littermates. In conclusion, these results demonstrate similar categorization of high- and low-salience stimuli in *Fmr1*^{-/-} and WT mice.

***Fmr1*^{-/-} mice show reduced impact of categorization on stimulus discrimination**

Higher-order processes such as categorization can amplify perceptual differences between stimuli belonging to different categories (Goldstone, 1994 [↗](#)). Alterations in this behavioral process have been reported in autistic individuals, who, despite exhibiting intact visual categorization (in line with our findings in the tactile domain, Fig. 3F-H [↗](#)), show a reduced influence of categorization on perceptual discrimination that leads to diminished facilitation for stimuli belonging to different categories (Soulières et al., 2007 [↗](#)). To examine whether salience categorization differentially impacts tactile discrimination in WT and *Fmr1*^{-/-} mice, we compared the discrimination accuracy for stimulus pairs that differ by 2 μm and either span across different salience categories (across-category, i.e., 18 μm and 20 μm stimuli) or fall within the same category. Discrimination accuracy was calculated as the difference in rightward choices between each pair of stimuli.

In WT mice, discrimination accuracy was higher for across-category stimulus pairs than for both within-category low- (Fig. 4A-left [↗](#); Paired t-test, $t = 4.452$, $p = 0.007$) and high-salience pairs (Fig. 4B-left [↗](#); Paired t-test, $t = 5.453$, $p = 0.003$), indicating a robust facilitatory effect of categorization. *Fmr1*^{-/-} mice, in contrast, did not show this facilitation for low-salience stimuli, exhibiting a trend with medium effect size toward improved discrimination for across-category versus within-category low-salience pairs (Fig. 4A-right [↗](#); Wilcoxon signed-rank: $\text{stat} = 6.000$, $p = 0.055$; Paired Hedges' $g = 0.640$). For high-salience stimuli, however, *Fmr1*^{-/-} mice performed similarly to WT, showing enhanced discrimination for across-category pairs relative to within-category high-salience comparisons (Fig. 4B-right [↗](#); Paired t-test, $t = 3.496$, $p = 0.008$).

To directly compare WT and *Fmr1*^{-/-} mice, we quantified the categorical facilitation effect as the difference in discrimination accuracy between across- and within-category (high and low-salience) stimulus pairs. *Fmr1*^{-/-} mice showed a trend with a strong effect size toward reduced facilitation (T test: $t = 1.81$, $p = 0.095$; Hedge's $g = 0.86$), which became significant after exclusion of outliers (Fig. 4C [↗](#); T test: $t = 4.57$, $p = 0.001$; Hedge's $g = 1.94$).

Together, these findings suggest that reduced categorization influence in *Fmr1*^{-/-} mice diminishes discrimination facilitation for stimuli belonging to different categories, revealing a genotype-specific alteration in how categorical information modulates tactile perception.

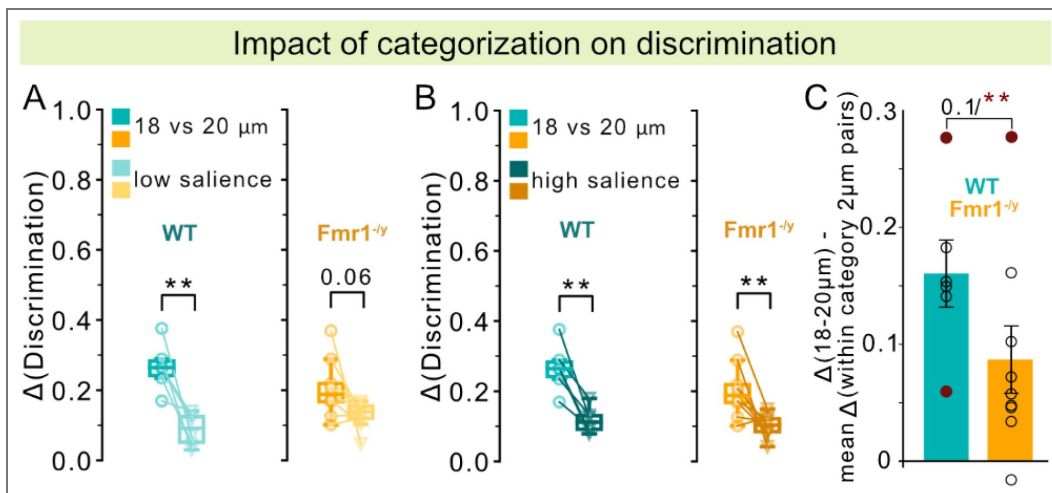


Figure 4. Impact of categorization on across-categories and within-category discrimination.

n=6 WT, 9 *Fmr1*^{-/-} male mice. Delta discrimination accuracy, calculated as the difference in the rate of high-salience licks across stimulus pairs. **(A)** Delta discrimination accuracy between across-category stimuli (18 μm vs 20 μm) and within-category low-salience stimulus pairs, averaged as “low salience.” **(B)**, Same as **(A)**, but for within-category high-salience stimulus pairs. **(C)**, Delta discrimination accuracy across all stimulus pairs within the low-salience category. **(D)**, Same as **(C)**, but across all stimulus pairs within the high-salience category. P values were computed using two-sided paired t-tests for panels **A-left**, **B**; Wilcoxon signed-rank test for panel **A-right**, and two-sided t-test for panel **C**; **P < 0.01, or n.s., not significant.

High cognitive load conditions reveal salience-dependent attention deficits in *Fmr1*^{-/-} mice

Our results during perceptual learning revealed comparable, salience-dependent attention in WT and *Fmr1*^{-/-} mice (Fig. S3D-E). During the tactile discrimination/categorization phase of our task, animals were exposed to a high cognitive load, as they needed to discriminate and categorize eight stimulus intensities to obtain a water reward. To assess whether *Fmr1*^{-/-} mice exhibit attentional deficits in these high cognitive load conditions, we analyzed the rate of Miss trials as a proxy for attention.

While miss rates for high-salience stimuli did not differ between genotypes (Fig. 5A; all genotype \times amplitude interactions $p > 0.296$), *Fmr1*^{-/-} mice showed elevated miss rates for low-salience stimuli during categorization (Fig. 5B). A mixed-effects linear model revealed that *Fmr1*^{-/-} mice had significantly higher miss rates than WT controls at the reference amplitude of 12 μm ($\beta = 0.067$, SE = 0.024, $z = 2.77$, $p = 0.006$, 95% CI [0.019, 0.114]). The genotype differences at 14 μm ($\beta = -0.015$, SE = 0.021, $z = -0.70$, $p = 0.483$) and 16 μm ($\beta = -0.029$, SE = 0.021, $z = -1.37$, $p = 0.171$) did not differ significantly from the effect observed at 12 μm . However, a significant genotype \times amplitude interaction was observed at the highest amplitude (18 μm ; $\beta = -0.045$, SE = 0.021, $z = -2.16$, $p = 0.031$, 95% CI [-0.087, -0.004]), indicating that genotype differences diminished the highest stimulus intensity of the low-salience range. Post-hoc comparisons further indicated a trend for increased misses at 12 μm with a large effect size (T-test: $t = -2.8437$, $p = 0.058$, Hedge's $g = 1.23$), but showed no significant differences for the other low-salience stimuli ($p > 0.21$). Notably, during the training period—when cognitive load was lower—miss rates were comparable across genotypes (Fig. S3D-E).

Together, these results reveal a salience-specific attentional deficit in *Fmr1*^{-/-} mice under high cognitive load, with low-salience stimuli being particularly vulnerable.

Fmr1^{-/-} mice show preserved choice perseveration but disrupted sensory history integration during tactile categorization

We next examined how trial history—including prior stimulus, choice, and outcome—shapes current decisions during tactile categorization. To do so, we used generalized linear models (GLMs) with a binomial link function to predict high-salience licks (right-lick choices) based on the current stimulus, trial history, genotype, and their interactions. We first fit a main-effects model including the current stimulus, previous stimulus, previous outcome, previous choice, and genotype, and then extended this model to assess genotype-specific modulation of history effects through interactions between genotype and previous choice, outcome, and stimulus (Fig. 6a).

As expected, the current stimulus was the dominant driver of choice in both genotypes (Fig. 6A-B; $\beta = 1.94$, SE = 0.15, $z = 12.96$, $p < 0.001$, 95% CI [1.64, 2.23]). However, previous choice also strongly influenced behavior (Fig. 6A). Both genotypes exhibited perseveration, as psychometric curves conditioned on the previous choice were systematically shifted following both prior right and left choices, indicating a robust tendency to repeat prior responses (Fig. 6A-C; $\beta = 1.16$, SE = 0.10, $z = 11.85$, $p < 0.001$, 95% CI [0.97, 1.36]). In contrast to the increased choice consistency bias observed during training (Fig. 2C-E), WT and *Fmr1*^{-/-} mice exhibited comparable levels of perseveration during categorization (genotype \times previous choice interaction; $\beta = 0.27$, SE = 0.19, $z = 1.47$, $p = 0.142$, 95% CI [-0.09, 0.64]).

Figure 5. Attention in perceptual decision-making under high cognitive load.

n=6 WT, 9 *Fmr1*^{-/-} male mice. **A**, Proportion of missed trials for high-salience stimuli. **B**, Proportion of missed trials for low-salience stimuli. P-values were obtained using mixed-effects linear models accounting for repeated measures across stimulus amplitudes and animals for panels **A**, **B**; Post-hoc two-sided t-test for panel **B**, -12 μ ($p = 0.06$); ** $P < 0.01$, or n.s, not significant.

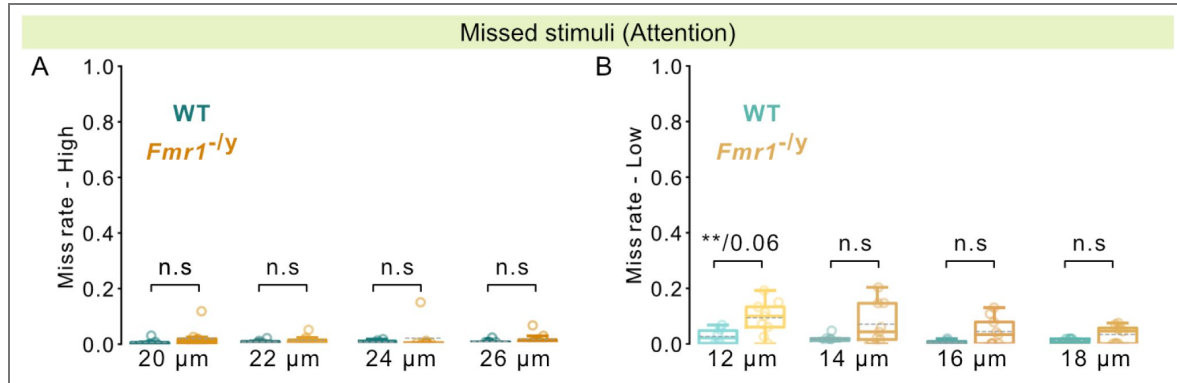
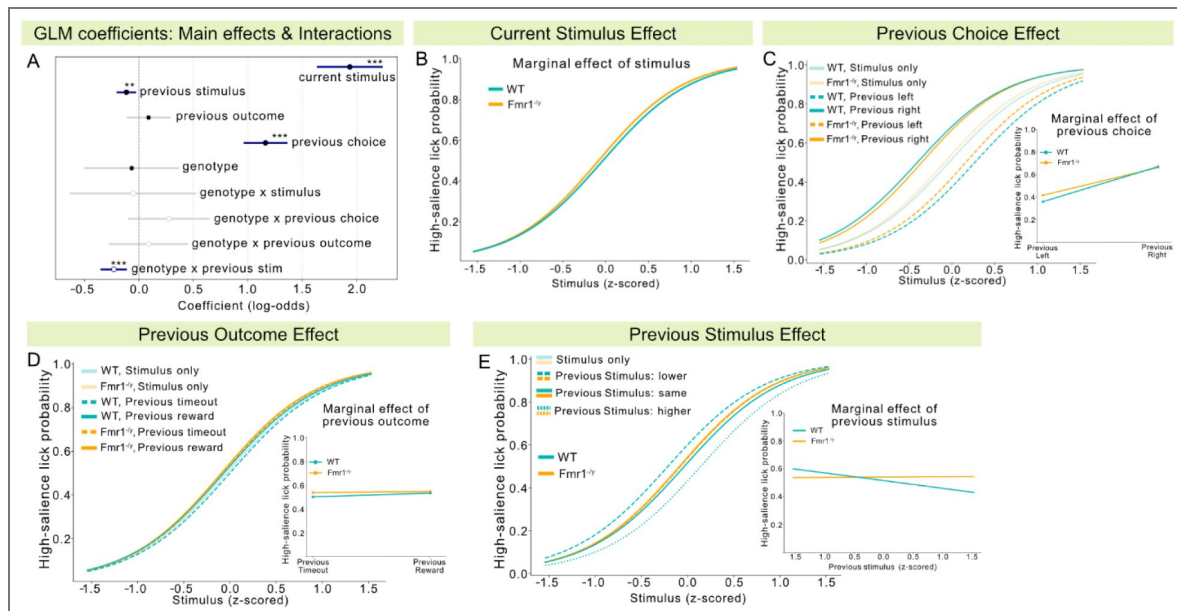


Figure 6. Trial history integration during tactile categorization.

n=6 WT, 9 *Fmr1*^{-/-} male mice. **(A)** Generalized linear model (GLM) coefficients from binomial regression predicting high-salience (right-lick) choices based on current stimulus amplitude, previous stimulus amplitude, previous outcome, previous choice, genotype, and their interactions. Filled circles indicate coefficients from the main-effects model; open circles indicate coefficients from the extended model including genotype \times history interactions. Error bars represent $\pm 95\%$ confidence intervals. Dark blue lines denote statistically significant effects. **(B)** Psychometric functions showing the effect of the z-scored current stimulus amplitude for WT and *Fmr1*^{-/-} mice. **(C)** Psychometric curves conditioned on the previous choice (left vs. right lick) for WT and *Fmr1*^{-/-} mice. **(D)** Psychometric curves conditioned on the previous trial outcome (reward vs. timeout). **(E)** Psychometric curves conditioned on the intensity of the previous stimulus (z-scored). P values were computed using Mixed Linear Model Regression. *** $P < 0.001$, ** $P < 0.01$.



