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Institute of Neurosciences of Castilla y León

Sex, age, and etiology effects on auditory processing in two rat models of autism: evidence from auditory brainstem responses and contextual neural and behavioral measures

Sara Cacciato Salcedo

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Sara Cacciato Salcedo

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Supervised by

Prof. Manuel S. Malmierca, M.D., Ph. D.

Prof. Ana Belén Lao Rodríguez, Ph. D.

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LIST OF ABBREVIATIONS

Auditory brainstem response/s: ABR/ABRs

Auditory cortex: AC

Cascade: CAS

Cochlear nucleus complex: CNC

Correct rejections: CR

Deviant: DEV

Electroencephalography: EEG

False alarms: FA

Hits: HIT

Inferior Colliculus: IC

Inter-stimulus interval/s: ISI/ISIs

Medial geniculate body: MGB

Mismatch field: MMF

Mismatch negativity: MMN

Misses: MISS

Neuronal mismatch: nMM

N-methyl-D-aspartate: NMDA

Neonatal intensive care unit: NICU

Neuronal mismatch index: iMM

Nuclei of the lateral lemniscus: NLL

Postnatal day: PND

Prediction error index: iPE

Repetition suppression index: iRS

Standard: STD

Superior olivary complex: SOC

Typically developing: TD

Valproic acid: VPA

1. Introduction

1. 1. Distributed processing along the auditory pathway

The acoustic environment is rich, structured, and continuously changing, and this complexity is mirrored in the organization of the auditory system itself. To transform dynamic soundscapes into meaningful representations, auditory processing unfolds along a hierarchically organized and densely interconnected pathway that supports both precise sensory encoding and flexible integration over time (**Figure 1**).

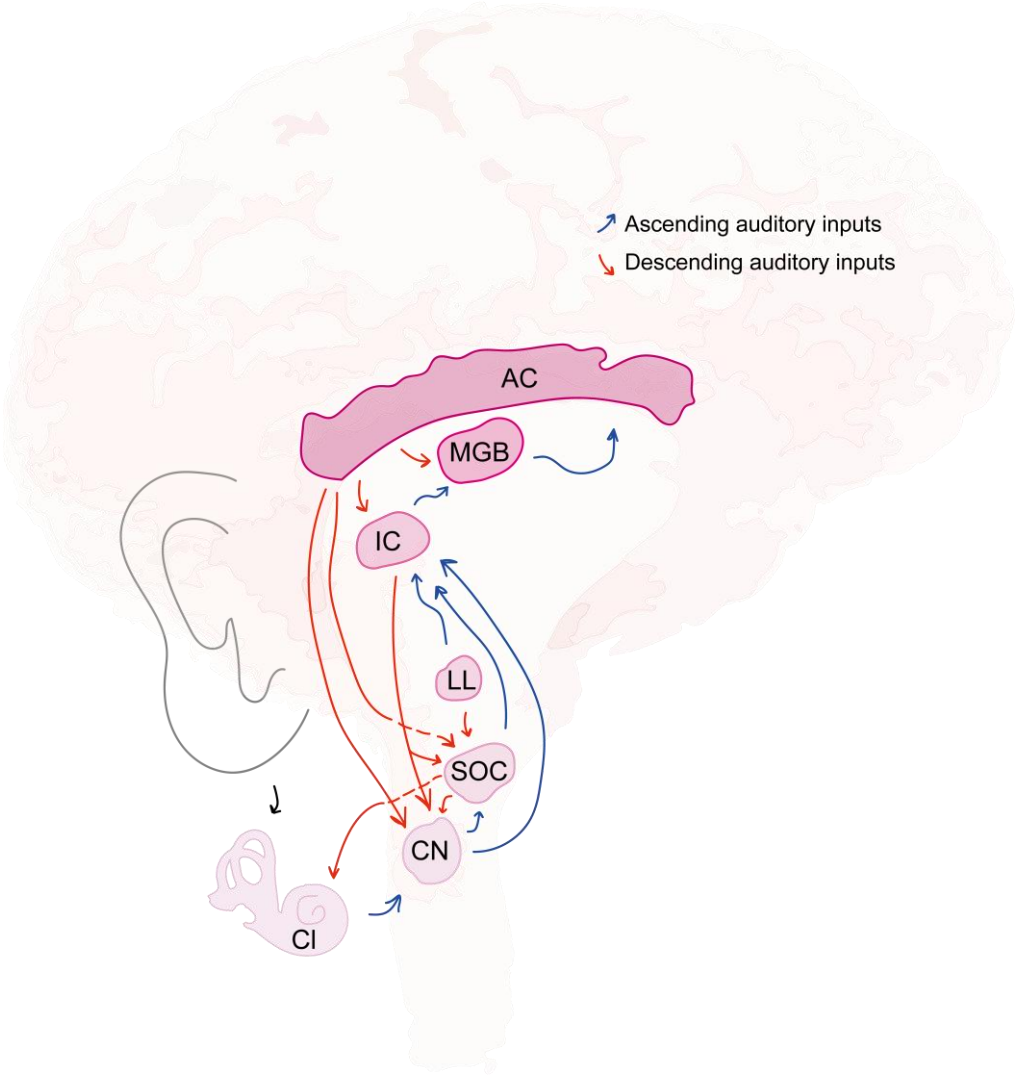


Figure 1. Ascending and descending auditory connectivity. This schematic illustrates the major ascending (blue) and descending (red) pathways of the auditory system. Ascending auditory information originates in the cochlea (CI) and is transmitted via the auditory nerve to the cochlear nucleus (CN). From the CN, parallel projections convey temporally and binaurally processed signals to the superior

olivary complex (SOC) and the nuclei of the lateral lemniscus (NLL), which relay this information to the inferior colliculus (IC). The IC serves as a central midbrain hub by integrating ascending inputs from all lower auditory brainstem nuclei and forwarding processed signals to the medial geniculate body (MGB) of the thalamus, which subsequently projects to the auditory cortex (AC). In parallel, descending auditory inputs originate primarily in the auditory cortex and project to the MGB and IC through cortico-thalamic and cortico-collicular pathways. Additional descending projections from the IC target the LL, SOC, and CN, providing modulatory feedback to earlier stages of the auditory pathway. Through these recurrent connections, auditory processing emerges from continuous interactions between ascending sensory signals and descending influences, rather than from a strictly feed-forward flow of information.

Auditory information enters the central nervous system via the auditory nerve and first synapses in the cochlear nucleus complex (CNC), which distributes parallel ascending pathways specialized for temporal, spectral, and binaural processing through the superior olivary complex (SOC) and nuclei of the lateral lemniscus (NLL) (Cant & Benson, 2003; Winer & Schreiner, 2005). These parallel streams converge in the inferior colliculus (IC), a major midbrain integrative hub that receives ascending input from nearly all lower auditory nuclei and integrates them with extensive descending projections, including dense corticofugal inputs from auditory cortex (AC) that differentially target its subdivisions (Malmierca et al., 2008; Winer, 2005).

Through this convergence, the IC plays a central role in integrating acoustic features across time and frequency and in shaping response properties based on recent stimulus history. From the IC, auditory signals are relayed to the medial geniculate body (MGB) of the thalamus, whose ventral, dorsal, and medial divisions differ in connectivity and functional specialization and participate in recurrent thalamo-cortical loops with primary and non-primary auditory cortical fields (Lee & Murray Sherman, 2010; Winer & Schreiner, 2005).

Importantly, the auditory pathway is therefore not strictly feed-forward: descending cortico-thalamic and cortico-collicular projections provide anatomical substrates through which contextual information and expectations can influence auditory processing at multiple hierarchical levels (Malmierca et al., 2019; Winer, 2005).

This hierarchical and recurrent architecture allows auditory processing to extend beyond moment-to-moment encoding by retaining information over short time scales and biasing responses based on recent input. As a result, neural activity reflects not only the immediate physical properties of sounds but also the broader statistical structure of acoustic sequences, laying the groundwork for the context-dependent auditory processing mechanisms described next.

1. 2. Processing auditory context in acoustic environments

Auditory environments are characterized by statistical regularities, yet they are continually punctuated by events that deviate from recent patterns. The auditory system exploits these regularities by extracting structure from ongoing sound streams and by signaling when incoming sounds violate established expectations (Garrido et al., 2009; Näätänen et al., 2001, 2011). In this thesis, we define *context* as the probabilistic structure of the auditory environment—namely, the repetition and stability of acoustic events that allow listeners to form predictions and flexibly adjust sensory processing (Barch & Ceaser, 2012; Javitt & Sweet, 2015).

The extraction of regularities and the detection of deviations rely largely on automatic, pre-attentive mechanisms that maintain short-lived representations of recent sensory input and continuously compare new events against these internal models (Näätänen et al., 2011, 2012). The ability of the auditory system to automatically filter out these predictable stimuli and highlight unique, unpredictable sounds is known as *deviance detection* (Escera & Malmierca, 2014; Grimm & Escera, 2012). In other words, deviance detection is a key process that arises from finely tuned internal mechanisms that can discriminate between familiar and novel sounds.

1.2. Autism and heterogeneous auditory features in sensitivity and complex acoustic scenes

In autism spectrum disorder, hereafter referred to as *autism*, recent accounts propose that internal representations of environmental regularities may diverge from typical representations, with

consequences for adaptive responses to unexpected events (**Figure 2**) (Kujala et al., 2013; Rapaport & Sowman, 2024).

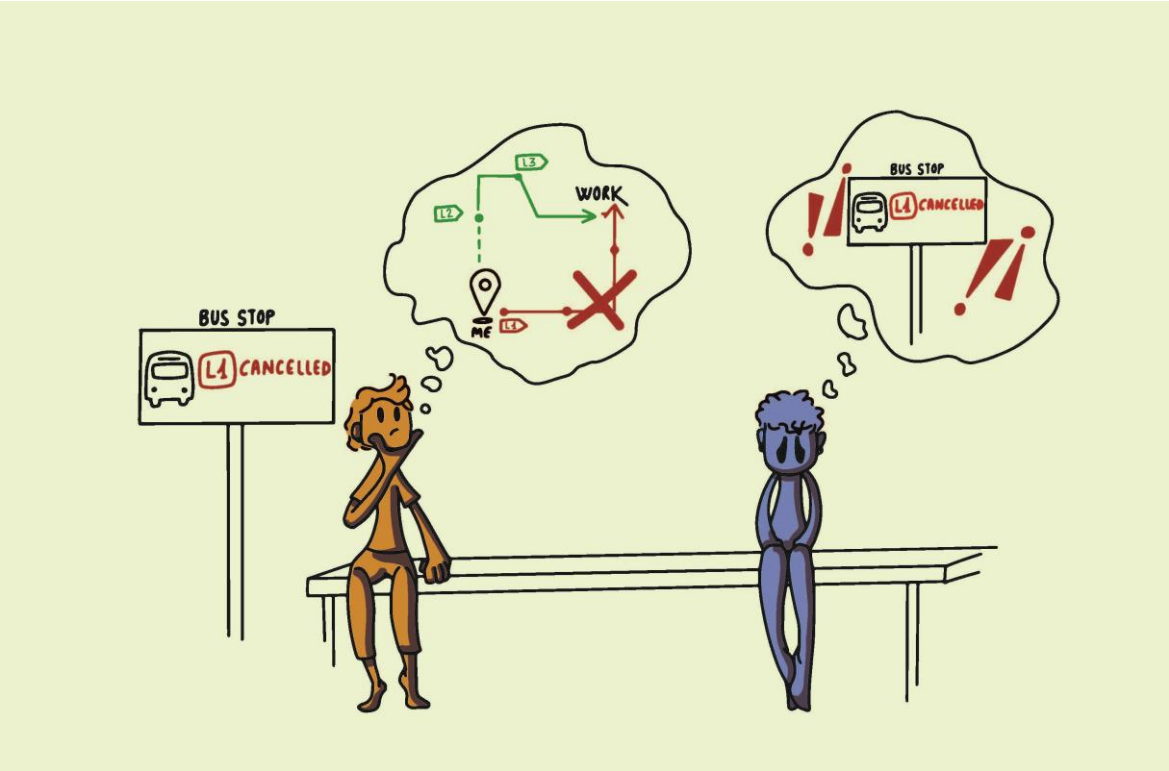


Figure 2. Illustration of context-dependent inference and prediction updating. This illustration depicts two individuals confronted with the same unexpected sensory event—a cancelled bus service—but engaging different internal processes in response. The external cue (bus stop sign indicating cancellation) is identical for both individuals; however, the left, typically developing individual generates an internal representation that integrates prior knowledge, alternative routes, and goal-directed planning, leading to flexible updating of expectations and the selection of a new action strategy. In contrast, the right, autistic individual focuses primarily on the salient unexpected event itself, with limited integration of contextual alternatives, resulting in a heightened response to the violation of expectation. The figure provides an intuitive analogy for how identical sensory inputs can give rise to divergent internal models and behavioral outcomes depending on how contextual information and predictions are formed and updated.

In both autistic and typically developing (TD) individuals, these mechanisms are not static; regularity formation and deviance detection continue to mature across development (Bishop et al., 2011; Millin et al., 2018; Sinha et al., 2014), yet it remains unclear whether and how these trajectories differ as a function of biological sex.

Autism is a neurodevelopmental condition characterized by differences in social communication and interaction, alongside restricted and repetitive patterns of behavior (American Psychiatric Association, 2022). Autistic individuals frequently report distinctive sensory experiences, and auditory perception contributes prominently to this heterogeneity (Gonçalves & Monteiro, 2023; Marco et al., 2011).

Within the auditory domain, studies describe marked variability in sensitivity and responsiveness. Reports span heightened sensitivity to specific sounds as well as reduced sensitivity depending on stimulus features and contextual demands (Glod et al., 2015; Gomes et al., 2008; Ha et al., 2015). Additional work documents challenges in complex acoustic environments that require filtering competing inputs and tracking targets over time, including scenes in which relevant sounds must be segregated from concurrent sources (Mansour & Kulesza, 2020; Smith et al., 2019).

Taken together, these observations motivate a mechanistic focus on how listeners use recent acoustic history to form stable expectations and detect departures from them. Auditory context processing—regularity formation and deviance detection under controlled stimulus statistics—therefore provides a tractable dimension for examining heterogeneity in autism without presupposing a single uniform direction of effect across listening contexts (Kujala et al., 2013; Orekhova & Stroganova, 2014).

1.3. Developmental stage and biological sex as structured moderators in autism

Developmental timing shapes auditory context processing because regularity formation and deviance detection continue to mature across childhood, adolescence, and adulthood, and trajectories depend on stimulus characteristics and paradigm context (Bishop et al., 2011; Gaeta et al., 1998; Lindín et al., 2013). In autism, deviance detection depends on stimulus context and varies across individuals and ages, so collapsing across broad age ranges can yield underconstrained interpretations (Chen et al., 2020; Gomot et al., 2006; Haesen et al., 2011; Kujala et al., 2013; Marco et al., 2011).