In contrast, previous outcome (reward or timeout) had a negligible effect on current choice in either genotype (Fig. 6A, D [↗](#); $\beta = 0.09$, SE = 0.10, $z = 0.89$, $p = 0.373$, 95% CI [-0.11, 0.28]). Interestingly, the amplitude of the previous stimulus influenced decision-making (Fig. 6A [↗](#); $\beta = -0.12$, SE = 0.04, $z = -2.82$, $p = 0.005$, 95% CI [-0.20, -0.04]) in a genotype-specific manner (Fig. 6A, E [↗](#); genotype x previous stimulus interaction, $\beta = -0.23$, SE = 0.06, $z = -4.03$, $p < 0.001$, 95% CI [-0.34, -0.12]). In WT mice, larger-amplitude stimuli on the preceding trial slightly reduced the probability of choosing right on the subsequent trial, whereas lower-amplitude stimuli increased it (Fig. 6E [↗](#)). In contrast, choices of *Fmr1*^{-/-} mice were not modulated by the amplitude of the previous stimulus.

Together, these results show that tactile decisions in both genotypes are dominated by current sensory evidence and strongly biased by prior choices. While choice perseveration is preserved in *Fmr1*^{-/-} mice, integration of recent sensory history is selectively disrupted, revealing a genotype-specific deficit in how past sensory information informs ongoing decision-making.

Discussion

Here, we developed a decision-making task based on psychophysics to dissociate stimulus-driven from cognitively-modulated tactile responses in the *Fmr1*^{-/-} mouse model of autism. Our findings reveal salience-dependent cognitive alterations that shape sensory performance. During perceptual learning, *Fmr1*^{-/-} mice exhibited an increased choice consistency bias during low-salience trials, which contributed to reduced task performance. During discrimination, *Fmr1*^{-/-} mice displayed an enhanced tactile sensitivity under low-salience conditions alongside decreased facilitation of across-category discrimination. Despite this increased sensitivity, these mice showed low salience-specific attentional impairments under high cognitive load, as well as faster updating of their world model with a decreased impact of sensory history on their current choice. Our findings highlight the interplay between sensory and cognitive alterations in autism, emphasizing the importance of cognitive context in interpreting sensory phenotypes, and advocating for a shift beyond traditional sensory–cognitive dichotomies to better understand autism-related phenotypes.

Learning alterations in autism and reliance on priors

Learning disability and intellectual disability are the second and third most common co-occurring neurodivergencies of autism, observed in 23.5% and 21.7% of autistic individuals, respectively (Khachadourian et al., 2023 [↗](#)). Notably, even in the absence of these co-occurring conditions, autistic individuals exhibit differences in learning processes and altered neural mechanisms of learning (Mercado et al., 2020 [↗](#)). In our study, we observed reduced performance in salience-based perceptual learning, shaped by a higher consistency bias in choice selection in *Fmr1*^{-/-} mice. These results align with findings in autistic individuals showing a stronger influence of previous choices on current perceptual decisions (Feigin et al., 2021 [↗](#)). Moreover, decreased flexibility in perceptual decision-making is consistent with evidence of altered auditory and visual learning in autism (Harris et al., 2015 [↗](#); Alispahic et al., 2022 [↗](#)), decreased performance under volatile conditions (Goris et al., 2021 [↗](#)), as well as increased perseveration and diminished sensitivity to feedback (Crawley et al., 2020 [↗](#)). Perceptual category learning was also found to be slower in autistic individuals, potentially due to the use of strategies that prioritize response guessing over rule application (Bott et al., 2006 [↗](#); Soulières et al., 2011 [↗](#)). Impairments in visual, tactile, and audio-visual perceptual learning have also been shown in *Fmr1*^{-/-} mice (Arnett et al., 2014b [↗](#); Goel et al., 2018 [↗](#); Mol et al., 2024 [↗](#)).

Our findings extend this body of work by identifying a salience-dependent shift in reliance on priors in autism, with lower-salience stimuli more strongly evoking dependence on previous choices and impacting perceptual learning.

Increased sensory discrimination in autism

Several theories of autism, including the *weak coherence* (Frith, 2003 [↗](#)), *enhanced perceptual functioning* (Mottron et al., 2006 [↗](#)), and *reduced generalization theories* (Plaisted, 2001 [↗](#)), support the notion of a superior perception of low-level information in autism. Indeed, a body of work has

confirmed superior pure tone discrimination (Bonnell et al., 2003 [↗](#); O’Riordan and Passetti, 2006 [↗](#)) and discrimination learning of highly confusable patterns (Plaisted et al., 1998b [↗](#)). Tactile discrimination in autism has been studied using diverse experimental protocols that target different tactile features, which has often led to contradictory results due to methodological variability and participant heterogeneity (reviewed in (Zetler et al., 2019 [↗](#))). Similarly, work on roughness discrimination in rodent models (Orefice et al., 2016 [↗](#); Ahmadi et al., 2023 [↗](#)) and human studies (O’Riordan and Passetti, 2006 [↗](#)) has shown discrepancies.

To address translational challenges between animal models and clinical research, our approach employed vibrotactile stimuli closely aligned with those used in human studies. Consistent with findings in autistic individuals (He et al., 2021b [↗](#)), *Fmr1^{-y}* mice showed intact amplitude discrimination for high-salience vibrotactile stimuli. Clinical studies have typically employed stimuli with more than 10-fold higher amplitudes compared to stimulus detection thresholds (He et al., 2021b [↗](#); Asaridou et al., 2022 [↗](#)). In contrast, our investigation focused on suprathreshold stimuli with much lower intensities (1.5-fold higher above threshold amplitude, 4-fold higher frequency). By employ such stimuli, our study uncovered enhanced discrimination of low-salience stimuli in *Fmr1^{-y}* mice, an aspect that remains underexplored in autistic individuals. Increased “local” processing could account for enhanced discrimination performance (Frith, 2003 [↗](#)). However, in our study, *Fmr1^{-y}* mice exhibited enhanced discrimination only under specific stimulus salience conditions, arguing against a global increase in sensory processing precision. Future clinical studies assessing the discrimination of lower-level stimuli are necessary to explore whether enhanced low-salience discrimination also characterizes autistic individuals.

Intact categorization but decreased facilitation of across-category discrimination in autism

Most perceptual discrimination is influenced by categorization (Goldstone, 1994 [↗](#); Beauny et al., 2020 [↗](#); Micher et al., 2024 [↗](#)). As mentioned by Goldstone, “a clear distinction between sensory and cognitive processes is not tenable” (Goldstone, 1994 [↗](#)). The reduced generalization hypothesis of autism postulates that, apart from superior performance on a difficult discrimination task, autistic individuals will have inferior performance in stimulus categorization (Plaisted, 2001 [↗](#)). However, studies on rule-based and prototype categorization have yielded inconclusive results, reporting both intact (Klinger and Dawson, 2001 [↗](#); Molesworth et al., 2005 [↗](#)), slower (Soulières et al., 2011 [↗](#)), reduced (Froehlich et al., 2012 [↗](#); Gastgeb and Strauss, 2012 [↗](#)) and enhanced performance (Bonnell et al., 2003 [↗](#)) in categorization tasks in autistic individuals.

We assessed for the first time categorization and its impact on discrimination of vibrotactile stimuli in a mouse model of autism. Our results revealed intact tactile categorization but reduced facilitation of across-category discrimination in *Fmr1^{-y}* mice. Although no clinical studies to date have examined this question in the tactile domain, our findings are consistent with previous research in the visual modality. These studies suggest that enhanced discrimination in autistic individuals may stem from reduced generalization (Plaisted et al., 1998b [↗](#); Plaisted, 2001 [↗](#)), and further indicate that discrimination processes may operate with increased independence from the influence of categorization (Soulières et al., 2007 [↗](#)). These findings suggest a bidirectional interaction between sensory and cognitive alterations in autism, indicating that not only atypical sensory perception can impact cognition (Haigh, 2018 [↗](#)), but also that cognitive differences can, in turn, shape sensory processing.

Attentional alterations in autism

Although attention deficits are not considered a general characteristic of autism (Grubb et al., 2013 [↗](#)), reduced attention in the presence of salient distractors (Venker et al., 2021 [↗](#)) and weaker accuracy in executive attention (Ridderinkhof et al., 2018 [↗](#)) have been reported in autistic individuals. Cognitive load is known to modulate attentional capacity (Lavie and Dalton, 2014 [↗](#); Murphy et al., 2016 [↗](#)), and prior work has shown that high cognitive load alters selective attention and distractor filtering (Head and Helton, 2014 [↗](#); Lavie and Dalton, 2014 [↗](#); Brockhoff et

al., 2022 [↗](#)). However, less is known about attention to task-relevant stimuli in these conditions. Our results support the view that attention deficits emerge under conditions of high cognitive load in autism. Miss rates increased in our task when *Fmr1*^{-/-} mice were required to discriminate and categorize eight stimulus intensities within a single session for water reward, but not during training sessions with only two stimulus intensities.

Notably, cognitive load appears to disproportionately affect attention to low-salience stimuli in *Fmr1*^{-/-} mice, suggesting a disruption in late-stage attention processes, which take place after the stimulus is perceived and are involved in top-down goal-directed behavior (Calvillo and Jackson, 2014 [↗](#)). In contrast, high-salience stimuli, which tend to capture attention automatically (Smallwood, 2013 [↗](#)), may engage early attentional processes and thus less affected by cognitive load. This context-dependent attentional modulation aligns with previous findings in autistic individuals, showing stimulus-dependent auditory attention deficits (Čeponiene et al., 2003 [↗](#)). These findings suggest that attentional alterations in autism may be conditionally expressed, particularly under tasks requiring increased cognitive resources.

Our results further dissociate attentional and tactile alterations in *Fmr1*^{-/-} mice, as low-salience stimuli were more accurately discriminated yet less attended to in *Fmr1*^{-/-} mice. These findings align with studies on linguistic processing in autistic children (Järvinen-Pasley et al., 2008 [↗](#); Ploog, 2010 [↗](#)) and extend clinical research demonstrating that tactile sensitivity alterations in autism are not linked to attentional difficulties (He et al., 2021b [↗](#)).

Trial history integration during perceptual decision-making in autism

Sensory perception is shaped not only by stimulus characteristics but also by trial history. Our results show that current stimulus intensity was the primary factor influencing the animal's choice, together with a strong perseveration across genotypes, consistent with prior work on perceptual decision-making in mice (Aguillon-Rodriguez et al., 2021 [↗](#)). This effect remained intact in *Fmr1*^{-/-} mice during tactile categorization. Interestingly, previous work in rats and humans has revealed that stimulus history strongly influences current perceptual choices under healthy conditions (Hachen et al., 2021 [↗](#)). Our results confirmed these results in control mice and further revealed that this sensory history effect was absent in *Fmr1*^{-/-} mice. These findings suggest poor sensory history integration and support models of autism proposing faster world model updating, with new sensory information weighting higher than previous experience (Goris et al., 2022 [↗](#)).

Motivation and reward valuation during perceptual decision-making

Motivation and reward valuation are two crucial factors impacting performance during perceptual decision-making. In this study, we minimized confounds from fatigue, satiety, or disengagement by restricting analyses to sessions and epochs in which animals were actively performing the task. Under these conditions, *Fmr1*^{-/-} and WT mice showed indistinguishable task engagement, learning rates and learning trajectories, which would not be expected if motivation, reward value, or reinforcement efficacy were altered in our mouse model of autism.

During testing, only the sessions where the mice achieved high accuracy on well-learned training stimuli were included in the analysis. Several additional observations further argue against altered reward valuation as a primary driver of behavioral alterations in *Fmr1*^{-/-} mice. We observed no genotype differences in categorical response bias (criterion *c*), nor any effect of previous reward outcome on subsequent choices, indicating that reward history did not differentially influence decision-making in *Fmr1*^{-/-} mice. In contrast, we found reduced across-category discrimination facilitation and diminished influence of recent sensory history on choice, pointing to altered perceptual-decision processes rather than global motivational deficits. Moreover, *Fmr1*^{-/-} mice exhibited increased miss rates that emerged selectively under high cognitive load and reduced sensory salience conditions. The salience- and context-dependent nature of these effects, together with preserved engagement and reward sensitivity, supports the

conclusion that the observed behavioral differences reflect specific disruptions in how sensory information is integrated and utilized during decision-making, rather than nonspecific changes in motivation, fatigue, or stereotyped responding.

Conclusion and Future Perspectives

Numerous hypotheses have sought to provide a unified explanation for the diverse symptoms of autism. Our findings support the view that altered cognitive processes shape perception in autism, influencing how autistic individuals learn and engage with their environment. We demonstrate differences in choice bias during perceptual learning and increased tactile discrimination in trained animals. These changes are accompanied by reduced categorization influence, sensory history integration, and attention. Rather than reflecting a global sensory deficit or enhancement, our results point to context-dependent alterations in how sensory information is integrated, weighted, and used for decision-making.

Future work will be needed to identify the circuit mechanisms driving these effects, and to test whether they reflect intrinsic changes in top-down cognitive networks or altered feedback between cognitive and sensory circuits that reshape sensory representations. In addition, although the present study focused on amplitude discrimination within the flutter range (40 Hz) to align with translational tactile paradigms, extending this approach to a broader range of vibrotactile frequencies will be important to determine whether sensory–cognitive alterations in autism generalize across stimuli that engage different mechanoreceptor populations. Finally, while the present study focused on vibrotactile processing due to its strong translational relevance, previous studies in the visual modality have reported similar cognitive influences on perceptual decision-making, suggesting that these effects may generalize across sensory systems. Future studies directly comparing modalities within the same experimental framework will be important to confirm this. Elucidating how cognition modulates sensory perception may offer valuable insights for clinical practice, help reconcile conflicting findings in the field, and inform the development of more targeted, mechanism-based interventions.

Materials and Methods

Experimental design

To study tactile perception as well as attention and perceptual biases in autism, we developed a novel 2-Alternative Choice task for the categorization and discrimination of flutter-range vibrotactile stimuli. Throughout the text, we use terms that are preferred in the autistic community and are less stigmatizing (Bottema-Beutel et al., 2021 [↗](#)).

Ethical statement

All experimental procedures were performed in accordance with the EU directive 2010/63/EU and French law following procedures approved by the Bordeaux Ethics Committee and Ministry for Higher Education and Research. Mice were maintained in reversed light cycle under controlled conditions (temperature 22–24 °C, humidity 40–60%, 12 h/12 h light/dark cycle, light on at 21:00) in a conventional animal facility with *ad libitum* access to food and *ad libitum* access to water before the water restriction period. All experiments were performed during the dark cycle, under red light.

Mice

Second-generation *Fmr1* knockout (*Fmr1*^{-/-}) and wild-type littermate mice 5–16 weeks old were used in our study. Mice were maintained in a C57Bl/6 J background (Mientjes et al., 2006 [↗](#)). Male wild-type and *Fmr1*^{-/-} littermates were generated by crossing *Fmr1*^{+/-} females with *Fmr1*^{+/-} male mice from the same production, and the resulting progeny used for our experiments was either *Fmr1*^{+/-} (wild type) or *Fmr1*^{-/-} (KO). Mice were maintained in collective cages following weaning (2–4 litter males per cage). Cages were balanced for genotype and supplemented with cotton nestlets and carton tubes.

The perceptual decision-making data were collected from 5 different cohorts of mice at different time-points during their active phase of the day. Mice of both genotypes were littermates and represented in each cohort. The number of mice is provided in the figure captions. The experimenter was blind to the animals' genotypes throughout the experiment. The genotype of experimental animals was re-confirmed post hoc by tail-PCR.

2-Alternative Choice task Setup

The vibrotactile decision-making setup was positioned in an isolation cubicle to minimize interference during the experiment. Mice were placed in a body tube and were head-fixed with their forepaws resting on two steel bars (6 mm diameter, Thorlabs). The right bar was mounted to a Preloaded Piezo Actuator (P-841.6, Physik Instrumente) equipped with a strain gauge feedback sensor and controlled (E-501, Physik Instrumente) in a closed loop, as described before (Prsa et al., 2019; Semelidou et al., 2024 [↗](#)). A 12.7 mm stainless steel post (ThorLabs) was mounted on the actuator vertically and a 0.6 mm stainless steel rod (ThorLabs) was clamped horizontally onto this post. The horizontal rod served as the contact bar on which the animal rested its right forepaw. Water reward was delivered through either of the two metal feeding needles (20G, 1.9mm tip, AgnTho's AB), placed left and right of the mouse's mouth, each connected to a lickport interface with a solenoid valve (Sanworks) equipped with a capacitive sensor (https://github.com/poulet-lab/Bpod_CapacitivePortInterface [↗](#)). The perceptual decision-making setup was controlled by Bpod (Sanworks) through scripts in Python (PyBpod, <https://pybpod.readthedocs.io/en/latest/> [↗](#)). The lickport interface (Sanworks) was equipped with a capacitive sensor (https://github.com/poulet-lab/Bpod_CapacitivePortInterface [↗](#)).

Habituation to head-fixation and water restriction

Mice (P40-P50) were handled using carton tubes and the cupping technique until they were comfortable in the experimenter's hands, attested by eating while handled. Mice were gradually habituated to the experimental setup and head fixation for 5 days. The third day of habituation, a water-restriction protocol was implemented, where mice had access to liquid water in the setup and to a solid water supplement (Hydrogel, BioServices) in their home cage. The water supplement was divided into small, individual portions, and each mouse received its allotment after the daily training/testing session. Daily body weight measurements were used to monitor hydration and ensure that all animals maintained stable body weight. If necessary, supplemental water was adjusted to maintain animals within the approved weight range. In total, the animals received 1.5-2 ml of water per day, which corresponds to 50-65% of their *ad libitum* consumption, while ensuring that they did not lose more than 10% of their weight. Each mouse received 6-8 g of Hydrogel (*ad libitum*) during the weekend. This water restriction protocol was maintained throughout behavioral training and until the end of behavioral testing.

2-Alternative Choice task training and testing Vibrotactile Stimuli

Stimuli were sinusoidal vibrations at 40 Hz with peak-to-peak displacements of 12 μm amplitude (low salience) or 26 μm amplitude (high salience), well above the detection threshold of both groups (10 Hz, 4.46 μm for WT; 10Hz, 7.29 μm for *Fmr1^{-/-}* mice) (Semelidou et al., 2024 [↗](#)).

Animals were positioned in the setup to ensure stable and consistent forepaw contact with the rod delivering the vibration. Pilot experiments with a sensor to monitor forepaw placement confirmed that the mice did not remove their forepaws from the bar before stimulus delivery.

Analysis of trials where no response followed stimulus delivery (Miss trials) showed that the 12 μm stimulus consistently elicited a higher proportion of missed responses compared to the 26 μm stimulus across animals, indicating lower behavioral performance for the lower-amplitude stimulus. We therefore referred to the 12 μm stimulus as "low salience" and the 26 μm stimulus as "high salience" to denote relative differences in perceptual strength and attentional engagement within the suprathreshold range.

Habituated mice (8 weeks old) were trained to associate high- (26 μm) and low-salience (12 μm) vibrotactile stimuli (pure sinusoid, 500 ms duration, 40 Hz frequency) with a water reward (8 μl) at the right- or left-placed lickport of the setup, respectively. All trials consisted of stimulus delivery followed by a 2 s response window during which the mice could lick to receive the reward. Inter-trial intervals were variable (5-10 s). Training was subdivided in 4 phases: (a) automatic water delivery at the beginning of the response window at the corresponding lickport (left for 12 μm stimuli, right for 26 μm stimuli). (b) Training in blocks: lick-triggered water delivery during blocks of 20 trials with the same vibrotactile stimulus, of either 12 μm or 26 μm amplitude. Licking at the wrong port resulted in 5 s timeout. (c) Training with pseudorandomly delivered high- and low-salience trials: lick-triggered water delivery following pseudorandom delivery of 12 μm or 26 μm amplitude stimuli. Licking at the wrong port resulted in 5 s timeout.

All sessions consisted of 200-300 trials with a 1:1 ratio of high and low-salience stimuli. During training, this ratio was modified when an animal showed consistent bias for one of the two lickports. Pilot experiments with an extra sensor to monitor forepaw placement confirmed that the mice did not remove their forepaws from the bar before stimulus delivery. To complete training in blocks, mice needed to perform with 70% correct choices and 30% incorrect choices for both stimulus amplitudes. To complete training with pseudorandomly delivered high- and low-salience trials, mice needed to reach the criterion of more than 70% correct choices and less than 30% incorrect choices as an average for 3 consecutive days. All mice that fulfilled this criterion were tested for the categorization/discrimination of vibrotactile stimuli. During testing, stimuli (pure sinusoid, 500 ms duration, 40 Hz frequency) were delivered in a pseudorandom manner with a 50% High-salience: 50% Low-salience ratio. Amplitudes varied on a range between 12 μm and 26 μm . Stimuli of 20, 22, 24 and 26 μm were considered high-salience stimuli and rewarded at the right lickport while stimuli of 12, 14, 16 and 18 μm were considered as low-salience stimuli and rewarded at the left lickport.

2-Alternative choice vibrotactile task analysis

All analysis was performed with custom-made Python scripts that can be available upon request. Behavior was quantified based on the lick events and three main outcomes were measured for each stimulus salience: Correct choice rate (number of correct licks divided by the total number of high- or low-salience trials), Incorrect choice rate (number of wrong licks divided by the total number of high- or low-salience

trials), and Missed stimuli rate (number of trials in which the animal did not lick, divided by the total number of high- or low-salience trials). Sessions in which animals disengaged were analyzed only during epochs in which the animal was actively performing the task. Training duration was calculated based on the total number of days each animal passed in training in blocks and with pseudorandom stimulus delivery.

For testing, only sessions with more than 70% correct choices for the training stimuli (12 μm and 26 μm) were analyzed. Psychometric curves were fitted on the rightwards lick rate for each stimulus amplitude using a general linear model. An average of 84 repetitions for each amplitude was used to calculate rightward lick rates.

Based on the signal detection theory (Hautus et al., 2021 [DOI](#)), sensitivity d' was calculated as:

$$d' = z(\text{lick right} / \text{high amplitude stimulus trials}) - z(\text{lick right} / \text{low amplitude stimulus trials})$$

Sensitivity d' for high- and low-salience stimuli was calculated based on the Correct and Incorrect choice rate for high- and low-salience stimuli, respectively.

The strategy of the animals was assessed through their criterion, which was calculated as:

$$c = -1/2 \times [z(\text{lick right} / \text{high amplitude stimulus trials}) + z(\text{lick right} / \text{low amplitude stimulus trials})]$$

Categorization bias was calculated as the inflection point (i.e., the midpoint parameter μ) of the fitted logistic psychometric function and categorization precision as the slope of the curve.

Prior choice impact was calculated separately for each type of the current trial (high- or low-salience). For low-salience trials, the prior choice impact was calculated as the rate of correct low and incorrect-low trials, divided by the rate of all correct and all incorrect trials. Similarly, for high-salience trials, the prior choice impact was calculated as the rate of correct high and incorrect-high trials, divided by the rate of all correct and all incorrect trials.

Learning trajectory analysis

Learning curves were quantified from the training phase with mixed high- and low-salience trials by calculating, for each mouse, the proportion of correct choices on each training day. For group-level comparisons, performance was plotted across days for WT and *Fmr1*^{-/-} mice, and mean learning trajectories with 95% confidence intervals were computed for each genotype.

To statistically compare learning trajectories across genotypes, we used a linear mixed-effects model with fixed effects for Genotype, Day, and their interaction, and a random intercept and random slope for each animal. This model tested whether performance differed between genotypes across days and whether the rate of learning (performance change per day) differed between WT and *Fmr1*^{-/-} mice.

To quantify individual learning rates, we computed the slope of performance as a function of training day for each animal. For each mouse, performance values (proportion of correct choices) were regressed against each Day using a simple linear regression model:

$$\text{Performance}_{\text{animal}} = \beta_0 + \beta_1 * \text{Day}$$

The slope (β_1) provides an estimate of the rate of improvement per training day.

Intermediate-stage slopes (middle 3 days of each mouse's training) were calculated in the same manner. Categorization bias was calculated based on the psychometric curves, as the stimulus amplitude at the inflection point of the sigmoid fitting curve. Categorization precision was calculated based on the slope of the psychometric curve.