Biological sex adds a second, frequently under-modeled moderator. Epidemiological work reports that autism is diagnosed more often in males and shows that the male-to-female diagnosis ratio decreases

across development, from approximately 4:1 in childhood to about 2.6:1 in adulthood (Loomes et al., 2017). Diagnostic practices and phenotypic presentation likely contribute to under-recognition in females, and many datasets underrepresent autistic females, which constrains sex-dependent inference (Dean et al., 2017; Lai et al., 2015; Rippon, 2024). Independent of autism, physiological studies report sex-related differences in auditory timing and synchrony, which makes sex a plausible determinant of how auditory systems encode regularities and register deviations (Dehan & Jerger, 1990; Michalewski et al., 1980; Møller & Moore, 2000; Zakaria et al., 2019).

Accordingly, this thesis explicitly examined auditory context processing across developmental stages and biological sex, treating both as structured moderators of neurodevelopmental variation in autism.

1.4. Neural measures of auditory deviance detection

1.4.1. Mismatch negativity (MMN) as an operational index

Researchers most commonly assess neural detection of auditory change with mismatch negativity (MMN; **Figure 3**), an event-related potential recorded with electroencephalography (EEG). Mismatch negativity (MMN) is a component of the auditory event-related potential that reflects the brain's ability to detect changes in the auditory scene, that is, deviance detection. MMN can be elicited by any discriminable alteration in auditory input using a classical oddball paradigm, in which infrequent auditory stimuli (deviant, unpredictable; ~10% probability) are randomly interspersed within a sequence of regular stimuli (standard, predictable; ~90% probability) (Näätänen, 2018). The MMN amplitude reflects the magnitude of the neural difference between responses to standard and deviant tones and typically reaches its maximum between approximately 100 and 250 ms after stimulus onset.

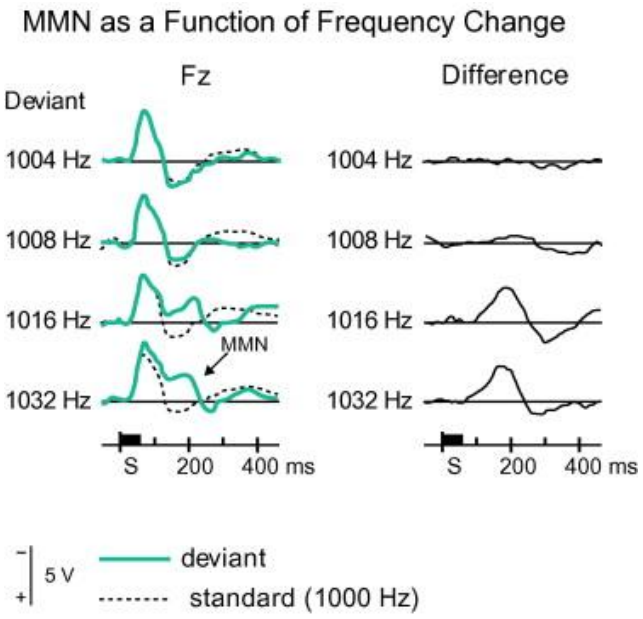


Figure 3. Frontal event-related potentials averaged across subjects in response to the standard tone (black dotted lines, 80% appearance, 1000Hz) and randomized deviant tones (green lines, 20% appearance of difference frequencies). Adapted from Näätänen et al., 2007.

Passive oddball paradigms elicit MMN by presenting infrequent deviants that violate a regularity established by repeated standards (Garrido et al., 2009; Näätänen et al., 2001, 2011). Because MMN does not require an overt response, it supports assessment of regularity formation and deviance detection under minimal task demands and reduces sensitivity to confounds linked to instruction comprehension, strategic responding, sustained attention, and response selection (Chen et al., 2020; Foss-Feig et al., 2012; Kujala et al., 2013).

In autism, MMN studies report heterogeneous findings, with amplitudes and latencies varying across stimulus classes, probability structures, timing, age ranges, and participant characteristics (Chen et al., 2020; Foss-Feig et al., 2012; Haesen et al., 2011; Schwartz et al., 2018).

1.4.2. MMN under typical development and autism

Across typical development, mismatch responses changed from childhood through adolescence, but reported age-related trajectories in MMN amplitude and latency remained heterogeneous and strongly dependent on stimulus context and task design (Bishop et al., 2011; Gaeta et al., 1998; Lindín et al.,

2013)(Bishop et al., 2011; Gaeta et al., 1998; Lindín et al., 2013). Some paradigms showed increasing or decreasing amplitudes with age, whereas others showed minimal change, which supported the view that auditory regularity representations and change detection mature over a prolonged period rather than following a single uniform trajectory (Bishop et al., 2011; Lindín et al., 2013).

In autism, developmental patterns appeared even more variable, with age-related changes in mismatch responses diverging across studies rather than converging on a consistent direction. In childhood, several studies reported reduced MMN amplitudes relative to TD peers, whereas others reported comparable or enhanced responses, which suggested that differences in stimulus context modulated how regularity violations were expressed in neural responses (Abdeltawwab & Baz, 2015; Čeponiene et al., 2004; Ferri et al., 2018; Gomot et al., 2011; Vlaskamp et al., 2017). Evidence from adolescent and adult samples further indicated that group differences could attenuate or persist depending on paradigm characteristics, which was consistent with divergent developmental trajectories rather than a uniform delay (da Silva Mayerle et al., 2023; Fan & Cheng, 2014; Hudac et al., 2018; Kujala et al., 2005; Lassen et al., 2022).

Latency findings were similarly heterogeneous across development, with studies reporting both earlier and prolonged mismatch timing depending on age and paradigm, and speech-based and magnetoencephalography studies further showing that timing differences varied across samples rather than appearing consistently across autistic cohorts (Berman et al., 2016; Gomot et al., 2002; Green et al., 2020; Matsuzaki et al., 2019; Roberts et al., 2011).

Together, these findings motivated developmentally informed approaches that treat stimulus context as a central determinant of age-related variation in mismatch amplitude and latency. Within this framework, classic cognitive interpretations of the MMN and more recent theoretical accounts offer complementary perspectives that can help explain how developmental stage and stimulus context shape the expression of mismatch responses across paradigms and populations.

1.4.3. Classic cognitive interpretations of the MMN

Several accounts have been proposed to explain how the auditory system generated mismatch responses, and these frameworks helped interpret why MMN amplitude and latency varied across paradigms, developmental stages, and clinical cohorts. Two influential perspectives included the adaptation hypothesis and the model-adjustment or memory-trace hypothesis, which emphasized physiological and cognitive mechanisms, respectively (May & Tiitinen, 2010; Winkler, 2007).

Importantly, the memory-trace account emerged largely from human electrophysiological work, whereas adaptation-based explanations were strongly informed by animal neurophysiology, where stimulus-specific adaptation could be directly measured (May & Tiitinen, 2010; Näätänen & Michie, 1979; Winkler, 2007).

The *adaptation hypothesis* attributed mismatch-like effects to stimulus-specific adaptation, whereby repeated standards reduced neural responsiveness in auditory cortex through passive mechanisms such as synaptic depression, while neural populations tuned to the deviant remained relatively less adapted and therefore responded more strongly when the deviant occurred (Fishman, 2014; Jääskeläinen et al., 2004; May et al., 1999; May & Tiitinen, 2010; Ulanovsky et al., 2003). This account predicted that mismatch magnitude and timing would depend on stimulus statistics and repetition structure, because these factors controlled the strength and selectivity of adaptation to the standard (May and Tiitinen, 2010; Fishman, 2014). In contrast, the *model-adjustment* or *memory-trace hypothesis* proposed that repetition of the standard established a short-lived sensory representation, supported primarily by auditory cortical generators, and that mismatch activity reflected a discrepancy between this representation and incoming input (Näätänen & Michie, 1979; Nyman et al., 1990; Winkler, 2007; Winkler et al., 1996). This framework predicted heightened sensitivity to factors that altered the stability or updating of regularity representations, including task demands, stimulus complexity, and individual profiles (Winkler, 2007).

Together, these perspectives offered complementary routes to heterogeneity: adaptation-weighted accounts predicted variability when paradigms differed in repetition and spectral overlap, whereas memory-trace accounts predicted variability when paradigms differed in the strength of regularity formation and maintenance (May & Tiitinen, 2010; Winkler, 2007). This distinction was particularly relevant for autism, because divergent developmental trajectories could reflect shifts in how strongly repetition-based adaptation versus regularity-based representations shaped mismatch responses, yielding reductions, enhancements, or null effects across studies depending on stimulus statistics and cohort characteristics.

At the same time, several empirical properties motivated a broader theoretical approach. MMN emerged under passive listening and without conscious awareness, and it could reflect violations of complex regularities, which supported automatic inference mechanisms beyond attention-dependent model updating (Winkler, 2007). In addition, stimulus-specific adaptation and mismatch-related activity have been observed across multiple stages of the auditory pathway, including subcortical levels, which suggested distributed contributions that were not captured by a single cortical mechanism alone (Koelsch, 2014; Malmierca et al., 2019). In autism, this broader view aligned with non-uniform age- and context-dependent findings in mismatch amplitude and latency, suggesting that variability could arise from changes in the relative weighting of sensory input and contextual regularities. This background motivated the use of *predictive coding* as a unifying framework.

1.4.4. Predictive coding: The unifying theory

Predictive coding frames perception as inference in which neural systems form expectations from environmental regularities and update those expectations when input deviates from what the system predicts (**Figure 4**) (Friston, 2005; Garrido et al., a2009).

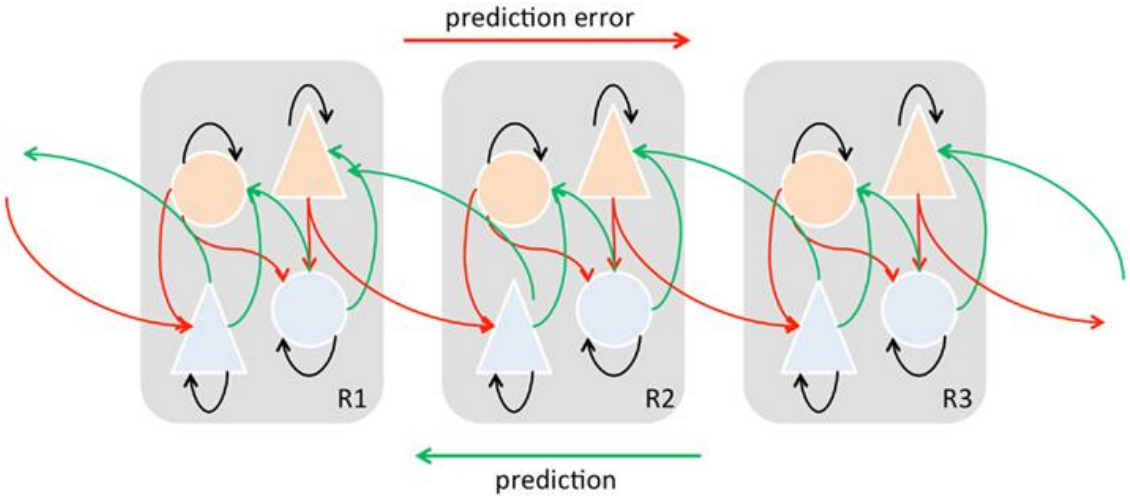


Figure 4. Schematic illustration of hierarchical predictive coding across three cortical regions, with the lowest level (R1) shown on the left and the highest level (R3) on the right. Light blue units denote state units, and orange units denote prediction-error units. Predictions and prediction-error signals are exchanged bidirectionally between hierarchical levels. Feed-forward prediction-error signals originate predominantly in superficial layers and terminate in deep (infragranular) layers, whereas feedback predictions originate in deep layers, project to superficial layers, and are commonly associated with beta-band oscillatory activity. Adapted from Seth et al. (2012).

Within this framework, mismatch responses were commonly interpreted as bottom-up prediction error signals elicited when established regularities were violated, whereas predictable input evoked reduced responses in part because it conveyed less information for updating internal models. Once models updated, top-down predictions propagated through the auditory hierarchy to suppress responses to expected stimuli and to shape neural sensitivity to future deviations, thereby linking repetition-related attenuation and deviance-related enhancement within a single computational scheme (Garrido et al., 2009; Näätänen et al., 2012).

Predictive coding is among the most influential contemporary frameworks of neural function, in part because it reframes perception and cognition as inferential processes rather than purely feed-forward transformations (Heilbron & Chait, 2018). Empirical support for this framework has emerged prominently from studies of stimulus-specific adaptation reported across multiple stages of the auditory pathway, including subcortical and cortical structures (Casado-Román et al., 2020; Parras et al., 2017; Sánchez et al., 2025). These studies introduced a methodological shift in the investigation of

deviance detection by explicitly separating neuronal responses into repetition-related and deviance-related components using no-repetition control sequences originally developed in the MMN literature (Jacobsen et al., 2003; Jacobsen & Schröger, 2001; Schröger & Wolff, 1996). Within this framework, the response difference between deviant and standard stimuli is conceptualized as neuronal mismatch (nMM), providing a more mechanistic description of how contextual regularities and violations are represented at the single-neuron level (**Figure 5**).

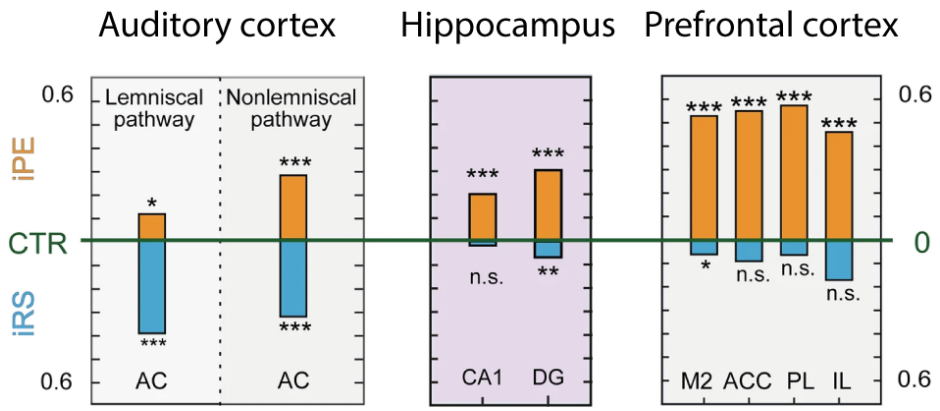


Figure 5. Median iPE (orange) and iRS (cyan) values for each AC, PFC or hippocampus subdivision recorded, referenced against the baseline set by the CTR. Here, iPE is plotted as positive in the upward direction, while iRS is plotted as positive in the downward direction. AC, Hippocampus, and PFC data originates from Parras et al. (2017), Sánchez et al. (2025), and Casado-Román et al. (2020), respectively.

Crucially, predictive coding accommodated contributions from multiple processing stages, allowing both cortical and subcortical responses to reflect interactions between sensory evidence and contextual expectations. In autism, this framework provided a principled way to interpret heterogeneous findings by proposing that developmental and individual differences could alter the balance or precision of predictions and sensory signals, leading to context-, age-, and possibly sex-, dependent variability in mismatch amplitude and latency rather than uniform shifts across paradigms.