Delta discrimination accuracy was computed as the difference in the rate of high-salience (rightward) licks between pairs of stimuli that differed by 2 μm . For analyses of low-salience and high-salience discrimination, delta discrimination accuracy values were calculated for each within-category stimulus pair and then averaged within the low-salience or high-salience category, respectively.

Statistics

All values are presented as mean \pm s.e.m. Box plots show the median, interquartile, range, mean and individual values. The numbers of animals used are indicated in the figure legends. Sample size was determined based on previous studies using similar behavioral paradigms. For experiments assessing tactile responses of trained animals, only animals that reached the training criterion were tested. For the discrimination & categorization task, all the testing sessions where the animals showed less than 70% correct responses to the training stimuli (12 μm and 26 μm) were excluded from tactile discrimination/categorization analysis. No samples or data points were excluded from the analysis.

All statistical analysis was done using Python (SciPy, Pingouin). All datasets were tested for normality using Shapiro–Wilk tests, and potential outliers were identified using a median absolute deviation–based modified Z-score ($|Z| > 3.5$). When an outlier was detected, statistical analyses were performed both including and excluding the outlier. In such cases, results from both analyses are reported when the inclusion or exclusion of the outlier altered the statistical outcome, to ensure transparency and robustness of the findings. For normally distributed data, two-tailed paired t-tests were used for within-subject comparisons, and Welch's independent-samples t-tests were used for between-group comparisons; otherwise, the Mann–Whitney U test (between groups) or the Wilcoxon signed-rank test (within subjects) was applied. Bonferroni correction was applied where multiple comparisons were performed. Effect sizes were calculated using Hedge's *g* for between-genotype comparisons and paired Hedge's *g* for within-genotype comparisons, particularly when statistical analyses showed trend-level differences ($p \approx 0.05$ – 0.1),

to provide a measure of the magnitude of the effect independent of sample size. Linear mixed-effects models were used to assess statistical differences in learning trajectories, psychometric curves, and miss rates.

Statistical modeling during categorization taking into account the trial history. Generalized linear models (GLMs) with a binomial link function were used to quantify the effects of current stimulus, previous trial history, genotype, and their interactions on the probability of choosing the right port. Trials without a defined history and Miss trials were excluded. Stimulus amplitudes were z-scored per mouse.

Two models were fit:

1. Main effects GLM – included current stimulus, previous stimulus, previous outcome, previous choice, and genotype.
2. Interaction GLM – extended the main effects model by including genotype × previous outcome, genotype × previous choice, and genotype × previous stimulus interactions.

Cluster-robust standard errors were calculated to account for repeated measurements within each mouse.

Marginal effects and psychometric curves

Predicted probabilities were computed from the interaction GLM to visualize the effect of stimulus amplitude, previous choice, and previous outcome on behavior, separately for WT and KO mice.

Supplementary figures

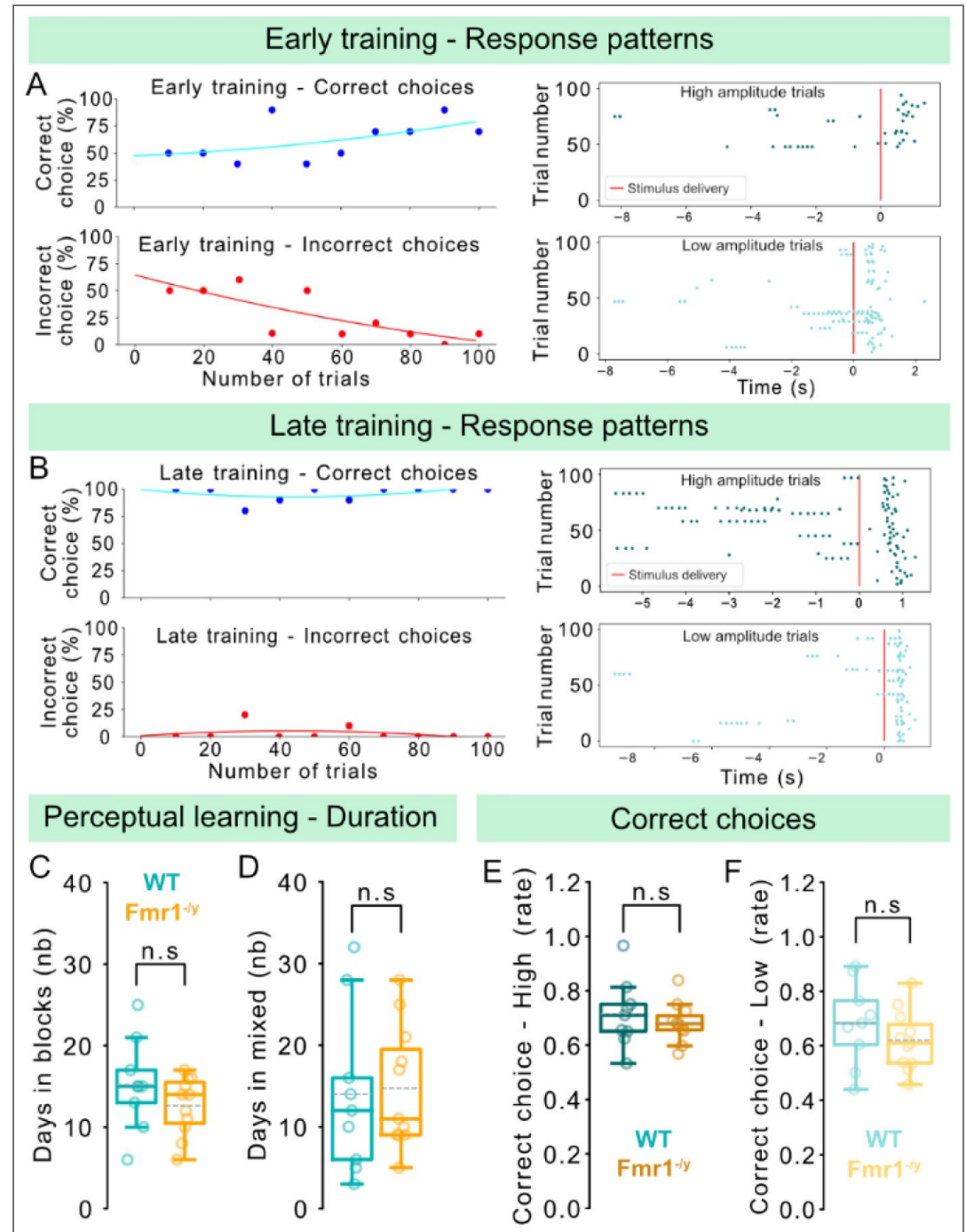


Figure S1. Perceptual learning duration for the different training phases and correct choice rates. n=9 WT, 11 *Fmr1^{-ly}* male mice for panels C-F. **A**, (Left) Example trace of 100 consecutive trials from an early (mixed) training session, showing the rates of correct (top) and incorrect (bottom) choices. (Right) Licking patterns from the same session for high-salience (top) and low-salience (bottom) trials. **B**, Same as in (A), but from a late training session of the same animal. **C**, Total number of days spent in the training phase where stimulus delivery is done in blocks of high- or low-salience stimuli. **D**, Total number of days spent in training with high- and low-salience stimuli are delivered in a pseudorandom manner. **E**, Correct choice rate for high-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. **F**, Correct choice rate for low-salience trials throughout the training period for WT and *Fmr1^{-ly}* mice. P values were computed using two-sided t-test for panels C, D, E, F; n.s, not significant.

Figure S2. Perceptual learning trajectories during training with mixed low- and high-salience trials.

n=7 WT, 9 *Fmr1^{-/-}* male mice for panels. **A**, (Top) Average learning trajectories for WT and *Fmr1^{-/-}* mice that completed the training phase, during mixed-trial training, calculated from the correct-choice rate for each training session (day) until each mouse reached the learning criterion. Shaded areas indicate 95% confidence intervals. (Bottom) Heat map of individual performance across mixed high- and low-salience sessions, showing the correct-choice rate for each session up to each mouse's learning criterion. **B**, Slope of the learning trajectory for each mouse, calculated using a linear regression model. **C**, Performance (correct choice rate) on the first day of the mixed-trial training phase. **D**, Intra-individual variability in performance across training days, assessed as the standard deviation of the correct choice rate. **E**, Slope of the learning trajectory during the intermediate learning stage, defined as the middle 3 days of training for each animal. **F**, Performance (correct choice rate) during the intermediate learning stage. P values were computed using linear mixed-effects model for panel **A**, Mann-Whitney test for panel **B**, and two-sided t-test for panels **C**, **D**, **E**, **F**; n.s, not significant.

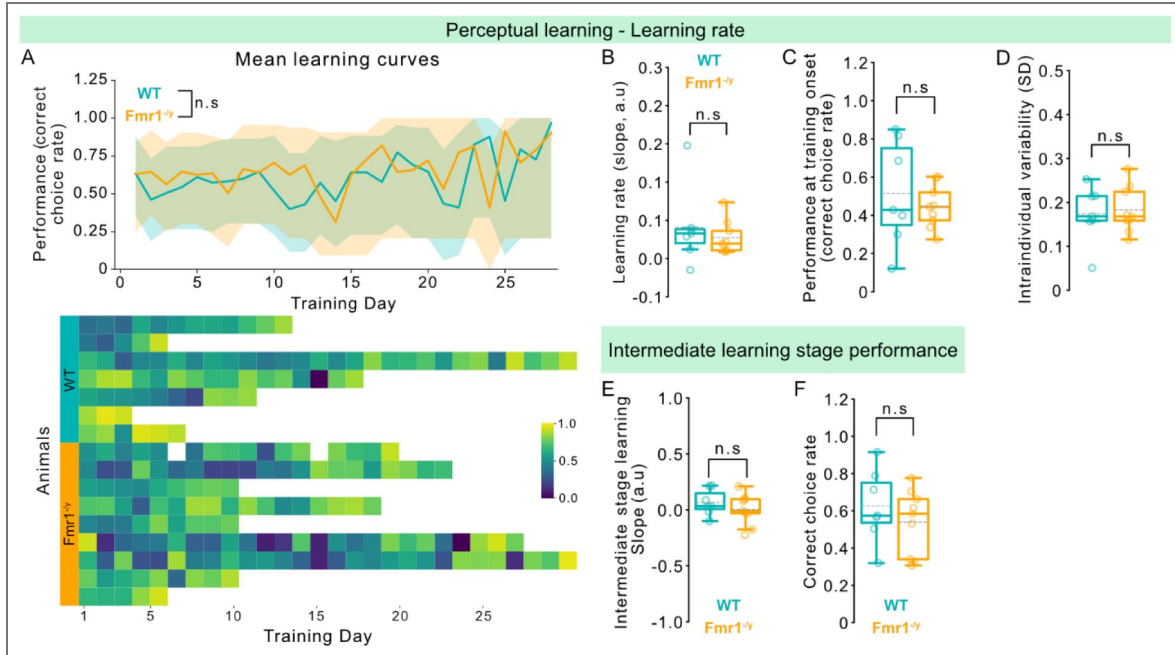


Figure S3. Prior strength and attention during perceptual learning.

n=9 WT, 11 *Fmr1^{-/-}* male mice. **A**, Strength of the prior build for high-salience trials, calculated as the proportion of correct high-salience and incorrect low-salience responses following a correct high-salience response. Rates are corrected over the rate of overall correct high-salience and incorrect low-salience responses. **B**, Strength of the prior build for low-salience trials, calculated as the proportion of correct low-salience and incorrect high-salience responses following a correct low-salience response. Rates are corrected over the rate of overall correct low-salience and incorrect high-salience responses. **C**, Within-genotype comparisons of the proportion of missed high- and low-salience trials. **D**, Proportion of missed high-salience trials. **E**, Proportion of missed low-salience trials. P values were computed using two-sided t-test for panel **A**; Mann-Whitney test for panels **B**, **D**, **E**; Wilcoxon signed-rank test for panel **C-left**; Paired t-test for panel **C-right**; **P < 0.01, or n.s, not significant.