1.5. The inferior colliculus as an integrative hub

Animal models enable localization and mechanistic decomposition of mismatch computations along the auditory hierarchy because they allow direct measurement of stimulus-locked neuronal activity

under tightly controlled stimulus statistics (Garrido et al., 2009; Näätänen et al., 2012). Within the ascending auditory pathway, the IC serves as a major midbrain integration stage. It receives convergent ascending input from lower brainstem nuclei, positioning it as a candidate site for early mismatch-related computation (Møller & Moore, 2000; Moore & Kitzes, 1985). Subcortical studies show frequency deviance sensitivity and discrimination-relevant responses in the IC, supporting the view that mismatch-like deviance sensitivity is not restricted to cortical circuits (Ayala et al., 2013).

Finally, IC subdivision supports mechanistic specificity. We defined the central nucleus of the inferior colliculus as the lemniscal region that primarily relays ascending, frequency-specific auditory input. In contrast, we refer to the rostral, lateral, and dorsal cortices of the IC as a non-lemniscal regions that integrate ascending input with descending corticofugal and contextual signals, supporting modulatory and predictive influences on auditory processing (Ayala et al., 2013, 2016; Duque et al., 2012, 2016; Parras et al., 2017).

Here, the term “non-classical auditory pathways,” as commonly used in the literature, refers to non-lemniscal auditory pathways, which have been proposed to contribute to the neurobiology of autism (Møller et al., 2005). This evolutionarily conserved system projects not only to auditory structures but also to limbic, paralimbic, and autonomic regions, influencing arousal regulation, emotional salience, and multisensory integration (Bartlett et al., 2000; Ibrahim et al., 2023; Lee, 2015; Lee & Murray Sherman, 2010; Macias & Llano, 2023). During typical development, the influence of this pathway diminishes as cortical hierarchies mature, and top-down control strengthens (Moller & Rollins, 2002). In autism, however, the non-lemniscal system may remain hyperactive or developmentally delayed, contributing to increased sensory gain, heightened emotional reactivity, and impaired filtering of irrelevant stimuli (Møller et al., 2005).

Consistent with corticofugal modulation of midbrain processing, some autism-related models show cortical dysmorphology alongside reduced cortico-collicular projections, identifying an anatomical

route through which neurodevelopmental variation may influence IC context computations (Kosmer & Kulesza, 2024).

1.6. Etiological axes in animal models of autism: prenatal valproic acid exposure and *Grin2b*+/− genetic variation

1.6.1. Environmental model: prenatal valproic acid exposure

Prenatal exposure to valproic acid (VPA), an antiepileptic and mood-stabilizing compound, provides a widely used environmental-exposure model for studying autism-related phenotypes. Epidemiological studies link prenatal VPA exposure to increased likelihood of autism-related outcomes, with estimates varying across ascertainment and definitions (Christensen et al., 2013). In rodents, prenatal VPA exposure induces neurodevelopmental phenotypes commonly used to model autism-relevant features and enables mechanistic testing under controlled developmental and sensory conditions (Chaliha et al., 2020; Chomiak et al., 2013; Nicolini & Fahnestock, 2018).

VPA models are relevant for auditory neurobiology because studies report anatomical differences along the auditory pathway, including differences in cytoarchitecture and neuronal density in brainstem and midbrain nuclei (Lukose et al., 2011; Mansour et al., 2021; Zimmerman et al., 2020). Physiological work also reports auditory brainstem response (ABR) latency prolongations and amplitude reductions consistent with differences in subcortical timing and synchrony (Arjun S. Malhotra & Kulesza, 2023).

1.6.2. Genetic model: the *Grin2b*+/− rat model and NMDA-receptor mechanisms

Human sequencing studies implicate rare de novo variants in synaptic genes in sporadic autism, including variants in GRIN2B, which encodes the GluN2B subunit of the N-methyl-D-aspartate (NMDA) receptor (Hu et al., 2016; O'Roak et al., 2011; Pan et al., 2015; Yoo et al., 2012). NMDA receptors support synaptic integration, temporal coordination, and experience-dependent plasticity, which plausibly shapes auditory predictive processing by influencing how systems form and update regularity representations under probabilistic structure (Garrido et al., 2009; Wang, 2010).

In this thesis, we model this genetic axis with heterozygous *Grin2b* deletion rats (*Grin2b*+/−), which reduce *Grin2b* gene dosage under a defined genetic manipulation and provide a mechanistically targeted contrast to prenatal exposure models (Brigman et al., 2010; Lee et al., 2024). Because *Grin2b*+/– auditory pathway structure and function remain undercharacterized, this model provides a targeted way to test whether NMDA-relevant genetic variation shifts subcortical timing and mismatch computations under matched stimulus statistics, alongside the VPA exposure model.

1.7. Translational bridges: ABRs and behavioral use of regularities under NMDA antagonism

ABRs provide a translational index of subcortical auditory processing. ABRs measure a sequence of time-locked deflections generated by synchronous activity along the auditory nerve and brainstem nuclei, with contributions extending to midbrain generators; latency and amplitude index conduction timing and neural synchrony (Jewett & Williston, 1971; Møller & Moore, 2000; Young et al., 2023). In autism, developmental studies frequently report longer latencies and smaller amplitudes, and a meta-analysis supports the view that latency differences appear robust during development but attenuate with age, highlighting developmental timing as a key moderator (Fujihira et al., 2021; Miron et al., 2018; Talge et al., 2018). ABR measures also vary by sex in neurotypical samples, with females often showing shorter latencies and larger amplitudes than males (Dehan & Jerger, 1990; Michalewski et al., 1980; Zakaria et al., 2019).

In VPA-exposed animals, studies report anatomical differences along the auditory pathway (Lukose et al., 2011; Mansour et al., 2021; Zimmerman et al., 2020) and ABR latency prolongations and amplitude reductions consistent with differences in subcortical synchrony (Arjun S. Malhotra & Kulesza, 2023).

ABRs index subcortical timing and synchrony, whereas operant paradigms quantify how animals use auditory regularities to guide action under controlled contingencies. Schizophrenia research provides convergent mechanistic evidence for NMDA-dependent context processing by linking disrupted contextual processing to NMDA receptor hypofunction and showing that NMDA receptor antagonism

alters mismatch-like responses (Javitt & Sweet, 2015; Sullivan et al., 2015; Vohs et al., 2012). NMDA-receptor signaling also provides mechanistic leverage on behavioral use of regularities, and this axis complements the genetic model because GRIN2B encodes an NMDA-receptor subunit implicated in autism-related phenotypes (Hu et al., 2016; Wang, 2010). Operant oddball discrimination tasks operationalize context as probabilistic structure with consequences for action selection: animals learn to suppress responses to frequent standards and selectively respond to rare deviants when deviants predict reinforcement (Barch & Ceaser, 2012; Javitt & Sweet, 2015; Quintela-Vega et al., 2023). In rodents, systemic administration of MK-801 (dizocilpine), a high-affinity non-competitive NMDA receptor antagonist, induces acute NMDA receptor hypofunction and modifies mismatch-like activity and behavioral use of regularities, supporting causal inference about NMDA-dependent contributions to how animals use auditory regularities for action (Quintela-Vega et al., 2023; Sullivan et al., 2015; Vohs et al., 2012).

2. Hypothesis

Auditory context processing depends on extracting probabilistic regularities and registering violations of established patterns (Garrido et al., 2009; Näätänen et al., 2001, 2011). In autism, auditory responses and mismatch measures vary substantially across individuals and developmental stages, and this variability has been linked to biological sex, stimulus class, and paradigm characteristics rather than reflecting random inconsistency across studies (Chen et al., 2020; Foss-Feig et al., 2012; Gomot et al., 2006; Haesen et al., 2011; Loomes et al., 2017; Kujala et al., 2013; Orekhova & Stroganova, 2014; Rippon, 2024). Environmental and genetic animal models provide etiological leverage to examine how such variability emerges from differences in neurodevelopmental timing and circuit-level computation, with VPA and Grin2b+/− models enabling assessment of subcortical auditory timing and neuron-level context sensitivity, and the MK-801 model isolating behavioral use of auditory regularities (Christensen et al., 2013; Hu et al., 2016; Miron et al., 2018; Quintela-Vega et al., 2023).

Based on this framework, we hypothesized that auditory processing would vary systematically as a function of **etiology, biological sex, and developmental stage**, rather than showing uniform alterations across models or ages. We further hypothesized that such variation would manifest differently across levels of analysis, reflecting partially dissociable contributions of early sensory encoding, midbrain context computation, and behavioral exploitation of auditory regularities.

At the brainstem level, we hypothesized that auditory brainstem response timing would differ across etiological models and developmental stages, consistent with altered maturation of subcortical auditory encoding that could constrain downstream context processing. At the neuronal level, we hypothesized that single-unit activity in the inferior colliculus would show sex- and age-dependent differences in mismatch-related components under contextual sound paradigms, reflecting differential engagement of repetition-related and deviance-related processes in autism-relevant models. At the behavioral level, we hypothesized that performance under an oddball operant task would differ across models, indicating

distinct strategies for using auditory regularities rather than a uniform reduction in sensitivity to contextual structure.

Finally, we hypothesized that these effects would not align uniformly across brainstem, neuronal, and behavioral measures, but would instead reveal coordinated yet non-identical profiles across levels of the auditory hierarchy, supporting the interpretation that autism-related auditory variability reflects structured interactions among development, sex, and etiology rather than a single disrupted mechanism.

3. Objectives

Objective 1. To characterize subcortical auditory timing and synchrony using ABRs across developmental stage and biological sex in the environmental (prenatal VPA exposure) and genetic (*Grin2b*+/−) models of autism.

Objective 2. To investigate neuronal mechanisms of auditory context processing in the inferior colliculus by quantifying single-unit mismatch-related responses under controlled stimulus statistics across developmental stage (prepuberty and adulthood), biological sex (female and male), and etiological model (prenatal VPA exposure and *Grin2b*+/−).

Objective 3. To assess how animals use auditory regularities to guide behavior by quantifying discrimination performance in probabilistic auditory paradigms across MK-801 injected female adult rats.

4. Material and methods

4.1. Animals, ethics, and models

We conducted all experiments at the University of Salamanca in compliance with European and Spanish animal-research regulations (86/609/EEC, 2003/65/EC, 2010/63/EU; RD 53/2013) with approval from the University of Salamanca Bioethics Committee (USAL-ID-574, USAL-ID-1193, USAL-ID-195). We housed Long–Evans rats in pairs or trios under a 12 h light/dark cycle with ad libitum food and water, except during behavioral testing, when we maintained body weight at 90–95% of baseline. We defined prepubertal and young adult stages as PND 30–45 and PND 65–120, respectively (Sengupta, 2013).

We studied three etiological conditions: TD controls, prenatal VPA exposure, and heterozygous *Grin2b* deletion (*Grin2b*+/–). For VPA, we confirmed gestational day 0 by vaginal cytology, administered sodium valproate (400 mg/kg, i.*p*.) on gestational day 12.5, weaned offspring on PND 21–23, and selected VPA-exposed animals showing mild tail malformations. For *Grin2b*+/–, we bred *Grin2b*+/– males (Long-Evans-*Grin2b*em1Mcwi) with wild-type females and confirmed genotype by PCR using the supplier protocol. We combined purchased and in-house control animals, including prenatal saline controls and wild-type littermates from the *Grin2b*+/– line, verified that control source did not affect primary electrophysiological measures, and pooled controls within sex- and age-matched strata (**Figure 6**).

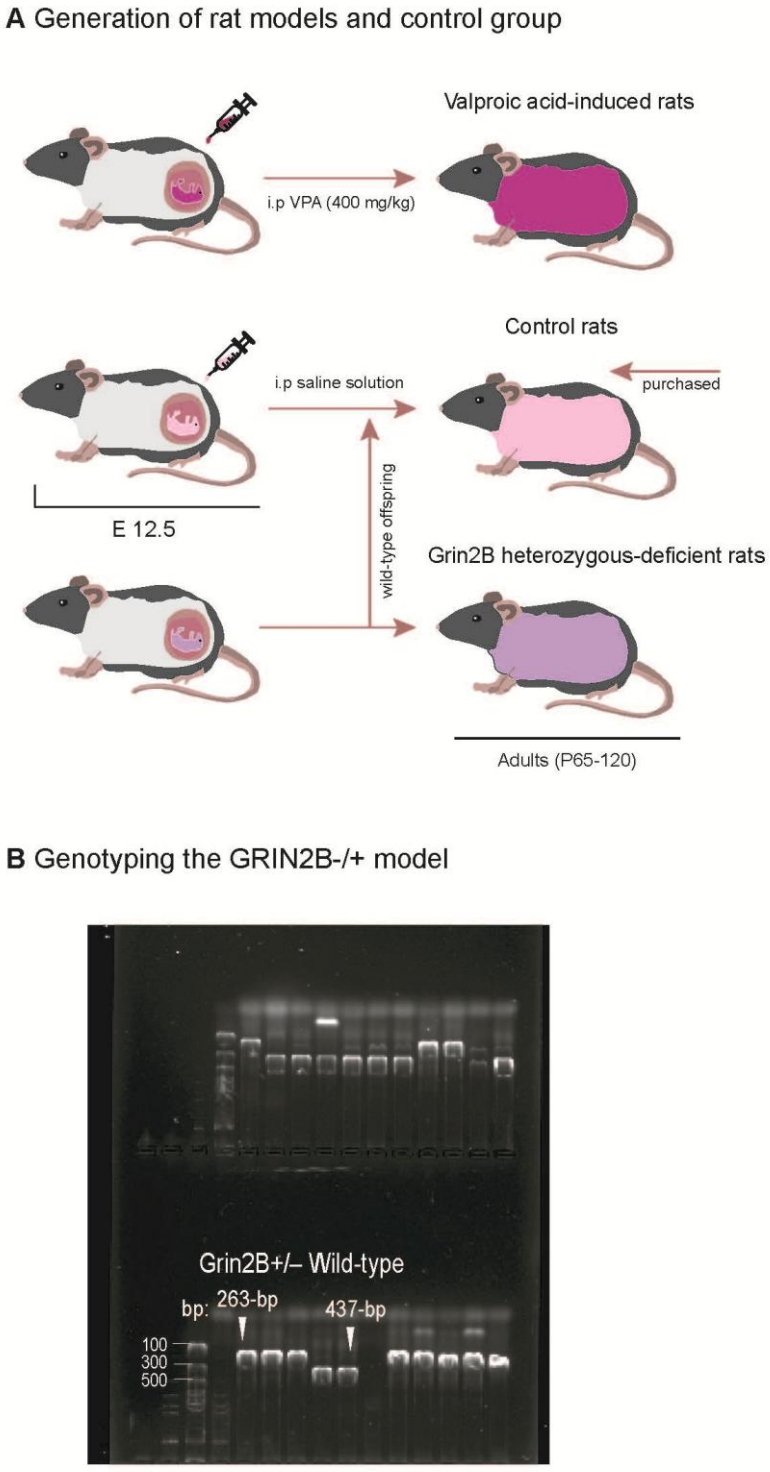


Figure 6. Rat model generation. A illustrates the generation of rat models. Valproic acid (VPA)–exposed rats were produced by administering an intraperitoneal injection of 400 mg/kg VPA on gestational day 12.5. *Grin2b*+/– heterozygous-deficient rats were generated by breeding wild-type females with *Grin2b*+/– males. The control cohort consisted of (i) adult animals purchased for the study, (ii) wild-type offspring from *Grin2b*+/– offspring, and (iii) pups prenatally injected with saline to control for injection-associated stress. We recorded from female and male rats at adult stages (P65–120) to assess sex- and model-dependent effects. **B** displays

polymerase chain reaction genotyping results on agarose gel, confirming the presence of wild-type and *Grin2b*+/– alleles in the heterozygous-deficient model.

We aligned three experimental arms: ABRs (subcortical timing/synchrony), IC single-unit recordings (neuronal context processing), and behavioral testing under NMDA receptor antagonism (adult female rats only).

4.2. Auditory brainstem responses (ABRs)

We recorded ABRs in an acoustically insulated, electrically shielded chamber using subdermal electrodes and monaural right-ear clicks delivered through a closed-field earphone (**Figure 7**).

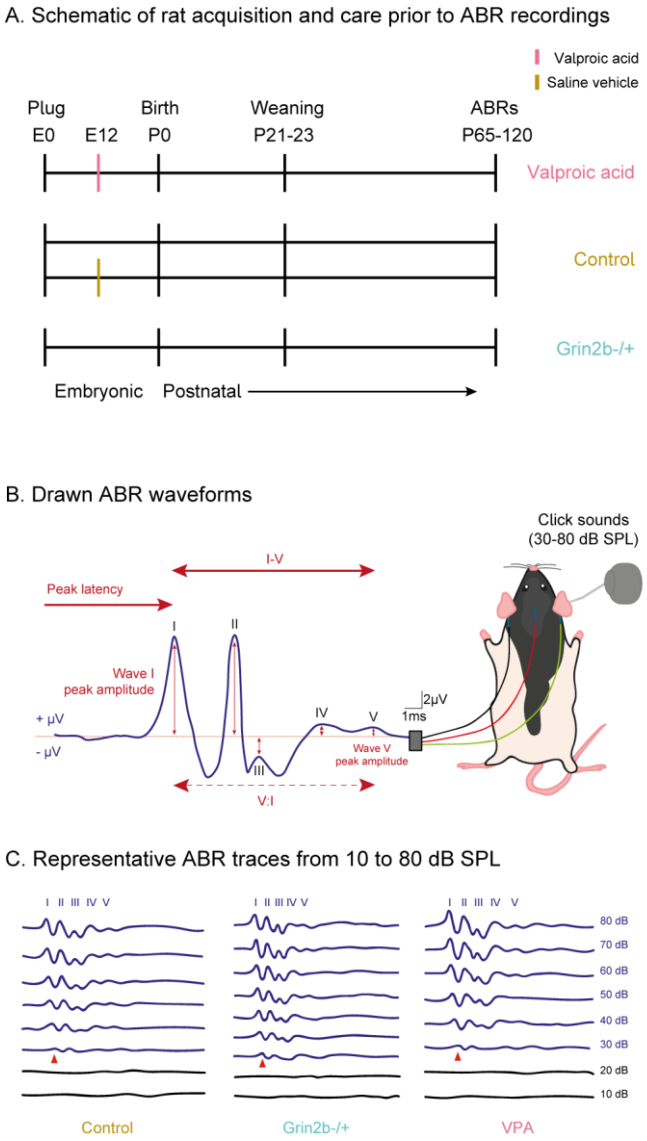


Figure 7. Experimental design. This figure summarizes the experimental framework and key methodological components. **A** illustrates the schematic of rat acquisition and care prior to ABR recordings. Pregnant dams received a prenatal injection of either valproic acid (VPA; pink line) or saline (yellow line), corresponding to the VPA-exposed and control groups, respectively. The timeline displays the six experimental groups used in the study: VPA-exposed (female, male), GRIN2B-/+ (female, male), and control (female, male), listed in descending order. **B** presents drawn ABR waveforms (I–V) with illustrative markers for computed examples. Responses were acquired monaurally using subdermal electrodes: the active electrode was placed below the right ear, the reference between the ears, and the ground below the left ear, maintaining impedance at or below 1 kΩ. We extracted peak amplitudes and latencies for all waves, calculated inter-peak latencies (I–III, I–V, III–V), and derived amplitude ratios (III:I, V:I, V:III). The orange dotted line indicates the baseline computed by the software. **C** shows representative ABR traces across stimulus intensities (10–80 dB SPL), with an auditory threshold identified at 30 dB SPL.

In electrophysiology cohorts, we anesthetized animals with urethane and maintained temperature at 37 ± 1°C. We presented 0.1 ms clicks at 21/s in 10 dB steps across the tested intensity range, averaged responses across repeated presentations per level, acquired responses with Tucker-Davis Technologies hardware/software, band-pass filtered traces (100–3000 Hz), and rejected artifacts.

In the behavioral cohort, we recorded ABRs under ketamine/dexmedetomidine anesthesia before and after drug manipulation, reversed anesthesia with atipamezole, and used the same click parameters. Thresholds remained stable and did not differ between saline and MK-801 conditions. We defined threshold as the lowest intensity that evoked a recognizable Waveform. A trained rater marked Waveform peaks according to standard rat ABR conventions. In **Papers 3 and 4**, we extracted baseline-to-peak (hereafter, peak) amplitudes relative to a short pre-stimulus baseline and, where applicable, evaluated effects of sex, age, and etiology using Sidak-corrected *t*-tests in **Paper 3** and Tukey–Kramer (HSD) post hoc comparisons in **Paper 4**.

4.3. Inferior colliculus single-unit recordings

We induced deep anesthesia with urethane (and supplemented as needed), confirmed hearing with ABRs, maintained temperature at 37 ± 1°C, monitored respiration, and stabilized the head in a stereotaxic frame. We performed a craniotomy over the left IC, removed the dura, and protected the surface with agar.

We recorded extracellular single-unit activity using high-impedance microelectrodes in a sound-insulated, electrically shielded chamber. We generated pure-tone stimuli with a programmable sound system and delivered them monaurally through a calibrated closed-field earphone. We digitized and filtered signals for spike detection and accepted single units when Waveforms remained stable and clearly isolated.

Searching for evoked auditory neuronal responses from the IC, white noise bursts and sinusoidal pure tones of 75 ms duration with 5 ms rise–fall ramps were presented while varying stimuli parameters manually to prevent frequency-specific adaptation. The stimulation protocol to obtain the frequency response area consisted of a sequence of sinusoidal pure tones ranging between 0.7 and 44 kHz, 75 ms of duration with 5 ms rise–fall ramps, presented at a 4 Hz rate, randomly varying frequency and intensity (3–5 repetitions of all tones). For each neuron, we mapped the frequency response area and selected 10 tones spaced by 0.5 octaves (typically 10–20 dB above threshold) for contextual sequences. We presented (i) oddball sequences (STD 90%, DEV 10%) and (ii) cascade control sequences (CAS: ordered ascending/descending scales without immediate repetition), and we matched sequences for stimulation rate and deviant probability. We presented sequences at fixed intensity and, when unit stability permitted, at additional intensities. In oddball sequences, we required ≥3 STDs before each DEV and analyzed the last STD preceding each DEV.

We quantified responses as a peri-stimulus histogram representing a histogram of action potential density over time (in action potentials per second, or Hz) from −75 to 250 ms around stimulus onset, using the 40 trials available for each tone and condition. Every peri-stimulus histogram was smoothed with a 6 ms gaussian kernel (“ksdensity” function in Matlab) in 1 ms steps to estimate the spike-density function over time, and the baseline spontaneous firing rate was determined as the average firing rate (in Hz) during the 75 ms preceding stimulus onset. We retained unit–frequency combinations only

when at least one condition evoked significant activity (Monte Carlo test against Poisson spike trains matched to baseline firing).

We treated the index of neuronal mismatch (iMM) as a cellular-level analogue of MMN by quantifying stimulus-locked spiking under contexts that differ in predictability and repetition history (Malmierca et al., 2009; Parras et al., 2017; Ulanovsky et al., 2003). Because control choice critically shapes mismatch interpretation (Ruhnau et al., 2012), studies increasingly incorporate predictable controls in rodents (Harms et al., 2014). In our implementation, oddball sequences contrast DEV and STD events, whereas cascade control sequences provide a predictable, ordered context in which tones appear in ascending or descending series without immediate repetitions (Cacciato-Salcedo et al., 2025). Within the predictive coding framework, this design minimized confounds from immediate stimulus repetition and enabled dissociation of *repetition suppression* (CAS–STD) from deviance-related, or *prediction error*, signaling (DEV–CAS), allowing interpretation beyond the DEV–STD contrast alone that is typically captured by the MMN (Garrido et al., 2009; Harms et al., 2014; Näätänen et al., 2012; Ruhnau et al., 2012) (**Figure 8**).

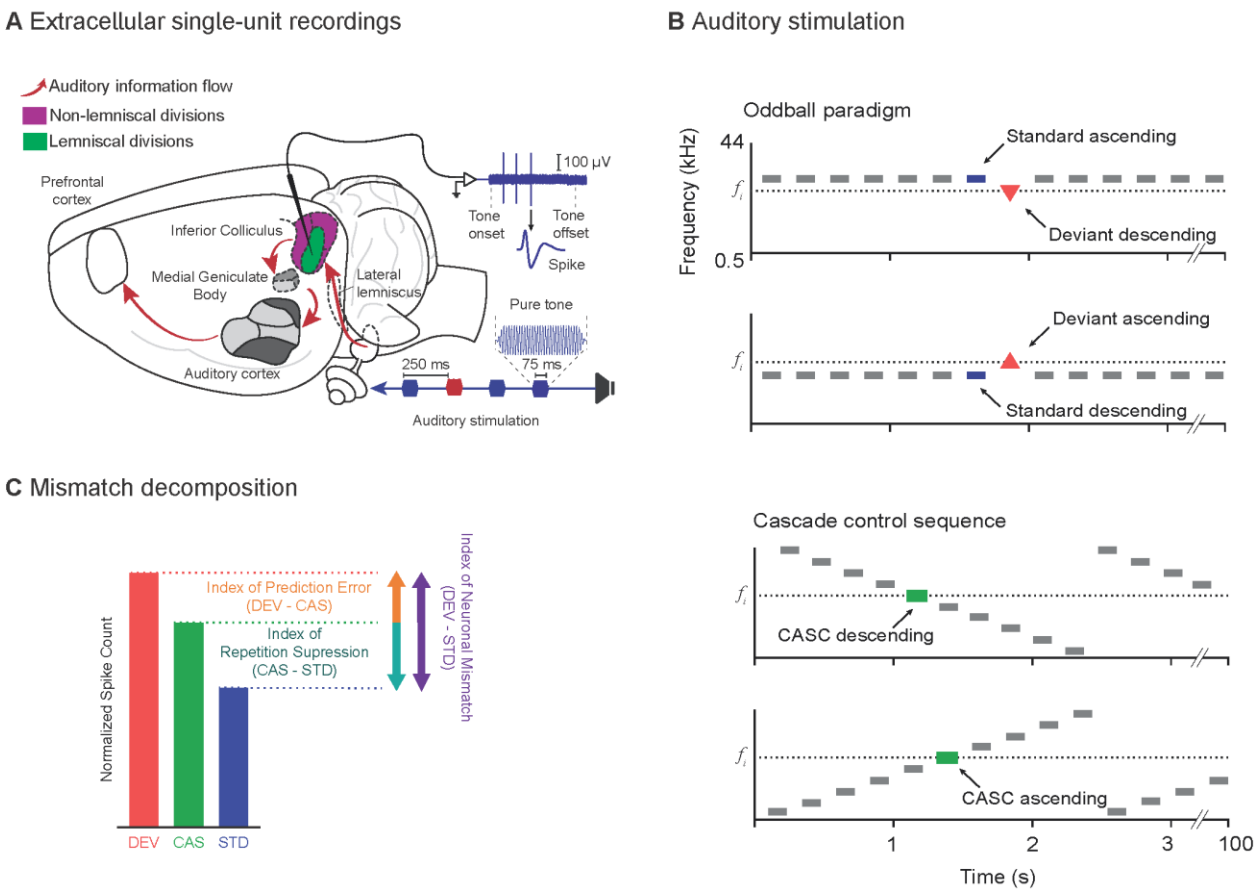


Figure 8. Methodology and experimental design. A Schematic of extracellular single-unit recordings in the lemniscal (green) and non-lemniscal (purple) regions of the IC in response to pure-tone auditory stimulation (red and blue). **B** Pure-tone stimulation sequences included ascending and descending versions of the classical oddball paradigm and cascade control sequences, which elicited deviant (DEV; red), cascade (CAS; green), and standard (STD; blue) responses. **C** These stimuli conditions were decomposed to compute predictive processing components: neuronal mismatch (iMM = DEV – STD), repetition suppression (iRS = CAS – STD), and prediction error (iPE = DEV – CAS). Neuronal mismatch was also obtained by summing iRS and iPE. Neuronal mismatch was also obtained by summing iRS and iPE.

To compare neurons with different firing scales, we normalized DEV/STD/CAS responses by the Euclidean norm $N = \sqrt{(DEV^2 + STD^2 + CAS^2)}$ and computed the predictive components: iMM = DEV_N − STD_N, iRS = CAS_N − STD_N, and iPE = DEV_N − CAS_N. We assessed age, sex, and etiological differences, when possible, between these predictive indices. For this purpose, we performed such comparisons with two distinct statistical approaches. We tested pairwise Wilcoxon rank-sum comparisons in **Paper 1** to assess group differences directly from the observed data. In **Paper**

2, we used hierarchical generalized linear mixed-effects models and performed inference on estimated marginal means using planned contrasts, allowing us to account explicitly for the nested structure of the data and to test model-based effects (McCulloch et al., 2008; Stroup et al., 2024).

Then, we verified recording sites histologically using electrolytic marking and Nissl staining and assigned sites to IC subdivisions using atlas ladnmarks.

4.4. Behavioral assessment under NMDA receptor antagonism

We assessed behavioral use of auditory regularities in a go/no-go operant task after MK-801 (0.1 mg/kg, s.c.) or saline in adult female rats. Rats progressed through shaping to oddball training, in which deviants (10%) occurred among standards (90%); we rewarded hits and penalized false alarms with timeouts. During testing, we varied the inter-stimulus interval (1.0, 1.5, 2.0 s) while holding tone duration and rise/fall constant and included a many-deviant variant in which multiple deviant frequencies shared the 10% probability.

We quantified task performance using response categories—hits (HIT), false alarms (FA), correct rejections (CR), and misses (MISS) (**Figure 9**).