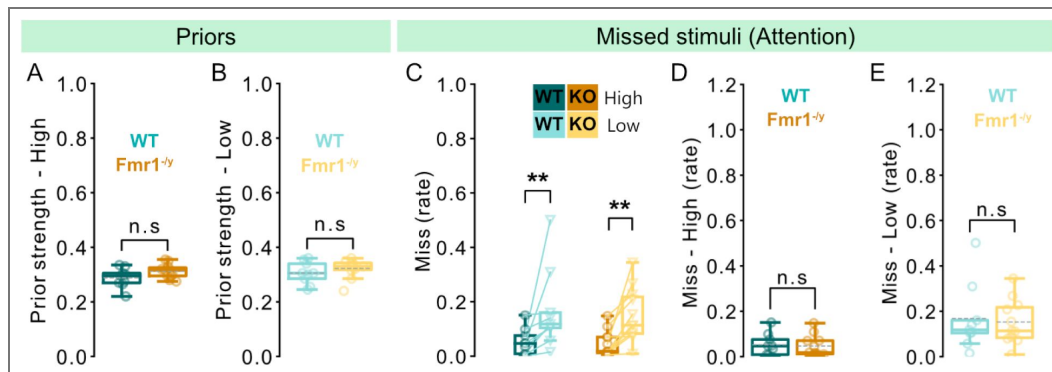


Figure S4. Perceptual learning performance during the last three days of training, for mice that were tested in tactile discrimination.

n=6 WT, 9 *Fmr1*^{-/-} male mice. **A**, Sensitivity *d'* throughout the last three days of the training period for WT and *Fmr1*^{-/-} mice. **B**, Proportion of correct choices for high-salience trails throughout the last three days of the training period. **C**, Proportion of correct choices for low-salience trails throughout the last three days of the training period. **D**, Proportion of incorrect choices for high-salience trails throughout the last three days of the training period. **E**, Proportion of incorrect choices for low-salience trails throughout the last three days of the training period. **F**, Criterion depicting the licking strategy of the animals. **G**, Proportion of correct responses in high-salience trials immediately following a correctly rewarded high-salience trial. **H**, Proportion of correct responses in low-salience trials immediately following a correctly rewarded low-salience trial. **I**, Proportion of incorrect responses in high-salience trials immediately following a correctly rewarded low-salience trial. **J**, Proportion of incorrect responses in low-salience trials immediately following a correctly rewarded high-salience trial. **K**, Proportion of correct responses in high-salience trials immediately following a correctly rewarded high-salience trial and incorrect responses in high-salience trials immediately following a correctly rewarded low-salience trial. Rates are corrected over the total number of correct and incorrect choices in high-salience trials. **L**, Proportion of correct responses in low-salience trials immediately following a correctly rewarded low-salience trial and incorrect responses in low-salience trials immediately following a correctly rewarded high-salience trial. Rates are corrected over the total number of correct and incorrect choices in low-salience trials. **M**, Proportion of missed high-salience trials. **N**, Proportion of missed low-salience trials. P values were computed using two-sided t-test for panels **A, B, C, D, E, G, H, I, J, K, L, N**; Mann-Whitney test for panel **F, M**; n.s., not significant.

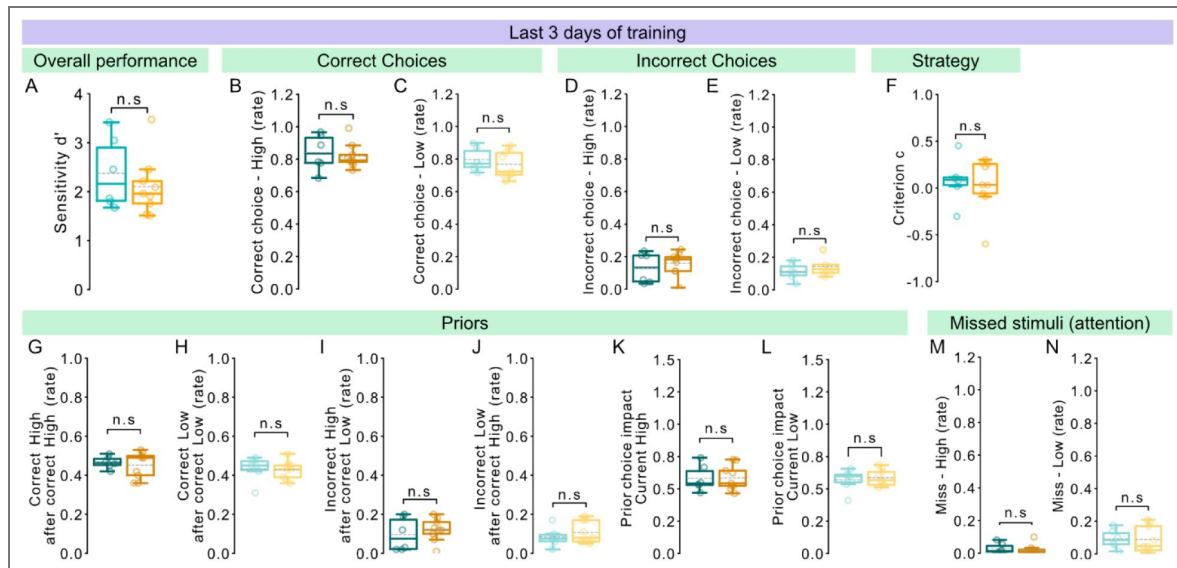
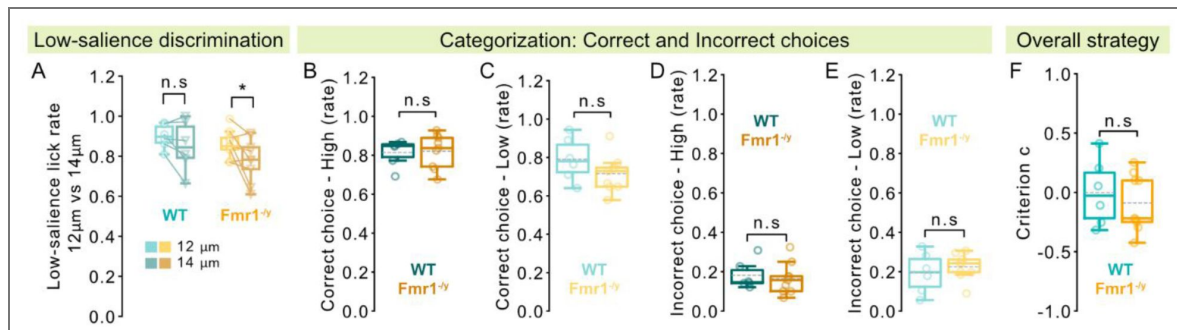


Figure S5. Sensitivity, correct, and incorrect choices during categorization of high- and low-salience stimuli.

n=6 WT, 9 *Fmr1*^{-/-} male mice. **A**, Sensitivity *d'* for high-salience stimuli during categorization. **B**, Sensitivity *d'* for low-salience stimuli during categorization. **C**, Correct responses for high-salience stimuli during categorization. **D**, Correct responses for low-salience stimuli during categorization. **E**, Incorrect responses for high-salience stimuli during categorization. **F**, Incorrect responses for low-salience stimuli during categorization. P values were computed using two-sided paired t-test for panel **A**; two-sided t-test for panels **B, C, D, E, F**; *P < 0.05, or n.s., not significant.



Data availability

The raw data of behavioral experiments generated in this study have been deposited on the figshare database: 10.6084/m9.figshare.29459771. Source data for each figure and the Python code used for all analyses are provided with the paper.

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Additional information

Contributions

A.F. and O.S. conceived the project. O.S. designed the experiments. O.S., M.T-M.F. and A.W. performed the experiments. O.S. and A.W. wrote the Python code for the behavioral experiments. O.S. analyzed the data and wrote the necessary Python scripts. O.S. interpreted the data. O.S. prepared the figures. O.S. wrote the manuscript, and A.F. and M.T-M.F. provided feedback.

Inclusion and diversity statement

We support inclusive, diverse, and equitable conduct of research. We tried to use inclusive language as much as possible.

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Additional files

Supplementary file 1.  Mixed models statistics.

Source data 1. 

Source code 1. 

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Peer reviews

Reviewer #1 (Public review):

[Editors' note: this version has been assessed by the Reviewing Editor without further input from the original reviewers. The authors have addressed the comments raised in the previous round of review.]

Summary:

This study addresses the important question of how top-down cognitive processes affect tactile perception in autism - specifically, in the *Fmr1-y* genetic mouse model of autism. Using a 2AFC tactile task in behaving mice, the study investigated multiple aspects of perceptual processing, including perceptual learning, stimulus categorization and discrimination, as well as the influence of prior experience and attention.

Strengths:

The experiments seem well performed, with interesting results. Thus, this study can/will advance our understanding of atypical tactile perception and its relation to cognitive factors in autism.

<https://doi.org/10.7554/eLife.108333.2.sa3>

Reviewer #2 (Public review):

Summary:

This manuscript presents a tactile categorization task in head-fixed mice to test whether *Fmr1* knockout mice display differences in vibrotactile discrimination using the forepaw. Tactile discrimination differences have been previously observed in humans with Fragile X Syndrome, autistic individuals, as well as mice with loss of *Fmr1* across multiple studies. The authors show that during training, *Fmr1* mutant mice display subtle deficits in perceptual learning of "low salience" stimuli, but not "high salience" stimuli, during the task. Following training, *Fmr1* mutant mice displayed an enhanced tactile sensitivity under low-salience conditions but not high-salience stimulus conditions. The authors suggest that, under 'high cognitive load' conditions, *Fmr1* mutant mouse performance during the lowest indentation stimuli presentations was affected, proposing an interplay of sensory and cognitive system disruptions that dynamically affect behavioral performance during the task.

Strengths:

The study employs a well-controlled vibrotactile discrimination task for head-fixed mice, which could serve as a platform for future mechanistic investigations. By examining performance across both training stages and stimulus "salience/difficulty" levels, the study provides a more nuanced view of how tactile processing deficits may emerge under different cognitive and sensory demands.

Weaknesses:

The study is primarily descriptive. The authors collect behavioral data and fit simple psychometric functions, but provide no neural recordings, causal manipulations, or computational modeling. Without mechanistic evidence, the conclusions remain speculative.

<https://doi.org/10.7554/eLife.108333.2.sa2>

Reviewer #3 (Public review):

Summary:

Developing consistent and reliable biomarkers is critically important for developing new pharmacological therapies in autism spectrum disorders (ASDs). Altered sensory perception is one of the hallmarks of autism and has been recently added to DSM-5 as one of the core symptoms of autism. Touch is one of the fundamental sensory modalities, yet it is currently understudied. Furthermore, there seems to be a discrepancy between different studies from different groups focusing on tactile discrimination. It is not clear if this discrepancy can be explained by different experimental setups, inconsistent terminology, or the heterogeneity of sensory processing alterations in ASDs. The authors aim to investigate the interplay between tactile discrimination and cognitive processes during perceptual decisions. They have developed a forepaw-based 2-alternative choice task for mice and investigated tactile perception and learning in *Fmr1*^{-/y} mice

Strengths:

There are several strengths of this task: translational relevance to human psychophysical protocols, including controlled vibrotactile stimulation. In addition to the experimental setup, there are also several interesting findings: *Fmr1*^{-/y} mice demonstrated choice consistency bias, which may result in impaired perceptual learning, and enhanced tactile discrimination in low-salience conditions, as well as attentional deficits with increased cognitive load. The increase in the error rates for low salience stimuli is interesting. These observations, together

with the behavioral design, may have a promising translational potential and, if confirmed in humans, may be potentially used as biomarkers in ASD.

<https://doi.org/10.7554/eLife.108333.2.sa1>

Author response:

The following is the authors' response to the original reviews.

eLife Assessment

This study provides valuable insights with solid evidence into altered tactile perception in a mouse model of ASD (Fmr1 mice), paralleling sensory abnormalities in Fragile X and autism. Its main strength lies in the use of a novel tactile categorization task and the careful dissection of behavioral performance across training and difficulty levels, suggesting that deficits may stem from an interaction between sensory and cognitive processes. However, while the experiments are well executed, the reported effects are subtle and sometimes non-significant. The interpretation of results may be overextended given the nature of the data (solely behavioral), the reliance on repeated d' measures may obfuscate some of the results without clearer psychometric or regressionbased analyses, and the absence of mechanistic, causal, or computational approaches limits the strength of the broader conclusions. The work will be relevant to those interested in autism, cognition, and/or sensory processing.

We thank the editors for their positive assessment of the data quality and the novelty of our behavioral task, and for pointing out the limitations inherent in behavioral studies.

We would like to clarify one important point regarding the use of d' measures. While d' was included to quantify sensitivity, our conclusions are not based solely on repeated d' measures. In addition to d', we analyzed raw behavioral data (correct and incorrect choice rates), and categorization performance was assessed using psychometric curves fitted with logistic regression models. These complementary analyses provide converging evidence and ensure that our interpretations are supported by multiple robust measures.

In the revised manuscript, we have further strengthened the analyses by including additional regression-based assessments, reporting effect sizes for subtle effects, and refining the statistical methods for clarity and transparency.

We fully acknowledge that this work is behavioral and does not directly reveal the underlying neural mechanisms. Nonetheless, the translational framework we have developed establishes a robust foundation for future studies. This platform can be directly applied in clinical research on autism and other neuropsychiatric conditions involving sensory-cognitive interactions, and provides a solid basis for subsequent mechanistic, causal, or computational investigations to uncover the neural circuits mediating these effects.

We greatly appreciate the editors' and reviewers' guidance and believe the revisions have clarified and strengthened the manuscript.