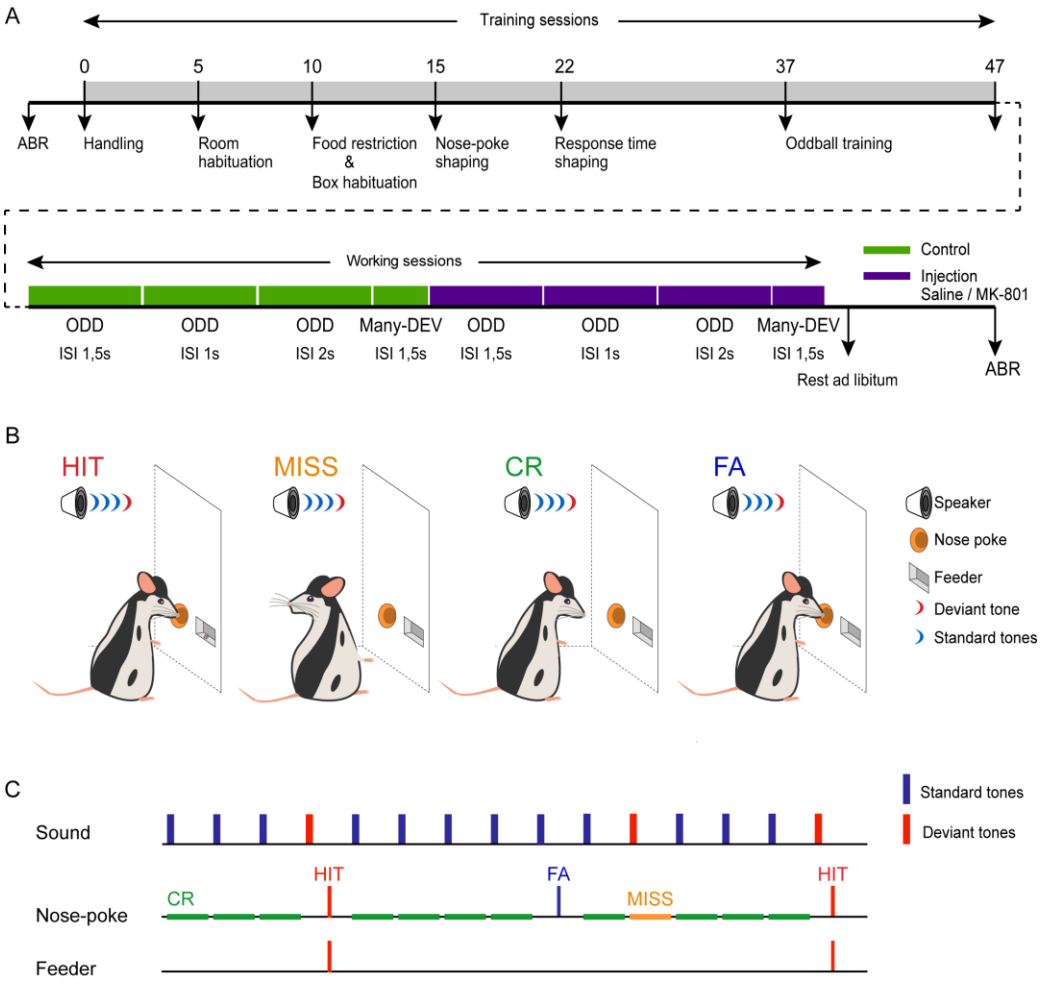


Figure 9. Schematic representation of training/test sessions scheduled across the course of the experiment. A Training was divided in 5 different stages, highlighted in bold. **B** Temporal structure of behavioural trials. **C** Cartoons showing all possible responses of the animals inside the operational chamber during behavioural sessions equipped with a speaker (1) to display sound sequences (red wave, deviant sound, blue wave, standard sound). Nose-poke (2) responses in the response window after a deviant tone (red wave) were rewarded with one pellet (3) and considered as Hits (HIT). The absence of response to deviant tone was computed as a Missed response (MISS). Correct rejections were absence of response after a standard tone (CR), and False alarms (FA) were responses to a standard tone (blue wave; followed by 5 s of timeout).

To stabilize rate estimates, we applied standard corrections for extreme values, computing HIT and FA rates as (count + 0.5)/(N + 1). We then analyzed these response measures with separate linear mixed-effects models including Treatment, Condition (pre vs. post), and inter-stimulus interval (ISI) as fixed effects and rat identity as a random intercept, and we used estimated marginal means and planned contrasts to test drug-related changes (**Paper 5**). We corrected contrasts using Holm methods.

4.5. Book chapter and systematic review

To synthesize current human evidence on auditory system maturation and age-related changes in mismatch responses in autism, we contributed a book chapter **(Book chapter)** and conducted a systematic review **(Systematic review)**.

The review protocol was registered in PROSPERO (CRD42025626806) and followed PRISMA guidelines (Page et al., 2021). We searched Embase, MEDLINE, and PsycInfo from inception to 31 May 2025 and screened reference lists of included studies.

We included original studies using passive oddball paradigms to assess MMN/MMF amplitude or power and latency in autistic and TD participants across development, requiring formal autism diagnoses (DSM-III to DSM-5). We excluded syndromic autism, active tasks, and paradigms involving background noise. Two reviewers independently screened studies, extracted participant, stimulus, and outcome data, and assessed methodological quality using the Newcastle–Ottawa Scale, resolving discrepancies by consensus. Fifty-two studies met inclusion criteria (**Figure 10**).

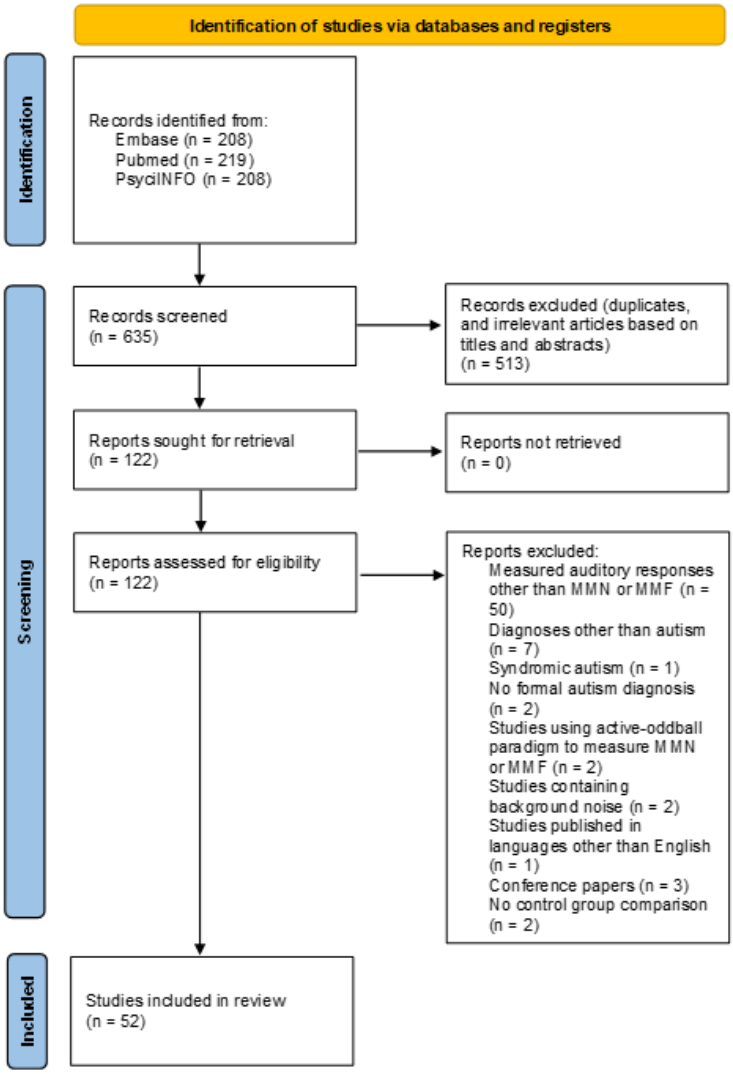


Figure 10. PRISMA flow diagram.

4.6. Science communication

To reinforce our strong commitment to high-quality science and social outreach, we engaged in science communication by disseminating our findings to the public, including through an accessible article summarizing our work on auditory processing in autism published on the online science platform *Scientias*. This outreach activity aimed to bridge the gap between our research and broader societal understanding of sensory differences in autism.

5. Results

5.1. Paper 1: Contextual auditory processing in the inferior colliculus is affected in a sex- and age-dependent manner in the valproic acid-induced rat model of autism

Diverse biological factors, including sex and age, introduce substantial heterogeneity in sensory processing in autism. A core feature underlying this heterogeneity is an altered ability to extract and update contextual information from the sensory environment. Within predictive coding frameworks, sensory systems continuously form expectations about incoming stimuli and signal deviations from these expectations when regularities are violated. Disruptions in this process impair the integration of contextual information and contribute to atypical responses to predictable and novel sensory events. Although sex- and age-related variability is increasingly recognized as critical for understanding these mechanisms, their contribution to predictive processing remains poorly characterized.

Animal models of autism provide a unique opportunity to investigate contextual processing at the single-neuron level and to isolate the neural computations underlying predictive coding. In the auditory system, predictive processing can be probed using oddball paradigms that elicit neuronal mismatch responses, the single-unit correlate of mismatch negativity. These responses reflect the integration of repetition suppression and prediction error signals and are generated early along the auditory hierarchy, including the inferior colliculus. Assessing how these components vary across biological factors and developmental stages is essential for understanding how predictive coding is shaped and disrupted.

Here, we investigated predictive processing of contextual auditory cues in the auditory midbrain of control rats and rats prenatally exposed to VPA, a well-established environmental model of autism. We performed single-unit recordings in the inferior colliculus of prepubertal and adult female and male animals using a classical oddball paradigm combined with a non-repetitive cascade control sequence. This approach allowed us to quantify neuronal mismatch and to dissociate its predictive components—indexing contextual adaptation and prediction error—across sex, age, and prenatal exposure.

5.1.1. Predictive components of mismatch processing

We fit a generalized linear mixed-effects models to examine how IC division, sound level, sex, age, and prenatal exposure influenced the predictive components of mismatch processing—indexed by iMM, iRS, and iPE. Each model included random intercepts and slopes for division, level, and exposure within subjects. We used a normal distribution with an identity link for all three indices.

The models demonstrated strong performance for iMM and iRS, with intraclass correlation coefficients of 0.856 and 0.681, and median absolute errors of 0.112 and 0.089, respectively. In contrast, the iPE model yielded a low intraclass correlation coefficient of 0.040, which aligns with theoretical expectations. Subcortical regions like the inferior colliculus generate relatively small prediction error signals, especially at the lemniscal level (Cacciato-Salcedo et al., 2025; Parras et al., 2017), and likely exhibit minimal inter-individual variability explained by experimental variables. Our modeling supports this view. Despite the low intraclass correlation, the model showed good fit (Akaike Information Criterion=–286.792; Bayesian Information Criterion=–151.700) and acceptable predictive accuracy (median absolute error of 0.070), indicating it reliably captured systematic effects of auditory division, sound level, sex, age, and prenatal exposure for iPE.

The iMM model revealed significant main effects of division (p<0.001), level (p<0.001), sex (p=0.001), age (p=0.002), and exposure (p=0.003). It also captured several significant two-way interactions, including sex × age (p<0.001), level × exposure (p=0.005), sex × exposure (p=0.013), and age × exposure (p=0.005). These results, together with the significant three-way interactions, indicate that both individual factors and their interactions contribute to modulating neuronal mismatch.

For iRS, the model detected significant main effects of division (p<0.001), sound level (p<0.001), sex (p<0.001), age (p<0.001), and prenatal exposure (p=0.004). It also revealed significant two-way interactions of division × level (p=0.001), level × sex (p=0.011), sex × age (p<0.001), sex x exposure

(p=0.034), and age × exposure (p=0.021). These patterns, indicate that experimental factors and their interactions jointly influence repetition suppression.

The iPE model identified significant main effects of sex (p=0.002) and a significant sex x age interaction (p=0.014), along with a marginally significant level × exposure interaction (p=0.048), division x level x age (p=0.002) and division x level x exposure (p=0.028). Other predictors did not reach significance, indicating that prediction error signals were more selectively modulated.

Higher-order interactions significantly modulated all predictive components, particularly iMM and iRS, highlighting the complex influence of sex, age, and prenatal exposure across IC divisions and stimulation levels. We further examined these effects for each index by sound level and IC division (**Figure 11**).

We further characterized these patterns at the experimental group level across auditory divisions and stimulation levels (**Figure 11**).

Neuronal mismatch index. Experimental group-level analysis of the neuronal mismatch index revealed significant effects of sex, age, and exposure, with patterns that varied across IC divisions and stimulation levels (**Figure 11**). For sex differences, control adult females showed significantly smaller iMM than males in both the lemniscal (p<0.001, median difference=–0.092) and non-lemniscal divisions (p<0.001, median difference=–0.177) at the high stimulation level. This pattern persisted in the VPA group, where adult females exhibited reduced iMM compared to males in the lemniscal division (p=0.010, median difference=–0.061). Among prepubertal VPA-exposed animals, females also showed reduced indices than males in both the lemniscal (p=0.012, median difference=–0.079) and non-lemniscal divisions (p=0.029, median difference=–0.062) under high stimulation. At the low sound level, control adult females again demonstrated reduced iMM index compared to males in the lemniscal division (p=0.013, median difference=–0.090).

Age comparisons revealed robust developmental effects that varied by sex and exposure (**Figure 11**). In the lemniscal division, control prepubertal females exhibited significantly greater iMM than adult females at both high ($p<0.001$, median difference=0.125) and low ($p=0.020$, median difference=0.119) stimulation levels. In the non-lemniscal division, control prepubertal females also showed an elevated score relative to adults under high stimulation ($p<0.001$, median difference=0.182). However, among VPA-exposed females, the trend reversed: prepubertal animals showed significantly attenuated iMM than adults at the same sound level ($p=0.004$, median difference=–0.106). At low stimulation in the non-lemniscal division, VPA-exposed prepubertal females also exhibited significantly smaller iMM than adult females ($p=0.008$, median difference=–0.146). Among males, prepubertal rats in the control group displayed a decreased iMM compared to adults in the non-lemniscal division at low stimulation ($p=0.008$, median difference=–0.118), a pattern that was also evident across VPA-exposed males ($p<0.001$, median difference=–0.118).

Prenatal VPA exposure produced divergent effects depending on age and IC division (**Figure 11**). In adult females, VPA exposure significantly increased iMM compared to controls in the non-lemniscal division under high stimulation ($p=0.002$, median difference=–0.153). Distinctly, among prepubertal females, prenatal VPA administration decreased iMM in both the lemniscal ($p=0.002$, median difference=0.104) and non-lemniscal divisions ($p<0.001$, median difference=0.136) at high sound level. Similarly, among males, VPA-exposed animals exhibited reduced iMM in prepuberty ($p=0.004$, median difference=0.058) and adulthood ($p=0.014$, median difference=0.054) at the same region and sound level.

Repetition suppression index. Experimental group-level analysis of the repetition suppression index revealed robust sex differences (**Figure 11**). Under high-level stimulation in the lemniscal division, control adult females exhibited significantly smaller iRS than males ($p=0.027$, median difference=–0.133), as did adult females in the non-lemniscal division ($p<0.001$, median difference=–0.282). VPA-

exposed adults maintained reduced lemniscal iRS relative to males (p<0.001, median difference=–0.130). At low-level stimulation, control adult females again showed smaller lemniscal iRS than males (p=0.007, median difference=–0.121) and reduced non-lemniscal iRS (p=0.002, median difference=–0.111). Among VPA-exposed prepubertals, females displayed greater non-lemniscal iRS than males at high stimulation (p=0.016, median difference=0.044).