Public Reviews:

Reviewer #1 (Public review):

Summary:

This study addresses the important question of how top-down cognitive processes affect tactile perception in autism - specifically, in the Fmr1-ly genetic mouse model of autism. Using a 2AFC tactile task in behaving mice, the study investigated multiple aspects of

perceptual processing, including perceptual learning, stimulus categorization and discrimination, as well as the influence of prior experience and attention.

We appreciate the reviewer's statement highlighting the importance of our study.

Strengths:

The experiments seem well performed, with interesting results. Thus, this study can/will advance our understanding of atypical tactile perception and its relation to cognitive factors in autism.

We thank the reviewer for recognizing the quality of our experiments and the relevance of our findings for understanding tactile perception and cognition in autism.

Weaknesses:

Certain aspects of the analyses (and therefore the results) are unclear, which makes the manuscript difficult to understand. Clearer presentation, with the addition of more standard psychometric analyses, and/or other useful models (like logistic regression) would improve this aspect. The use of d' needs better explanation, both in terms of how and why these analyses are appropriate (and perhaps it should be applied for more specific needs rather than as a ubiquitous measure).

We thank the reviewer for these constructive comments. We acknowledge that aspects of the analyses were previously difficult to follow, and we have reworked the Results section to improve clarity and transparency.

We would like to emphasize that all d' measures are complemented by analyses of raw response rates (correct and incorrect choices), ensuring that our interpretations are not solely dependent on this metric. In addition, we applied standard psychometric analyses wherever possible. For the training phase, only two stimulus amplitudes were presented, which precluded the construction of full psychometric curves; however, for the categorization phase, psychometric analyses were feasible and are reported in Figure 3. Specifically, psychometric functions were fitted to the data using logistic regression, allowing us to estimate both categorization bias (threshold) and precision (slope) across stimulus intensities. These analyses revealed no evidence of categorization bias or precision in *Fmr1*^{-/-} mice across stimulus strengths.

Following the reviewer's suggestion, we have also added general linear model analyses that account for trial history, providing a complementary perspective on decision-making dynamics. Finally, while the calculation of d' is detailed in the Methods, we have revised the Results to clearly explain its use and appropriateness in each relevant analysis.

These revisions aim to provide a clearer, more comprehensive picture of the data while ensuring that all conclusions are supported by multiple complementary measures.

Reviewer #2 (Public review):

Summary:

*This manuscript presents a tactile categorization task in head-fixed mice to test whether *Fmr1* knockout mice display differences in vibrotactile discrimination using the forepaw. Tactile discrimination differences have been previously observed in humans with Fragile X Syndrome, autistic individuals, as well as mice with loss of *Fmr1* across multiple studies. The authors show that during training, *Fmr1* mutant mice display subtle deficits in perceptual learning of "low salience" stimuli, but not "high salience" stimuli, during the task. Following training, *Fmr1* mutant mice displayed an enhanced tactile sensitivity under low-salience conditions but not high-salience stimulus conditions. The authors*

suggest that, under 'high cognitive load' conditions, Fmr1 mutant mouse performance during the lowest indentation stimuli presentations was affected, proposing an interplay of sensory and cognitive system disruptions that dynamically affect behavioral performance during the task.

Strengths:

The study employs a well-controlled vibrotactile discrimination task for head-fixed mice, which could serve as a platform for future mechanistic investigations. By examining performance across both training stages and stimulus "salience/difficulty" levels, the study provides a more nuanced view of how tactile processing deficits may emerge under different cognitive and sensory demands.

We thank the reviewer for emphasizing the strengths of our task design and analysis approach, and we appreciate that the potential of this platform for future mechanistic investigations is recognized.

Weaknesses:

The study is primarily descriptive. The authors collect behavioral data and fit simple psychometric functions, but provide no neural recordings, causal manipulations, or computational modeling. Without mechanistic evidence, the conclusions remain speculative.

We thank the reviewer for the careful reading of our manuscript and for these constructive comments. We agree that our study is purely behavioral, and we appreciate the opportunity to clarify the scope and interpretation of our findings. The primary goal of this work was to characterize behavioral patterns during tactile discrimination and categorization in a translationally relevant mouse model of autism.

Although we did not include direct neural recordings, causal manipulations, or computational modeling, our analyses combining choice behavior, sensitivity measures from signal detection theory, psychometric curves, and regression-based models of trial history provide a detailed and robust characterization of perceptual learning, stimulus discrimination, categorization, and the interplay of cognitive processes with tactile perception. The manuscript has been revised to explicitly state that our conclusions are behavioral, emphasizing that this work establishes a foundation for future studies aimed at elucidating the neural and circuit mechanisms underlying these sensory–cognitive interactions.

Second, the authors repeatedly make strong claims about "categorical priors," "attention deficits," and "choice biases," but these constructs are inferred indirectly from secondary behavioral measures. Many of the effects are based on non-significant trends, and alternative explanations (such as differences in motivation, fatigue, satiety, stereotyped licking, and/or reward valuation) are not considered.

Alternative explanations for our findings including differences in motivation, fatigue, satiety, stereotyped licking, or reward valuation were carefully considered. As described in the Methods, only testing sessions with >70% correct performance on the training stimuli (12 μm and 26 μm) were included, excluding sessions with reduced motivation, fatigue, satiety, or stereotyped licking that could confound performance on low- or high-salience stimuli.

Although differences in reward valuation could affect learning speed, we observed no genotype differences in training duration (Fig. 1B-D, Fig. S1C-D). Sessions with disengagement were analyzed only during epochs of active task performance (information added to the revised Methods section, lines 619-620). Reward-driven choice biases were unlikely, as no

genotype differences were observed in categorization bias (Fig. 3F) and GLM analyses confirmed that previous reward outcome did not affect current choices (Fig. 4D).

Finally, altered reward valuation could increase miss rates. Elevated miss rates in *Fmr1*^{-/-} mice were restricted to the lowest-intensity stimulus (12 μ m) under high cognitive load, demonstrating a salience- and context-specific effect inconsistent with generalized motivational or reward deficits. The Discussion has been updated to clarify these points and delimit the scope of our interpretations (lines 483-499).

Third, the mapping of the behavioral results onto high-level cognitive constructs is tenuous and overstated. The authors' interpretations suggest that they directly tested cognitive theories such as Load Theory, Adaptive Resonance Theory, or Weak Central Coherence. However, the experiments do not manipulate or measure variables that would allow such theories to be tested. More specific comments are included below.

This was not done intentionally. References to Load Theory were meant to provide conceptual inspiration for assessing attention in high cognitive load conditions during categorization, rather than to indicate a formal test. Moreover, we do not claim to have tested the Weak Central Coherence theory, although our results suggest reduced facilitation of across- category discrimination. Finally, we agree that citing Adaptive Resonance Theory, which is grounded in artificial neural network models, could be misleading, and we have revised the text accordingly.

(1) The authors employ a two-choice behavioral task to assess forepaw tactile sensitivity in Fmr1 knockout mice. The data provide an interesting behavioral observation, but it is a descriptive study. Without mechanistic experiments, it is difficult to draw any conclusions, especially regarding top-down or bottom-up pathway dysfunctions. While the task design is elegant, the data remain correlational and do not advance our mechanistic understanding of Fmr1-related sensory and/or cognitive alterations.

We thank the reviewer for this comment and agree that our study is purely behavioral and does not provide direct mechanistic evidence for top-down pathway dysfunction. In the first version of the manuscript, the term “top-down” was used at the behavioral level, referring to the influence of higher-order cognitive processes (e.g., categorization, attention, sensory and choice history integration) on tactile perception, rather than to imply specific neural circuits.

We acknowledge that identifying the neural pathways underlying these effects would require extensive mechanistic experiments, including identifying the specific top-down pathway that modulates the influence of categorization on discrimination without directly altering categorization itself and performing pathway-specific recordings and manipulations. Such work represents a substantial mechanistic research program beyond the scope of the present study.

To clarify that our study does not provide insights into the neural underpinnings of the studied behavioral processes, we have revised the manuscript, removing the term “top-down” or replacing it with “higher-order processes” where appropriate. We also explicitly noted that future work using neural recordings or causal manipulations will be needed to uncover the neural underpinnings of these behavioral phenomena (lines 508-510).

(2) The conclusions hinge on speculative inferences about "reduced top-down categorization influence" or "choice consistency bias," but no neural, circuit-level, or causal manipulations (e.g., optogenetics, pharmacology, targeted lesions, modeling) are used to support these claims. Without mechanistic data, the translational impact is limited.

We recognize that terms such as “reduced top-down categorization influence” and “choice consistency bias” are derived from behavioral observations. However, we respectfully note

that these behavioral inferences are widely used in clinical studies to characterize cognitive tendencies (Soulières et al., 2007; Feigin et al., 2021) and are not inherently speculative.

The translational impact of our work lies in the development of a robust behavioral platform that allows precise dissection of tactile perception and cognitive influences in a manner directly comparable to clinical studies. While we agree that neural, circuit-level, or causal manipulations would provide valuable mechanistic insight, the current study establishes a foundational behavioral framework that can guide and inform future investigations into the underlying neurobiological substrates.

To ensure clarity, we have revised the manuscript throughout to explicitly indicate that all conclusions are based on behavioral measures and do not imply mechanistic evidence.

(3) Statistical analysis:

(a) Several central claims are based on "trends" rather than statistically significant effects (e.g., reduced task sensitivity, reduced across-category facilitation). Building major interpretive arguments on non-significant findings undermines confidence in the conclusions.

We chose to present both statistically significant effects and trends to ensure transparency and to highlight that commonly used aggregate measures, such as d' , can sometimes obscure meaningful underlying patterns. In the text, p -values between 0.05 and 0.1 are described as trends without over-interpreting their significance. To further support interpretation, we have now computed effect sizes (Hedges' g) for all subtle effects. In the revised manuscript, all interpretations of non-significant effects have been reworded to avoid overstatement.

(b) The n number for both genotypes should be increased. In several experiments (e.g., Figure 1D, 2E), one animal appears to be an outlier. Considering the subtle differences between genotypes, such an outlier could affect the statistical results and subsequent interpretations.

The number of mice used per genotype is consistent with standard practices in behavioral studies of sensory processing. To complement statistical analyses and account for small sample sizes, we have calculated effect sizes (Hedges' g) for all subtle or trend-level effects ($p \approx 0.05$ –0.1), providing a measure of effect magnitude independent of sample size.

As the reviewer correctly noted, no animals were excluded as outliers, since observed variability reflects true biological differences rather than experimental or technical errors. In the revised manuscript, we re-examined all datasets for potential outliers, and when identified, analyses were performed both with and without the data point. Any results sensitive to single animals are explicitly reported. This procedure is now detailed in the Methods section (lines 675–679).

(c) The large number of comparisons across salience levels, categories, and trial histories raises concern for false positives. The manuscript does not clearly state how multiple comparisons were controlled.

We thank the reviewer for highlighting this important point. To control for false positives arising from multiple comparisons, we applied the Bonferroni correction. This information has been added to the Methods section (line 682) to ensure transparency and reproducibility of all statistical tests.

(d) The data in Figure 5, shown as separate panels per indentation value, are analyzed separately as t -tests or Mann-Whitney tests. However, individual comparisons are inappropriate for this type of data, as these are repeated stimulus applications across a given session. The data should be analyzed together and post-hoc comparisons reported.

Given the very subtle difference in miss rates across control and mutant mice for 'low-salience' stimulus trials, this is unlikely to be a statistically meaningful difference when analyzed using a more appropriate test.

We thank the reviewer for raising this point, as this was not done intentionally. In the revised manuscript, miss rates for high- and low-salience stimuli were reanalyzed using a mixed-effects linear model, which appropriately accounts for repeated measurements within sessions (Fig. 5; Results section: lines 320-340). This analysis confirmed that *Fmr1*^{-/-} mice exhibit increased miss rates specifically at the 12 μ m amplitude, with the effect disappearing at higher low-salience amplitudes (18 μ m). Post-hoc comparisons with Bonferroni correction revealed a strong trend for increased misses at 12 μ m (T-test: $t = -2.8437$, $p = 0.058$, Hedge's $g = 1.23$), while no significant differences were found at other amplitudes. The Methods section has been updated to detail this statistical approach for analyzing miss rates (lines 686-687).

(4) Emphasis on theoretical models:

The paper leans heavily on theories such as Adaptive Resonance Theory, Load Theory of Attention, and Weak Central Coherence, but the data do not actually test these frameworks in a rigorous way. The discussion should be reframed to highlight the potential relevance of these frameworks while acknowledging that the current data do not allow them to be assessed.

As mentioned above, our goal was not to directly test theoretical frameworks such as Adaptive Resonance Theory, Load Theory of Attention, or Weak Central Coherence, but rather to provide a context for interpreting our behavioral findings. In the revised manuscript, we have removed references to the Load Theory from the Results section and reframed the Discussion to emphasize that our results are consistent with certain predictions from these cognitive theories, without implying that the experiments directly assessed them. This clarifies that the interpretations are based on observed behavioral patterns, while still acknowledging the potential relevance of these frameworks to better understand tactile perception and cognition in autism.