Age comparisons revealed divergent developmental trajectories of iRS. In the lemniscal division, control prepubertal females outperformed adults at both high (p=0.027, median difference=0.124) and low (p=0.003, median difference=0.167) levels, whereas VPA-exposed prepubertal males showed reduced iRS relative to VPA adults at high stimulation (p=0.026, median difference=–0.117). In the non-lemniscal division, control prepubertal females exhibited elevated iRS at both high (p<0.001, median difference=0.282) and low (p<0.001, median difference=0.286) levels. VPA-exposed prepubertal females mirrored these increases (high: p=0.028, median difference=0.032; low: p=0.015, median difference=0.121). Both control (p=0.001, median difference=0.121) and VPA (p=0.007, median difference=0.065) prepubertal males exceeded adults under low non-lemniscal stimulation.

Prenatal VPA exposure produced division- and group-specific effects. In the non-lemniscal division at high stimulation, VPA augmented adult female iRS (p<0.001, median difference=–0.228) but reduced adult male iRS (p=0.002, median difference=0.076). By contrast, among prepubertals, control females exceeded VPA-exposed females in the lemniscal division at high stimulation (p=0.025, median difference=0.059), and control males outperformed VPA males in the non-lemniscal division at both high (p=0.022, median difference=0.030) and low (p=0.042, median difference=0.041) levels. Finally, at low lemniscal stimulation, VPA-exposed adults, females (p=0.019, median difference=–0.173) and males (p=0.022, median difference=–0.121), displayed greater iRS than controls.

Prediction error index. Experimental group-level analysis revealed significant differences in the prediction error index, with effects varying across IC divisions and stimulation levels (**Figure 11**). In

the lemniscal division at high sound level, adult females exposed to VPA showed significantly greater iPE scores than males (p=0.042, median difference=0.058). In contrast, the non-lemniscal division showed more pronounced sex effects. Under high stimulation, control adult females exhibited significantly greater iPE than males (p<0.001, median difference=0.133). In the VPA group, prepubertal females had significantly smaller scores than males (p<0.001, median difference=–0.072).

We observed robust developmental influences on iPE in the non-lemniscal division (**Figure 11**). Among control females, prepubertal rats exhibited significantly smaller iPE compared to adults at both high (p<0.001, median difference=–0.120) and low (p<0.001, median difference=–0.356) stimulation. VPA-exposed females showed a similar pattern, with reduced scores in prepubertal animals at high (p<0.001, median difference=–0.119) and low (p<0.001, median difference=–0.284) levels. In males, control prepubertal rats showed a significant reduction in iPE at low stimulation (p<0.001, median difference=–0.224), and VPA-exposed prepubertals also demonstrated reduced iPE (p<0.001, median difference=–0.144) compared to their adult counterparts.

Prenatal VPA exposure significantly modulated prediction error processing, particularly in the non-lemniscal division of female rats under high stimulation. Adult control females displayed greater iPE values than their VPA-exposed counterparts (p<0.001, median difference=0.070), and the same pattern emerged among prepubertal females (p=0.003, median difference=0.069).

Sex, age, and prenatal VPA exposure distinctly modulated predictive coding indices across IC divisions and sound levels. Adult females consistently exhibited smaller iMM and iRS than males, especially in non-lemniscal regions, a pattern maintained in VPA-exposed animals. Developmentally, control prepubertal females showed elevated iMM and iRS, while VPA reversed these trajectories. iPE increased after puberty in controls but was reduced by VPA across ages, introducing prepubertal sex differences. Despite these disruptions, the typical shift from negative to positive iPE in non-lemniscal

circuits remained preserved. Sex and age influenced predictive coding, and prenatal VPA exposure particularly disrupted these processes, especially in non-lemniscal regions of the inferior colliculus.

Figure 11. Group-level comparisons of spike count to predictive components of mismatch processing. A Violin plots show normalized values for iMM (purple), iRS (turquoise), and iPE (orange) across experimental groups. Left panels correspond to the lemniscal division, and right panels to the non-lemniscal division of the IC. A solid vertical black line separates responses elicited at high sound levels (≥ 40 dB SPL) from those at low sound levels (< 40 dB SPL). Group abbreviations: FpC = female prepubertal control, FaC = female adult control, MpC = male prepubertal control, MaC = male adult control, FpV = female prepubertal VPA, FaV = female adult VPA, MpV = male prepubertal VPA, MaV = male adult VPA. General abbreviations: IC, inferior colliculus; VPA, valproic acid; iMM, neuronal mismatch index; iRS, repetition suppression index; iPE, prediction error index. **B** Heatmaps show statistical significance of pairwise group comparisons based on the Wilcoxon rank-sum test with false discovery rate correction ($p < 0.05$, $\boldsymbol{p} = 0.001$, $^{**}p < 0.001$).

As significance strengthens, the corresponding color becomes darker: purple for iMM, turquoise for iRS, and orange for iPE. Non-significant comparisons are shown in white (N.S.), and missing comparisons in grey (NaN).

5.2. **Paper 2: Sex- and etiology-specific effects on predictive processing in the inferior colliculus of two rat models of autism**

Atypical sensory processing is a common feature of autism, yet the neural computations that give rise to these differences, particularly in relation to biological sex and etiological origin, remain unclear. Here we examine predictive auditory processing at the single-neuron level in the inferior colliculus of two adult rat models of autism: a genetic model with a heterozygous *Grin2b* deletion (*Grin2b*+/–) and an environmental model based on prenatal valproic acid exposure. We recorded neuronal responses to an auditory oddball paradigm and a cascade control sequence across lemniscal and non-lemniscal IC divisions under high-intensity stimulation, allowing us to derive indices of repetition suppression, prediction error and neuronal mismatch. Using generalized linear mixed-effects models that accounted for animal identity, inferior colliculus division, sex, and rat model, followed by hierarchical group-level comparisons, we identified robust alterations in predictive processing in both autism-like models.

5.2.1. Predictive components of mismatch processing

Next, we examined contextual auditory processing within the predictive coding framework by deriving mismatch-related indices (iMM, iRS, and iPE) from the corresponding contrasts among the DEV, CAS, and STD conditions.

We fitted generalized linear mixed-effects models to quantify how IC division (lemniscal, non-lemniscal), sex (female, male), and rat model (Control, *Grin2b*+/, VPA) explained variability in the predictive components. To preserve the hierarchical structure of the data, we included random intercepts for animals and random slopes for IC division. Each model incorporated 68 division-level observations from 46 animals.

The models provided strong fits for iMM and iRS, with intraclass correlation coefficients of 0.761 and 0.854, respectively. In contrast, the iPE model yielded a lower intraclass correlation coefficient of

0.060, which aligns with theoretical expectations and our previous findings. Subcortical structures such as the inferior colliculus generate relatively small prediction error signals, particularly within lemniscal pathways, and show limited between-subject variability driven by experimental factors (Parras et al., 2017; Cacciato-Salcedo et al., 2025a).

Cross-validation confirmed model performance, yielding median absolute errors of 0.037, 0.031, and 0.026 for iMM, iRS, and iPE, respectively. These results indicate that the models accurately captured hierarchical influences on predictive auditory processing across IC divisions.

Neuronal mismatch index. The neuronal mismatch index quantifies the neuron's sensitivity to auditory deviance by comparing its responses to the same tone when presented as a rare deviant versus a frequent standard. It reflects the overall mismatch signal, integrating both adaptation and prediction-related components of auditory processing.

The model revealed significant main effects of IC division ($p < 0.001$), sex ($p = 0.005$), and rat model (*Grin2b*+/–: $p = 0.034$; VPA: $p = 0.030$) on iMM. These results indicate that iMM varied robustly across anatomical divisions, with additional modulation by sex and both autism-like conditions. The absence of significant interaction terms suggests that *Grin2b* heterozygous deletion and prenatal VPA exposure altered mismatch responses in a manner that was consistent across sexes and IC divisions.

Post hoc contrasts showed clear sex- and division-dependent modulation of iMM. Under control conditions, females generated significantly smaller iMM values than males in both the lemniscal (contrast estimate = –0.310, $p = 0.003$; **Figure 12A**) and non-lemniscal IC (contrast estimate = –0.157, $p = 0.007$; **Figure 12B**), indicating reduced sensitivity to auditory deviance in female rats. Autism-like phenotypes altered this pattern in a sex-specific manner. Both *Grin2b*+/– and VPA-exposed females showed higher iMM than control females in the lemniscal IC (*Grin2b*+/–: contrast estimate = –0.275, $p = 0.030$; VPA: contrast estimate = –0.272, $p = 0.026$; **Figure 12A**). In males, only the VPA group

differed from controls, exhibiting reduced iMM in the non-lemniscal IC (contrast estimate = 0.140, p = 0.043; **Figure 12B**).

Collectively, our results show that control females exhibited lower mismatch responses than males. Both *Grin2b* heterozygous deletion and prenatal VPA exposure atypically increased mismatch activity in females within the lemniscal IC, whereas prenatal VPA reduced mismatch responses in males within the non-lemniscal IC.

Repetition suppression index. The repetition suppression index quantifies neuronal adaptation to repeated auditory stimulation by comparing responses to standard and cascade tones, reflecting the adaptive component of predictive coding in the auditory pathway.

The model revealed significant main effects of IC division ($p < 0.001$), sex ($p = 0.004$), and *Grin2b* heterozygous deletion ($p = 0.010$) on iRS. These results show that iRS varied across anatomical divisions and was independently modulated by sex and *Grin2b* heterozygous deficiency.

Post hoc contrasts revealed strong sex- and model-dependent modulation of iRS that occurred in both IC divisions, but with markedly larger effects in the non-lemniscal pathway. In the lemniscal IC, control females generated significantly smaller iRS values than control males (contrast estimate = –0.345, $p = 0.003$; **Figure 12A**). Among female rats, *Grin2b* heterozygous deletion further heightened iRS values relative to control counterparts (contrast estimate = –0.368, $p = 0.008$; **Figure 12A**).

In the non-lemniscal IC, the pattern was stronger and more widespread. Control female animals again showed reduced iRS compared with males (contrast estimate = –0.248, $p < 0.001$; **Figure 12B**). Within females, both *Grin2b*+/– and prenatal VPA-exposed rats exhibited markedly increased iRS than control females (*Grin2b*+/–: contrast estimate = –0.259, $p < 0.001$; VPA: contrast estimate = –0.220, $p < 0.001$; **Figure 12B**). In contrast, neither rat model yielded significant effects in males across either IC division.

These findings demonstrate that neural suppression to repetitive stimulation is consistently lower in control females than in male counterparts. In the autism-like models, both *Grin2b* heterozygous deletion and prenatal VPA exposure atypically amplified repetition suppression in female rats, with the strongest effects in non-lemniscal circuits.

Prediction error index. The prediction error index quantifies a neuron's capacity to signal violations of auditory regularity by isolating the deviance-related response component not explained by adaptation.

The model identified significant main effects of sex ($p = 0.005$) and *Grin2b* heterozygous deletion ($p = 0.047$) on iPE, with no significant interactions. These results indicate that prediction error signaling in the IC varied modestly across sexes and was selectively modulated by *Grin2b* heterozygous deficiency.

Post hoc contrasts revealed clear sex differences in iPE under control conditions. In both lemniscal and non-lemniscal IC, control females exhibited significantly higher iPE values than control males (lemniscal: contrast estimate = 0.095, $p = 0.003$; non-lemniscal: contrast estimate = 0.130, $p = 0.003$; **Figure 12A-B**).

Autism-like phenotypes produced a single significant effect, confined to the non-lemniscal pathway. Prenatally VPA-exposed females showed lower iPE than control females (contrast estimate = 0.137, $p = 0.006$; **Figure 12B**), whereas *Grin2b* heterozygous deletion did not alter iPE in either sex or IC division.

Our results show that prediction-error encoding is stronger in females than in males under control conditions. Prenatal VPA administration weakened female-specific effects in prediction error signaling within the non-lemnsical IC, while remaining stable in autism-like males and unaffected in lemniscal pathways.

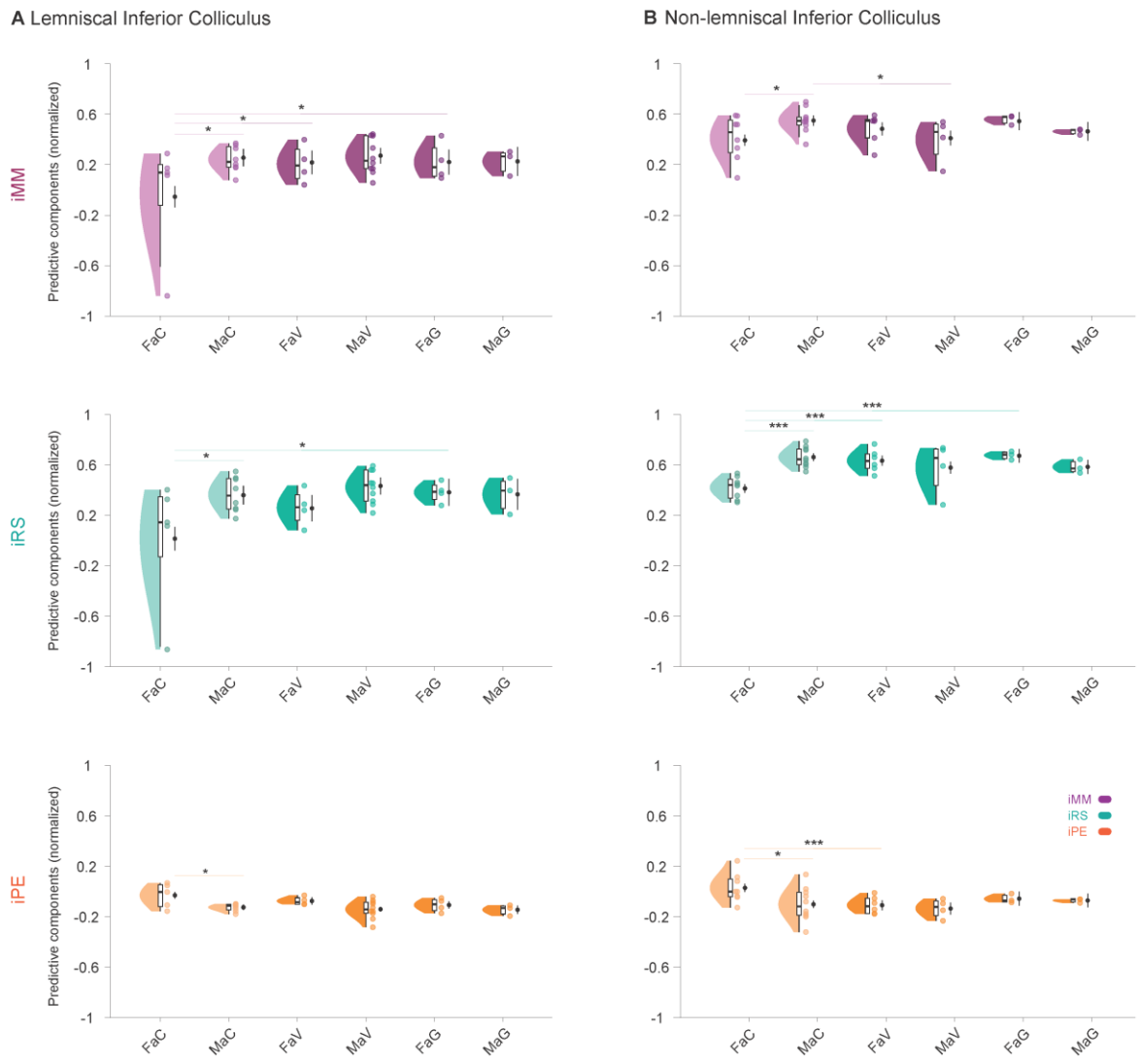


Figure 12. Predictive components of mismatch processing across sex, rat model, and IC division. A shows half-violin plots of group-level normalized spike counts for the neuronal mismatch (iMM; purple), repetition suppression (iRS; turquoise), and prediction error (iPE; orange) components in the lemniscal inferior colliculus. Lighter tones represent control animals, whereas darker tones indicate the autism-like groups. For each experimental group, the left half-violin depicts the distribution of subject-level component values, with the thick black bar marking the biological median. On the right, each dot corresponds to an individual animal, and the black circular marker indicates the estimated marginal mean with its standard error, derived from the mixed-effects model and used for statistical inference. **B** presents the corresponding predictive components in the non-lemniscal division using the same visualization scheme. Asterisks denote significant model-based pairwise contrasts ($p < 0.05$ *, $p = 0.001$ **, $p < 0.001$ ***). Group abbreviations: FaC = female adult control, MaC = male adult control, FaV = female adult VPA, MaV = male adult VPA, FaG = female adult *Grin2b*+/–, MaG = male adult *Grin2b*+/–.

5.3. Paper 3: Sex- and age-specific effects on auditory brainstem responses in the valproic acid-induced rat model of autism

Prenatal exposure to VPA is a well-established rodent model of autism, yet the effects on auditory brainstem processing remain incompletely characterized across sex and development. We recorded click-evoked ABRs in Long–Evans rats prenatally exposed to VPA (400 mg/kg, gestational day 12) and in matched controls at prepubertal (postnatal days 30–45) and adult (65–120) stages under urethane anesthesia. Peak amplitudes were analyzed across sound levels. Auditory thresholds did not differ among groups.

5.3.1. Peak amplitude of ABR Waveforms

Peak amplitude reflects the strength of the evoked neural response at each processing stage along the auditory pathway. We computed mean amplitudes across averaged sound levels per experimental group and conducted pairwise comparisons using Sidak-corrected *t*-tests to assess sex, age, and exposure differences at the group level (**Figure 13**).

We found that Waves I (mean difference = 0.511; $p < 0.023$) and II (mean difference = 1.224; $p < 0.011$) of control adult females exhibited significantly greater mean amplitude than respective Waveform of male counterparts (**Figure 13A**), and reduced Wave III (mean difference = -0.511; $p < 0.022$), resulting from the masking effect exerted by Wave II. Exposure differences emerged between adult female rats, where controls showed significantly larger mean amplitude of Wave II than VPA-exposed (mean difference = 1.12; $p < 0.032$; Figure 4A).

Then, we computed mean amplitudes at 10-dB steps and fitted linear mixed-effects models including sex, age, exposure, sound level, and their interactions to account for within-subject variability across intensities and between-subject differences.

Model reliability increased with sound level, with intraclass correlation coefficients of 0.090 at 30 dB SPL, 0.211 at 40 dB SPL, 0.294 at 50 dB SPL, 0.355 at 60 dB SPL, 0.398 at 70 dB SPL, and 0.434 at 80 dB SPL. We extracted estimated marginal means (**Figure 13B, insets**) to illustrate model effects.

For Wave II, amplitudes increased robustly with sound Level ($\beta = 0.069 \pm 0.006$, $p < 0.001$), reflecting enhanced recruitment of early brainstem generators with stronger stimulation. However, this amplitude growth was smaller in males (Sex × Level: $\beta = -0.029 \pm 0.009$, $p = 0.001$), in prepubertal rats (Age × Level: $\beta = -0.035 \pm 0.009$, $p < 0.001$), and under VPA exposure (Exposure × Level: $\beta = -0.020 \pm 0.008$, $p = 0.015$), indicating reduced excitability and weaker intensity scaling across these conditions.

For Wave V, males showed higher overall amplitudes ($\beta = 0.496 \pm 0.192$, $p = 0.010$), yet their amplitude–intensity relationship differed markedly across sex and exposure. The negative Sex × Level interaction ($\beta = -0.014 \pm 0.004$, $p < 0.001$) revealed that amplitude increased less steeply with intensity in males, suggesting reduced neural gain at higher levels. The Sex × Exposure interaction ($\beta = -0.839 \pm 0.257$, $p = 0.001$) indicated that VPA suppressed amplitudes more prominently in males, whereas the three-way Sex × Age × Level ($\beta = 0.010 \pm 0.005$, $p = 0.046$) and Sex × Exposure × Level ($\beta = 0.018 \pm 0.005$, $p < 0.001$) interactions suggested that these sex-specific differences in intensity scaling were mitigated in younger animals and further shaped by teratogenic exposure.

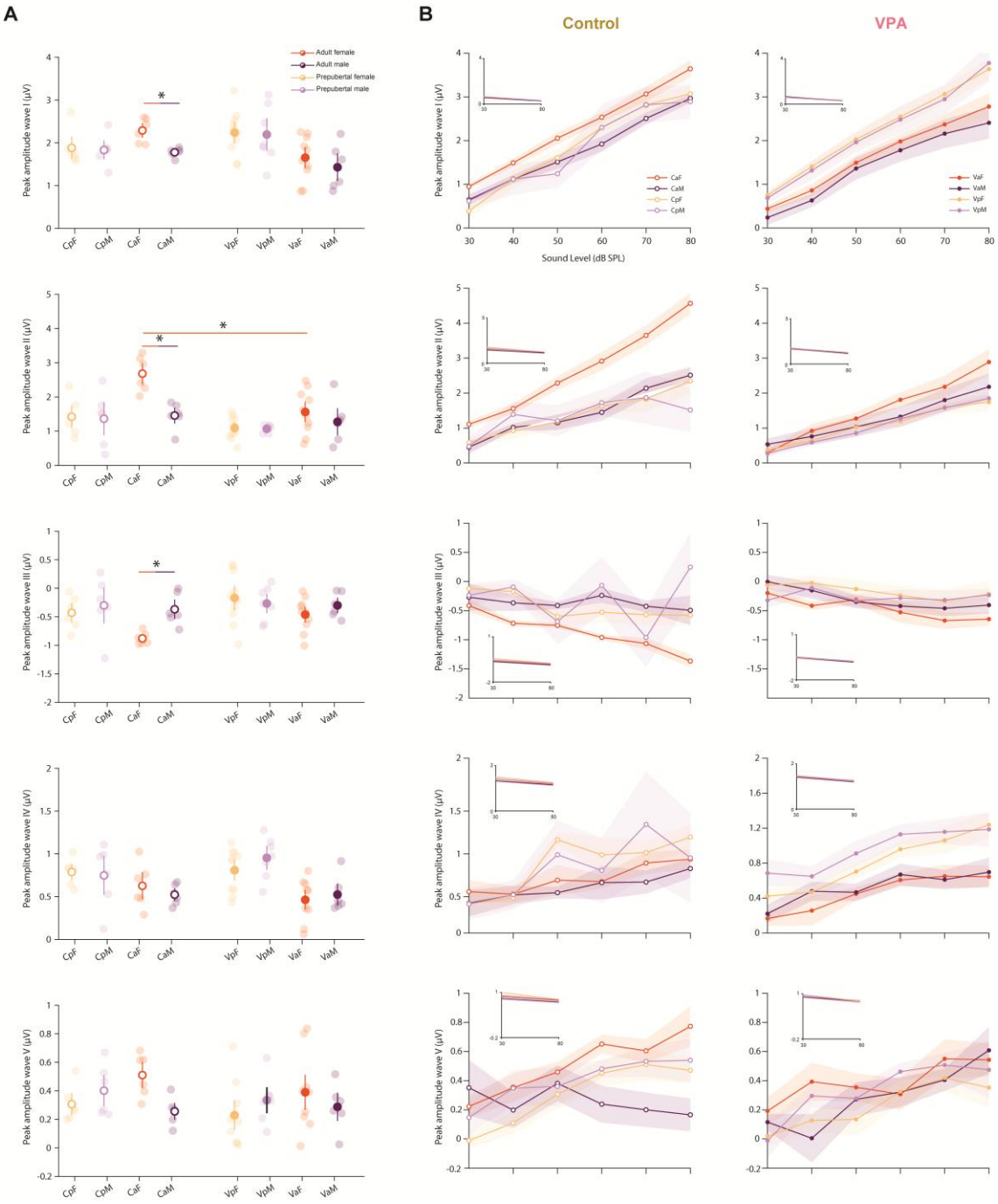


Figure 13. Peak amplitudes across rat groups. **A** Averaged peak amplitudes across sound levels for each group, shown for Waves I–V. **B** Peak amplitudes at each individual sound level across groups. Light colors denote prepubertal rats (yellow, females; purple, males), while dark colors indicate adults (orange, females; dark purple, males). Control groups are represented by white-filled symbols, and VPA-exposed groups by color-filled symbols which represent the group means, and error bars denote the standard error of the mean, shadowed for panels A-B. Significance is indicated as follows: $p < 0.05$ *, $p = 0.001$ **, $p < 0.001$ ***. Abbreviations: CpF, control prepubertal female; CpM, control prepubertal male; CaF, control adult female; CaM, control adult male; VpF, VPA prepubertal female; VpM, VPA prepubertal male; VaF, VPA adult female; VaM, VPA adult male.

5.4. **Paper 4: Sex Differences in Auditory Brainstem Responses of Two Rat Models of Autism: Environmental and Genetic Contributions to Autism-Like Auditory Function**

Autism is an early-onset neurodevelopmental disorder characterized by restricted, repetitive behaviors and atypical patterns of social communication and interaction. A considerable proportion of autistic individuals experience divergent auditory perception, which can interfere with their ability to navigate everyday sound environments.

Auditory brainstem responses are electrophysiological potentials elicited by auditory stimuli that evaluate neural activity along the auditory nerve and brainstem. Importantly, auditory brainstem response varies by sex, with females typically showing higher amplitudes and shorter latencies than males. This sex-specific neurophysiological profile is especially relevant in autism research, where the male-to-female diagnosis ratio is approximately 3:1. Thus, exploring the neurobiological mechanisms underlying sex-specific variations in autistic traits is essential. Furthermore, autism sensory profiles may vary based on the independent and mutual effects of environmental and genetic factors.

To deepen this understanding, we examined auditory brainstem responses in two rat models of autism: the GRIN2B rare mutation model and the prenatal valproic acid induction model, alongside control animals.

5.4.1**. Peak amplitude of ABR Waveforms**

To capture group-level differences in click-evoked ABRs peak amplitudes, we compared rat model groups at the population level (**Figure 14A**) and examined sex differences within each rat model group (**Figure 14C**).

Rat model comparisons revealed the following distinctions. Control rats exhibited greater amplitudes in Waves I and II than both *Grin2b*+/– and VPA animals (Wave I: Control vs GRIN2B, mean difference = 0.477, $p = 0.026$; Control vs VPA, mean difference = 0.464, $p = 0.028$; Wave II: Control vs GRIN2B, mean difference = 0.845, $p = 0.005$; Control vs VPA, mean difference = 0.616, $p = 0.044$). In Wave

III, *Grin2b*+/– rats showed responses closer to baseline than control rats (mean difference = −0.597, $p < 0.001$) and VPA animals (mean difference = 0.375, $p = 0.004$). In Wave IV, *Grin2b*+/– rats exhibited larger amplitudes than VPA animals (mean difference = 0.190, $p = 0.020$).

Significant sex differences emerged only within the control group: females showed greater amplitudes in Waves I, II, and V (Wave I, mean difference = 0.985, $p = 0.002$; Wave II, mean difference = 1.534, $p < 0.001$; Wave V, mean difference = 0.359, $p = 0.007$), whereas males produced Wave III responses closer to baseline than females (mean difference = −0.903, $p < 0.001$).

Next, we examined how these effects varied across stimulus intensity (**Figure 14B**). Females exhibited significantly greater amplitudes than males in Wave I at 40, 50, 60, and 80 dB SPL (40 dB: mean difference = 0.302, $p = 0.041$; 50 dB: mean difference = 0.409, $p = 0.009$; 60 dB: mean difference = 0.534, $p = 0.001$; 80 dB: mean difference = 0.505, $p = 0.032$) and in Wave II at 50, 60, and 80 dB SPL (50 dB: mean difference = 0.463, $p = 0.027$; 60 dB: mean difference = 0.654, $p = 0.009$; 80 dB: mean difference = 0.785, $p = 0.035$). In Wave II, control animals exhibited larger amplitudes than *Grin2b*+/– animals across all intensities (30 dB: mean difference = 0.366, $p = 0.034$; 40 dB: mean difference = 0.667, $p = 0.003$; 50 dB: mean difference = 0.650, $p = 0.035$; 60 dB: mean difference = 0.867, $p = 0.018$; 70 dB: mean difference = 1.125, $p = 0.008$; 80 dB: mean difference = 1.394, $p = 0.007$) and exceeded VPA animals at 30 and 70 dB SPL (30 dB: mean difference = 0.394, $p = 0.019$; 70 dB: mean difference = 0.857, $p = 0.049$). The sex × rat model interaction in Wave II showed that control females had the largest amplitudes among all groups, exceeding female-GRIN2B (mean difference = 1.224, $p < 0.001$), female-VPA (mean difference = 1.390, $p < 0.001$), male-control (mean difference = 1.534, $p < 0.001$), male-GRIN2B (mean difference = 1.120, $p < 0.001$), and male-VPA (mean difference = 1.408, $p < 0.001$).

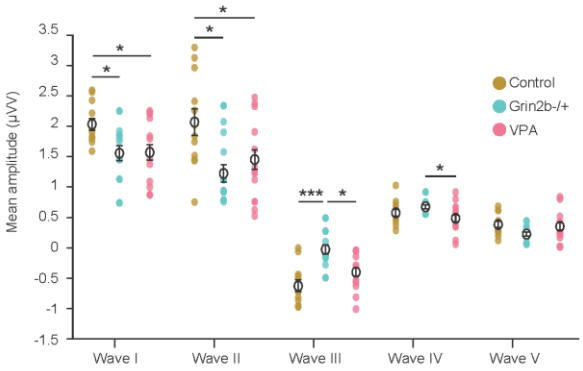
In Wave III, control rats produced more negative-going responses than *Grin2b*+/– animals from 40 to 80 dB SPL (40 dB: mean difference = −0.415, $p = 0.002$; 50 dB: mean difference = −0.580, $p < 0.001$;

60 dB: mean difference = −0.576, p = 0.004; 70 dB: mean difference = −0.708, p = 0.0010; 80 dB: mean difference = −1.075, p < 0.001). At 50 dB SPL, *Grin2b*+/– animals also differed from VPA animals (mean difference = 0.323, p = 0.006), and this contrast persisted at higher intensities (60 dB: mean difference = 0.465, p = 0.012; 70 dB: mean difference = 0.556, p = 0.004; 80 dB: mean difference = 0.701, p = 0.005).