Reviewer #3 (Public review):

Summary:

*Developing consistent and reliable biomarkers is critically important for developing new pharmacological therapies in autism spectrum disorders (ASDs). Altered sensory perception is one of the hallmarks of autism and has been recently added to DSM-5 as one of the core symptoms of autism. Touch is one of the fundamental sensory modalities, yet it is currently understudied. Furthermore, there seems to be a discrepancy between different studies from different groups focusing on tactile discrimination. It is not clear if this discrepancy can be explained by different experimental setups, inconsistent terminology, or the heterogeneity of sensory processing alterations in ASDs. The authors aim to investigate the interplay between tactile discrimination and cognitive processes during perceptual decisions. They have developed a forepaw-based 2-alternative choice task for mice and investigated tactile perception and learning in *Fmr1*^{-/-} mice.*

Strengths:

*There are several strengths of this task: translational relevance to human psychophysical protocols, including controlled vibrotactile stimulation. In addition to the experimental setup, there are also several interesting findings: *Fmr1*^{-/-} mice demonstrated choice consistency bias, which may result in impaired perceptual learning, and enhanced tactile discrimination in low-salience conditions, as well as attentional deficits with increased cognitive load. The increase in the error rates for low salience stimuli is interesting. These*

observations, together with the behavioral design, may have a promising translational potential and, if confirmed in humans, may be potentially used as biomarkers in ASD.

We appreciate the reviewer's positive assessment regarding our study's translational value and the importance of our behavioral findings.

Weaknesses:

*Some weaknesses are related to the lack of the original raster plots and density plots of licks under different conditions, learning rate vs time, and evaluation of the learning rate at different stages of learning. Overall, these data would help to answer the question of whether there are differences in learning strategies or neural circuit compensation in *Fmr1*^{-/-} mice. It is also not clear if reversal learning is impaired in *Fmr1*^{-/-} mice.*

We thank the reviewer for these helpful suggestions. We agree that visualizing behavioral patterns, such as raster and density plots of licks, as well as learning rate over time, provides additional insights into learning dynamics. In response, we have added these analyses to the revised manuscript (Fig. S1, Fig. S2), which illustrate both individual and group-level learning trajectories and trial-by-trial licking patterns.

There was no assessment of reversal learning in *Fmr1*^{-/-} mice in this study. While this is an interesting and important question, and is motivated by previous preclinical and clinical findings, it falls outside the scope of the current manuscript.

Recommendations for the authors:

Reviewer #1 (Recommendations for the authors):

Main Comments

*(1) This study addresses the important question of how top-down cognitive processes affect tactile perception in autism - specifically, in the *Fmr1*^{-/-} genetic mouse model of autism vs. WT controls. Using a 2AFC tactile task in behaving mice, the study investigated multiple aspects of perceptual processing, including perceptual learning, stimulus categorization and discrimination, as well as the influence of prior experience and attention. The experiments seem well performed, with interesting results. I found certain aspects of the analysis not clearly explained, which made it difficult at times to understand.*

Please see specific details in the comments below.

(2) To measure sensitivity, the authors present many comparisons of d' - sometimes between pairs of stimuli (or sometimes even for a single stimulus level).

(a) Firstly, the calculation of d' for a single stimulus value is unclear (because the same proportion of high/low choices for a given stimulus can result from shifts in bias/criterion).

We agree with the reviewer that calculating d' for a single stimulus conflates sensitivity with response bias/criterion differences. For this reason, the panels showing d' for individual stimulus amplitudes during training (Fig. 1F and 1G in the original manuscript) have been removed from the manuscript.

In addition, we revised our d' (Fig. 1E) and criterion calculations (Fig. 2A), treating the high amplitude stimuli as “signal” and low amplitude stimuli as “noise”, based on the Signal Detection Theory. The formulas used in the revised manuscript take into account correct responses during high amplitude stimuli and wrong responses during low amplitude stimuli to calculate the sensitivity and bias of the mice during discrimination in the training period.

Sensitivity (d') is now computed as:

$$d' = z(\text{lick right} \mid \text{high amplitude stimulus}) - z(\text{lick right} \mid \text{low amplitude stimulus})$$

and the criterion (c) as:

$$c = -1/2 \times [z(\text{lick right} \mid \text{high amplitude}) + z(\text{lick right} \mid \text{low amplitude})]$$

(b) Secondly, while calculating d' makes sense for comparing two stimulus levels (like in the training condition), in the test condition (with a spread of stimuli), this becomes a little tedious - at times difficult to follow and unclear.

I would have thought that sensitivity (at least for overall performance) would be better compared using data from all the stimuli - e.g. either using:

(i) the sigma of the psychometric curve (although the downside of that approach is that it ignores history effects), or

(ii) a logistic regression for the choices, given the stimuli, where the weights assigned to the stimulus magnitude indicate sensitivity (the advantage of that approach is that history effects, like the previous trials/choices can be used as regressors in the model). Accordingly, it can simultaneously also quantify the history effects. This could even be expanded to a GLMM (mixed effects for different mice).

We thank the reviewer for this very valuable feedback. Indeed, during the testing phase, we calculated sensitivity d' to probe the overall categorization sensitivity (Fig. 3H).

(i) This analysis was only complementary to the psychometric curves (fitted on the rightward lick rate for each stimulus amplitude using a general linear model – Fig. 3A). As the reviewer proposes, we had calculated the sigma of the psychometric curve (Fig. 3G, slope) to assess categorization precision. Sensitivity calculations have also now been revised using the aforementioned formula ($d' = z(\text{lick right} \mid \text{high amplitude stimulus}) - z(\text{lick right} \mid \text{low amplitude stimulus})$).

(ii) To incorporate history effects, we implemented generalized linear models (GLMs) with a binomial link function to predict high-salience licks (right-lick choices) based on the current stimulus, trial history, genotype, and their interactions. A main-effects model included current stimulus, previous stimulus, previous outcome, previous choice, and genotype, followed by interaction terms to assess genotype-specific modulation of history effects. These analyses are now presented in the new Figure 6.

The resulting coefficients are shown in Fig. 6A. As expected, decisions were primarily driven by current stimulus amplitude (Fig. 6A, B). Both genotypes displayed a tendency to repeat previous choices (Fig. 6A, C), while previous reward outcomes did not influence current choice (Fig. 6A, D). Notably, stimulus amplitude history showed genotype-specific effects: WT mice were negatively influenced by the previous stimulus, whereas *Fmr1*^{-/-} mice remained unaffected (Fig. 6A, E).

To clearly visualize these findings, we plotted psychometric curves and marginal effects accounting for current stimulus, previous choice, previous outcome, and previous stimulus (Fig. 6B-E). These analyses are now fully integrated into the Methods (lines 688-702), Results (Fig. 6, lines 341-369), and Discussion (lines 469-479) sections of the revised manuscript.

(3) I find some of the terminology used confusing/misleading:

(a) The term "Categorization thresholds" can be misleading - in psychometric curves, "thresholds" often refer to the sigma (SD) of the fitted curve used to measure sensitivity (inversely related). Here, I think that the meaning is in terms of the PSE/ criterion.

Perhaps the terminology can be improved to prevent confusion on this matter. E.g., I think that here the authors mean a measure of bias/criterion/PSE or similar. Correct? Not really a perceptual "threshold".

We thank the reviewer for pointing this out. In our analysis, the term “threshold” referred to the inflection point (i.e., the midpoint parameter μ) of the fitted logistic psychometric function used to categorize high- versus low-amplitude stimuli. We termed it “threshold” in the categorization of high and low amplitude stimuli. We agree with the reviewer that we could also use the term “Categorization bias”. We originally opted to avoid this term, not to confuse the readers when referring to the criterion (signal detection theory) as “response bias”. However, seeing as the term “threshold” may be confusing as well, we adopted the term “Categorization bias” in the updated version of the manuscript (lines 282, 284, 637-638, 785, Fig. 3F).

(b) Similarly, I think that "Categorization accuracy" can be misleading when describing the slope of the psychometric curve. Performance could have a steep slope but still be quite inaccurate (e.g., if there is a big bias). Perhaps "precision" is a better description of the slope?

We thank the reviewer for this suggestion. The slope of the psychometric curve is often referred to as “sensitivity” in the literature (Carandini and Churchland, 2014), but in our original manuscript we used the term “accuracy” to avoid confusion with the d' measure from signal detection theory. We have revised the manuscript and Figures with the term “precision” as the reviewer suggested (lines 282, 284, 637-638, 786, Fig. 3G).

Minor Comments

(1) Abstract: "determines how autistic individuals engage" - there are other factors too. So, I think that "determines" is a little strong. Perhaps "influences" is more appropriate.

We have incorporated the reviewer’s suggestion (line 7).

(2) Figure 1 F, G. On the one hand, d' is defined as "sensitivity (d') in discriminating between high- and low-salience stimuli" - that seems to make sense. But then d' is also calculated and presented for each salience level on its own. How was this done? Namely, percent correct (or proportion of choices high/low salience) could be affected by criterion shifts as well as sensitivity. This makes calculating the d' for a single (low or high) salience stimulus ambiguous. So, how do these authors make this conclusion?

We agree that calculating d' for a single stimulus amplitude is ambiguous, because the resulting value conflates true stimulus sensitivity with shifts in response bias or criterion. Consequently, all analyses and figures reporting d' for individual high- or low-salience stimuli (e.g., Figures 1F and 1G) have been removed from the revised manuscript.

In the updated analyses, d' is calculated only across high- versus low-salience stimuli, following standard Signal Detection Theory procedures, ensuring that it reflects true discriminability between the two categories (Methods, line 631; Figure 1E).

*(3) "Our results showed comparable correct choice rates in *Fmr1*^{-/-} and WT mice (Fig. 1H), for both high- and low-salience stimuli (Fig. S1C-D). In contrast, *Fmr1*^{-/-} mice presented a significantly higher rate of incorrect choices (Fig. 1I)." - aren't correct choices and incorrect choices complementary (i.e., 1-x) in a 2AFC? How is this possible?*

We thank the reviewer for pointing this out. Correct and incorrect choices are complementary at the single-trial level if miss trials are excluded. However, in our analyses, correct and incorrect choice rates were calculated by normalizing the number of correct or incorrect responses to the total number of trials (including misses), which breaks this

complementarity and contributes to the differences observed in Fig. 1H–I. This was clarified in the Methods section (lines 616–617). Moreover, incorrect responses were less frequent than correct ones and are thought to reflect lapses, response bias, and impulsive responding rather than sensory performance, making them more sensitive to genotype-dependent differences in behavioral control. Based on this concept, we further examined whether incorrect choices were preferentially associated with specific stimulus amplitudes and assessed response bias and prior effects.

(4) The conclusion that "they showed a strong trend toward reduced sensitivity for low-salience stimuli (Fig. 1G)" has a confound - it could be that there was a criterion shift (rather than differences in sensitivity)?

We agree with the reviewer that the previously reported trend in sensitivity for low-salience stimuli could reflect a criterion shift rather than true differences in sensory sensitivity. Because sensitivity estimates for individual stimulus amplitudes are not well-defined in a 2AFC framework, we have removed the sensitivity calculations for high- and low-salience stimuli considered independently. Instead, we now present salience-specific differences using correct and incorrect response rates for each stimulus amplitude, which more directly capture performance differences without assuming changes in sensory sensitivity (Fig. 1G–I, S1E–F).

(5) Figure 3D, E - I stumbled over this in comparison to Figure 3B, C. That is because (a) In D and E, the authors compare right-lick responses (reporting high salience) to stimuli of 12 μm and 14 μm amplitude (Figure 3D) and low-salience lick rates for the same (Figure 3E). I would have thought that these approaches are simply complementary (1-x) - see related minor question above/below. So, what is the advantage of presenting them both?

We presented both panels to clarify the source of the observed differences in performance. Specifically, showing right-lick responses (reporting high-salience choices) alongside low salience lick rates allows us to distinguish whether reduced high-salience reporting arises from an actual shift in choice (e.g., increased leftward licking) versus an increase in miss trials at the lowest amplitude (12 μm). By presenting both, we can demonstrate that the effect is primarily driven by an increase in leftward choices rather than by missed responses, providing a more precise interpretation of behavioral changes. The complementary analysis for leftward choices has now been moved to the supplemental material (Fig. S5A) and the reason for this analysis has been clarified in the Results (lines 275–276).

(b) In B and C, the authors compare two differences in stimulus magnitude (2 and 4 μm), but in Figure 3D and E, only one difference (2 μm) from two perspectives. I was expecting a comparison with stimuli differing by 4 μm in amplitude (comparable to the high stimulus comparison of 26 μm vs. 22 μm stimuli).

We have indeed analyzed the 12 μm versus 16 μm stimulus pair, which corresponds to a 4 μm difference and is reliably discriminated by both genotypes. In the original manuscript, we did not include this comparison because of the differences already seen at a 2 μm amplitude difference. Based on the reviewer's suggestion, we have now included the 12 μm vs. 16 μm comparison in the revised manuscript (Results, lines 270–272; Fig. 3E) to provide a complementary perspective consistent with the high-salience comparisons (26 μm vs. 22 μm).

(c) "Sensitivity d' for high- and low-salience stimuli was calculated based on the Correct and Incorrect choice rate for high- and low-salience stimuli respectively." How were trials for which the animal did not respond taken into account? Were these part of the denominator? Or were these excluded when calculating proportions? (related to the Q regarding Figure 3 D,E above).

Indeed, the Miss trials were part of the denominator. This is now clarified in the Methods section (line 631).

(d) "c = d'(high)- d'(low)." - I did not understand this fully. There were several high and several low stimuli - so how were these calculated? Pooled for high and pooled for low? Per stimulus difference?

This was indeed calculated for pooled high and low amplitudes during testing. In the revised manuscript, criterion c has been recalculated based on the average correct high rate (for stimuli of 20-26 μm amplitude) and average incorrect low rate (for stimuli of 12-18 μm amplitude), using the same formula as in the analysis of the training dataset:

$$c = -1/2 \times [z(\text{lick right} / \text{high amplitude}) + z(\text{lick right} / \text{low amplitude})]$$

Pooling across amplitudes allows us to obtain a single summary measure of response bias toward the right lickport, independent of stimulus discriminability. This approach is consistent with standard signal detection theory practices when multiple stimulus levels are present.

If the inter-trial interval is 5-10s, how is a 5s timeout a punishment?

The 5 s timeout serves as a punishment by temporarily delaying access to the next trial and potential reward, thereby reducing the overall reward rate. Even though the inter-trial interval (ITI) varies between 5 and 10 s, the timeout increases the effective delay before the next opportunity to earn a reward, discouraging incorrect responses. This is consistent with standard operant conditioning procedures, where brief timeouts act as negative consequences without being overly severe. Across most trials, the timeout effectively reduces expected reward rate, though its impact is minimal when the ITI is already long.

Reviewer #2 (Recommendations for the authors):

Task-related questions:

(1) What evidence is there that the 40 Hz, 12 μm stimulus is "low salience" while the 40 Hz, 26 μm stimulus is "high salience"? This seems like an arbitrary distinction without showing sensitivity curves across a group of animals. Better definitions of the stimuli and the actual forces applied are necessary.

We thank the reviewer for this comment. Based on our previous work (Semelidou et al., bioRxiv; Accepted in Advanced Science), both the 40 Hz, 12 μm and 40 Hz, 26 μm stimuli are clearly suprathreshold. In the present study, however, stimulus salience is defined in a relative and operational manner within this suprathreshold range.

Specifically, analysis of miss trials (Fig. S3E) shows that the 40 Hz, 12 μm stimulus consistently elicited a higher proportion of missed responses compared to the 40 Hz, 26 μm stimulus across animals, indicating lower behavioral performance for the lower-amplitude stimulus. We therefore refer to the 12 μm stimulus as "low salience" and the 26 μm stimulus as "high salience" to denote relative differences in perceptual strength and attentional engagement within the suprathreshold range, rather than differences in detectability or absolute sensory sensitivity. This definition has been clarified in the Methods (lines 583-587) and Results sections (lines 115-119; lines 225-227).

(2) Sensitivity curves/detection thresholds for each mouse should be included in the study.

We thank the reviewer for this suggestion. Sensitivity curves and detection thresholds for low-amplitude and low-frequency vibrotactile forepaw stimulation have been systematically

characterized in our previous study (Semelidou et al., bioRxiv, Accepted in Advanced Science). In that work, we demonstrated that stimuli with similar amplitudes and even lower frequency (10Hz) than those used in the present study are reliably detectable by mice, confirming that both the 40 Hz, 12 μm and 40 Hz, 26 μm stimuli fall within the suprathreshold range.

Because the goal of the present study was not to determine absolute detection thresholds but rather to examine discrimination and categorization performance within a suprathreshold range, we did not re-establish full psychometric detection curves for each mouse.

We have clarified this rationale in the revised manuscript (Results, lines 108-113; Methods, lines: 577-579).

(3) What force is being applied during stimulus presentations? 12 or 26 μm does not provide enough information about the stimuli applied. What are the physical parameters of the indenter? What material, what tip size?

Vibrotactile stimuli were delivered to the forepaw via a piezoelectric actuator. A 12.7 mm stainless steel post (ThorLabs) was mounted on the actuator vertically and a 0.6 mm stainless steel rod (ThorLabs) was clamped horizontally onto this post. The horizontal rod served as the contact bar on which the animal rested its right forepaw.

Stimuli were sinusoidal vibrations at 40 Hz with peak-to-peak displacements of 12 μm (low salience) or 26 μm (high salience). The actuator displacement was calibrated prior to experiments to ensure accurate vibration amplitudes.

Animals were positioned in the setup to ensure stable and consistent forepaw contact with the rod delivering the vibration. Pilot experiments with an extra sensor to monitor forepaw placement confirmed that the mice did not remove their forepaws from the bar before stimulus delivery. All this information is now added in the Methods section (lines 552-555, 580-582).

(4) Only one vibration stimulus was used (40 Hz) - this preferentially activates specific subsets of low-threshold mechanoreceptors and not others. A range of vibrotactile stimuli (with varying frequencies) would be more useful. From this limited range of stimuli, it is difficult to assess whether the findings would extrapolate to other types of stimuli.

We agree that using a single vibration frequency limits the generalization of our findings across the full range of mechanoreceptor subtypes and vibrotactile stimulus conditions. In the present study, we deliberately focused on amplitude discrimination within the flutter range (<50 Hz), as this frequency preferentially activates subsets of low-threshold mechanoreceptors relevant for flutter perception and is commonly used in clinical studies of tactile amplitude discrimination (Puts et al., 2014, 2017; Asaridou et al., 2022). By holding frequency constant and varying only amplitude, we were able to isolate amplitude-dependent perceptual and decision-making processes while minimizing frequency-dependent variability and to facilitate direct translational comparisons with human studies using similar flutter stimuli.

We acknowledge, however, that extending the paradigm to additional, high frequencies would help determine whether the observed effects generalize across mechanoreceptor channels. We have now added this point as a future direction in the Discussion section (lines 510-514).

(5) The methods indicate that during the implementation of the water-restriction protocol, mice had access to a solid water supplement in their home cage. How did they

control for how much water supplement was consumed by each mouse before the testing sessions?

We thank the reviewer for raising this point. The solid water supplement was divided into premeasured individual portions, and each mouse received its allotted amount only after the daily training/testing session. Daily body weight measurements were used to monitor hydration and ensure that all animals maintained stable body weight. If necessary, supplemental water was adjusted to maintain animals within the approved weight range. This procedure is now described in the Methods section (line 567-571).

(6) A control version of the test, perhaps using a different sensory modality, would be useful for making conclusions.

We agree that testing other sensory modalities would provide a useful control for assessing the generalizability of the observed effects. However, in the present study, we intentionally focused on the tactile modality, as touch has been shown to play a critical role in autism across sexes and predict other core behavioral symptoms. This makes touch particularly relevant for investigating translational mechanisms in this model.

By specifically targeting tactile perception, we aimed to investigate the link between sensory discrimination, decision-making, and cognitive modulation within a modality that is strongly implicated in autism. Previous studies in autistic individuals have demonstrated similar interactions between cognitive processes and perceptual decision-making in the visual domain, suggesting that such effects may not be modality-specific. Nevertheless, extending this paradigm to additional sensory systems would be valuable to directly test whether comparable cognitive influences on perception generalize across modalities. We have now incorporated this perspective as a future direction in the Discussion section (lines 514-518).

Reviewer #3 (Recommendations for the authors):

There are several questions:

*(1) It is important to show stimulus intensity-response curves representing tactile responses for both WT and *Fmr1*^{-/-} mice.*

We thank the reviewer for this important comment. Detection sensitivity curves for low-amplitude and low-frequency vibrotactile stimulation of the forepaw have been characterized in detail in our previous study (Semelidou et al., bioRxiv; now accepted in Advanced Science). In that work, we showed that stimuli at or above 8 μm amplitude and 10Hz frequency are reliably detected by both WT and *Fmr1*^{-/-} mice.

Based on these findings, the current study employed vibrotactile stimuli at a higher frequency (40 Hz) and amplitudes of 12 μm and above, ensuring that all stimuli were well within the suprathreshold range for both genotypes. This experimental choice was made to specifically probe discrimination, categorization, and decision-making processes, rather than basic sensory detection. As a result, the behavioral effects reported here cannot be attributed to differences in stimulus detectability.

We have clarified this rationale in the revised manuscript to make explicit that the absence of full intensity-response curves in the current study reflects a deliberate focus on suprathreshold perceptual and cognitive processes rather than sensory threshold differences (Results, lines 108-113; Methods, lines: 577-579).

*(2) There is no difference in the time it takes to learn the task between WT and *Fmr1*^{-/-} mice. But how does the learning rate curve look? Is there a difference in the slope between WT and *Fmr1*^{-/-} early vs late into learning?*

We thank the reviewer for this suggestion. To directly address whether learning dynamics differed between genotypes, we analyzed learning curves across training.

We first computed the correct choice rate per day for each animal (Fig. S2A) and fit a mixed-effects model including training day, genotype, and their interaction. This analysis revealed no genotype differences in baseline performance or learning rate with minimal Genotype \times Day interaction (Fig. S2A-top, Fig. S2C).

We additionally computed the slope of the learning curve for each individual, which also showed no difference across genotypes (Fig. S2B). In addition, within-animal day-to-day performance variability was also comparable across groups (Fig. S2A-bottom, S2D).

These analyses indicate that WT and *Fmr1*^{-/-} mice exhibit similar learning trajectories during training. The learning curves are now included in Figure S2, described in the Results (lines 140–151) and detailed in the Methods (lines 644–658).

| (3) *It would be useful to see raster plots of licks for different trials and the corresponding lick density plots for early vs late trials.*

We thank the reviewer for this suggestion. To visualize trial-by-trial behavior, we included example lick traces from an early 100-trial session and a late 100-trial session, alongside the corresponding raster plots of licks (Fig. S1A–B).

| (4) *Consistent with the first question, examples of intermediate learning stages would help gain more insight into how both WT and *Fmr1*^{-/-} mice learn.*

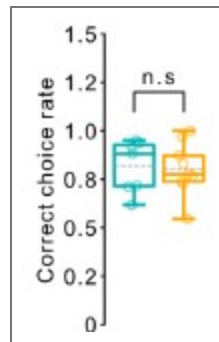
In line with the reviewer's suggestion, we examined whether WT and *Fmr1*^{-/-} mice showed different performance during intermediate stages of learning. To this end, we defined the middle three days of the training period of each animal as the intermediate learning phase. We compared both the mean correct-choice rate and individual learning slopes across this interval. Statistical analyses revealed no significant genotype differences in either measure, indicating comparable performance and learning dynamics during the intermediate phase of training (lines 152–156).

| (5) *How does the learning rate change with increased cognitive load for both WT and *Fmr1*^{-/-} mice?*

We thank the reviewer for this question. While our experimental design did not include a manipulation of cognitive load during the learning phase itself, we assessed whether increased cognitive load affected performance by analyzing behavior on the first day of testing, when animals were required to categorize and discriminate among a larger set of stimuli compared to training.

Using performance on the training stimuli during this first testing session as a proxy, we found no significant difference between WT and *Fmr1*^{-/-} mice in correct choice rate (Author response image 1). This indicates that increased cognitive load did not differentially affect performance on familiar stimuli across genotypes at this stage.

Because this analysis does not reflect learning rate per se, but rather performance under increased task demands after learning had already occurred, we did not incorporate it into the main Results section. Instead, it is presented here to directly address the reviewer's question.



Author response image 1. Correct choice rate for the 12 μm and 26 μm stimuli during the first day of testing when the cognitive load is high.

(6) How does the learning rate change if the sensory stimuli are more challenging for both WT and *Fmr1*^{-/-} to detect?

We thank the reviewer for this question. In the present study, animals were deliberately trained using well-separated, suprathreshold low- and high-salience stimuli to ensure reliable stimulus detection and to avoid confounding learning rate with perceptual difficulty or discrimination limits.

A recent study (Heimburg et al., 2025) has shown that learning is slower when the difference between the two training stimuli is reduced. Based on these results, we would expect that decreasing the separation between low- and high-salience stimuli would similarly increase training duration for both WT and *Fmr1*^{-/-} mice, since our results do not indicate any discrimination or categorization deficits in the mouse model of autism. However, directly testing how stimulus difficulty modulates learning rate would require a dedicated manipulation of stimulus spacing during training and was beyond the scope of the current study.

Editor's note:

Should you choose to revise your manuscript, if you have not already done so, please include full statistical reporting including exact p-values wherever possible alongside the summary statistics (test statistic and df) and, where appropriate, 95% confidence intervals.

These should be reported for all key questions and not only when the p-value is less than 0.05 in the main manuscript.

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