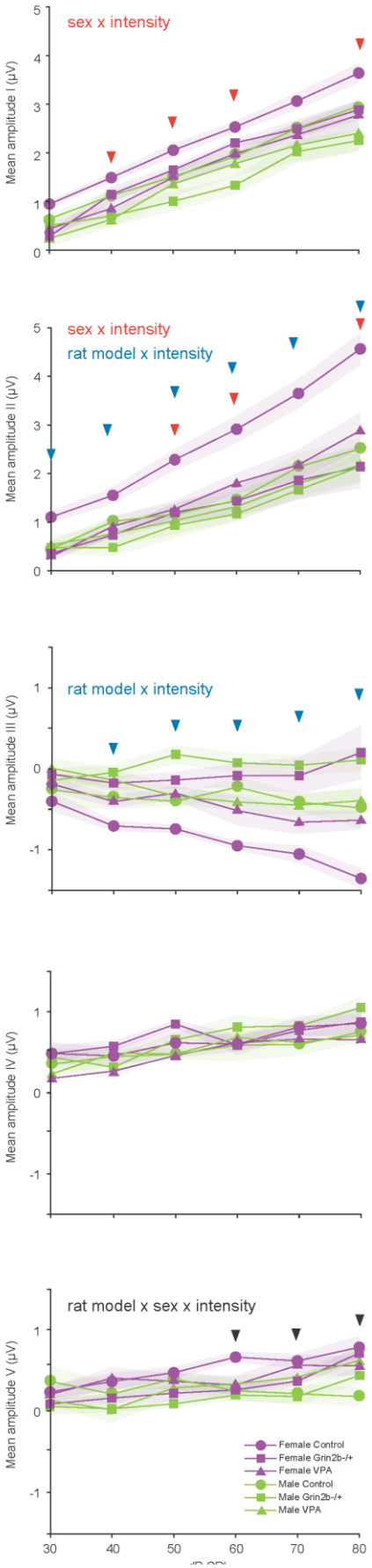
In Wave V, control females generated larger amplitudes than control males at 60–80 dB SPL (60 dB: mean difference = 0.413, p = 0.016; 70 dB: mean difference = 0.404, p = 0.019; 80 dB: mean difference = 0.608, p = 0.007), whereas sex differences were not significant in the *Grin2b*+/– or VPA groups.

differences were absent in the *Grin2b*+/– and VPA groups.

A. Rat model effect at the population level



B. Amplitude measures per intensity at the group level



C. Sex effect at the group level

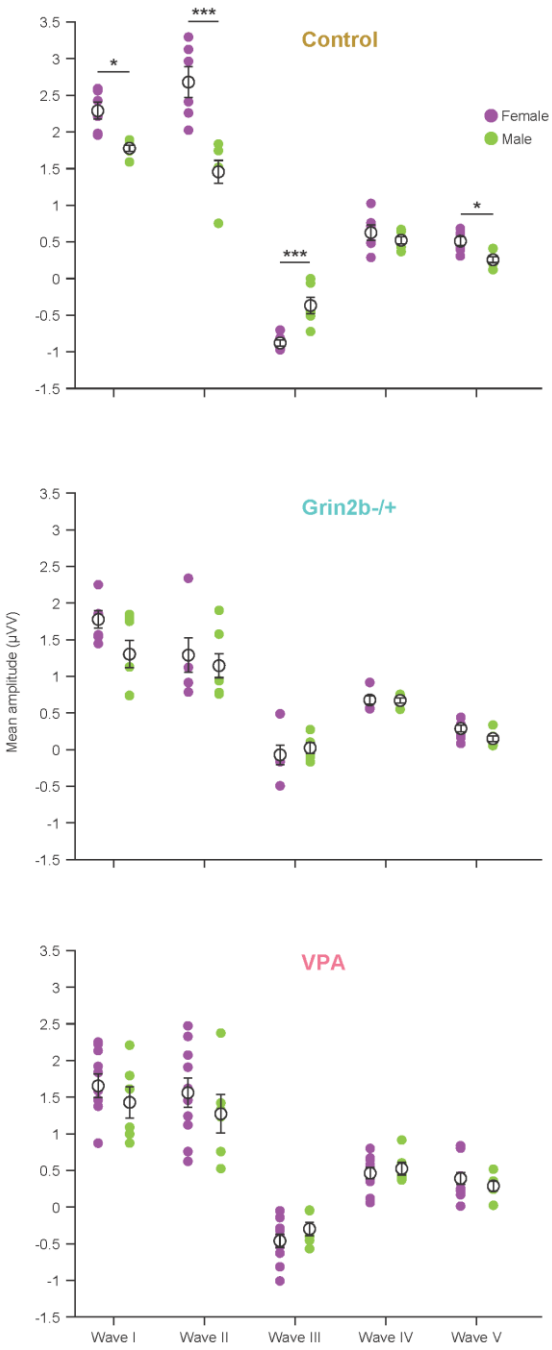


Figure 14. Peak amplitude differences across rat model, sex, and sound intensities. A shows mean peak amplitudes for ABR Waves I–V across the three rat models (Control, *Grin2b*+/–, and VPA), collapsed across sex and intensity. **B** presents group-level amplitude trajectories as a function of stimulus intensity (30–80 dB SPL), highlighting interactions with sex (red triangles), rat model (blue triangles), and three-way interactions (black triangles). **C** illustrates sex differences within each model (purple for females, green for males). Each dot represents an individual subject, with shaded lines depicting group means ± standard error. Significance is indicated as follows: $p < 0.05$ *, $p = 0.001$ **, $p < 0.001$ ***.

5.5. **Paper 5: The NMDA receptor antagonist MK-801 disrupts auditory-guided behavior in an operant oddball task**

Schizophrenia involves marked deficits in cognitive control and sensory-guided behavior, yet the behavioral consequences of NMDA receptor hypofunction for auditory decision-making remain unclear. We examined how systemic NMDA receptor antagonism affected performance in an operant auditory oddball task that required animals to respond to deviant tones (go context) while withholding responses to repetitive standard tones (no-go context) across varying inter-stimulus intervals (ISIs).

5.5.1. **MK-801 alters false alarm and correct rejection patterns**

We quantified how saline and MK-801 injections affected the distribution of behavioral outcomes: HIT, CR, FA, and MISS, expressed as session-averaged percentages at ISIs of 1, 1.5, and 2 s (**Figure 15**).

For each response type, we fit linear mixed-effects models with Treatment (Saline vs. MK-801), Condition (Pre vs. Post), and ISI as fixed effects and Rat as a random intercept. Median absolute errors (2.506 for HIT/MISS; 2.326 for CR/FA) indicated good model fit.

HIT performance remained stable across injections, with no significant main effects or interactions. MISS responses mirrored this pattern, as expected from their complementary structure.

In contrast, FA responses showed a significant effect of ISI ($F(2,10) = 9.809$, $p = 0.004$) and a significant Condition × ISI interaction ($F(2,10) = 4.623$, $p = 0.038$), indicating that the impact of

injection differed across temporal contexts. CR responses exhibited the same inferential pattern, consistent with their complementary relationship to FA.

To quantify condition-specific effects, we fit separate linear mixed-effects models for each ISI, including Treatment (Saline, MK-801) and Condition (Pre vs. Post) as fixed effects and Rat as a random intercept. From these ISI-specific models, we computed (ΔPercent = Post − Pre) using the estimated marginal means and applied Holm correction across ISIs.

HIT and MISS showed no significant ΔPercent changes under either treatment at any ISI. For CR responses, we observed clear injection-related effects at longer ISIs (**Figure 15**). At ISI 1.5 s, MK-801 decreased CR percentage (ΔPercent = 30.64, $p = 0.034$), with a similar reduction at ISI 2 s (ΔPercent = 25.06, $p = 0.030$). FA responses mirrored these CR effects (**Figure 15**). MK-801 markedly increased FA rate at ISI 1.5 s (ΔPercent = -30.64, $p = 0.034$) and ISI 2 s (ΔPercent = -25.06, $p = 0.030$; **Figure 15**), indicating less controlled or more impulsive responding under NMDA receptor blockade.

Finally, between-treatment contrasts (MK-801 vs. saline) for ΔPercent were non-significant for all response types after Holm adjustment, indicating that drug-related changes did not significantly differ from saline-induced fluctuations at the group level.

In summary, MK-801 selectively disrupted responses to the standard (non-target) tone by increasing FA and reducing CR, particularly at longer ISIs. These effects suggest impaired response inhibition or diminished behavioral precision emerging independently of deviant detection performance, which remained intact across injections.

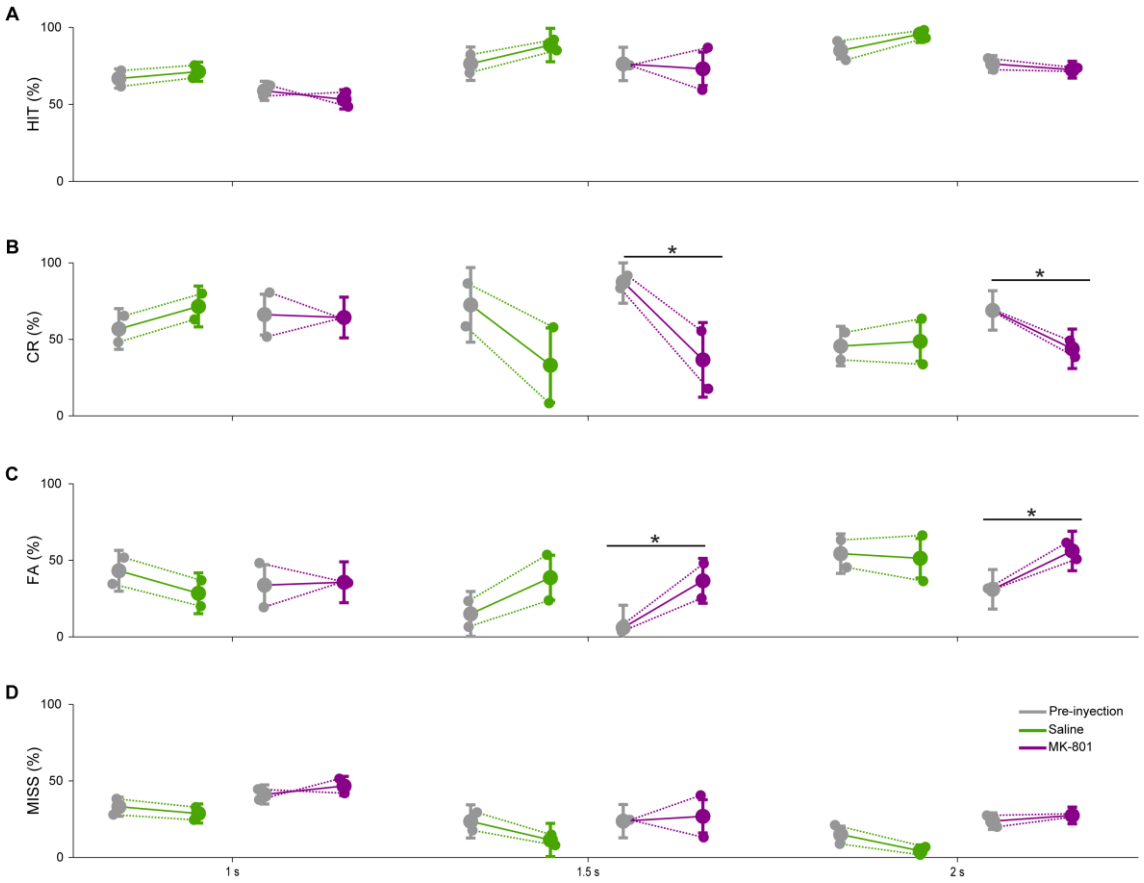


Figure 15. NMDA receptor antagonism alters the distribution of behavioral response types in an operant auditory oddball task. The proportion of hits (HIT), false alarms (FA), misses (MISS), and correct rejections (CR) is shown for saline and MK-801 conditions. For each response category, estimated marginal means (EMMs) derived from linear mixed-effects models are plotted, with error bars indicating the standard error of the mean. Small dots represent individual biological data points (one value per animal), and thin lines connect repeated measures from the same animal across conditions, illustrating within-subject changes in response proportions. Relative to saline, MK-801 administration increased the proportion of FA and reduced the proportion of responses requiring response withholding (CR). Horizontal bars denote significant pairwise contrasts between conditions for each response category, with significance levels indicated as $p < 0.05$ (*), $p = 0.001$ (**), and $p < 0.001$ (***).

5.6. **Book chapter**: **The Structural and Functional Organization of the Auditory System Across Development: Foundations for Music Perception**

5.6.1. Functional and Evolutionary Organization of the Auditory Brain

Although not essential for survival, music profoundly shapes human experience. Found in every culture, it accompanies individuals from early development through old age, influencing behavior, cognition, and emotion. Its effects on the brain are extensive (Bölte et al., 2011; Ueno & Shimada, 2024), altering neural activity and connectivity in ways that strengthen memory, attention, and

emotional control. Music also recruits the motor system, coordinating movement and timing whether one is listening, singing, or dancing. By simultaneously engaging sensory, cognitive, motor, and affective regions, music becomes a powerful modulator of both thought and emotion.

Beyond movement, music evokes intense affective responses, from pleasure and reward to nostalgia and awe (Trimble & Hesdorffer, 2017; Zatorre et al., 2007). It reshapes activity throughout the auditory brain and interacts closely with limbic and prefrontal circuits. The therapeutic potential of music has been recognized for decades, but the increasing accessibility of digital media has intensified interest in its clinical use. Evidence now supports music-based interventions across a broad spectrum of disorders, from psychiatric conditions such as depression, anxiety, and post-traumatic stress disorder to neurological and neurodevelopmental challenges including dementia, aphasia, traumatic brain injury, cerebral palsy, and Parkinson's disease (Koelsch, 2014; Sihvonen et al., 2017). Because music therapy is noninvasive and adaptable, it offers flexible clinical opportunities, though its efficacy depends strongly on individual, contextual, and neurobiological factors.

Despite encouraging results, many studies still struggle to identify which neural mechanisms best predict positive outcomes. A deeper understanding of the auditory brain; its architecture, connectivity, and development, is essential for explaining how music influences perception, cognition, and emotion. Current evidence suggests that supports music-based interventions primarily act through auditory brain that interface with motor, motivational, and affective networks (Zatorre et al., 2007). These interactions likely mediate the improvements observed in motor coordination, mood regulation, and stress resilience. However, the integration of auditory inputs with other sensory and interoceptive systems (such as vision, proprioception, and touch) remains underexplored. Mapping these multimodal connections could illuminate new therapeutic targets for conditions like Alzheimer's disease, dementia, cardiovascular dysfunction, and chronic pain.

To understand how music exerts such wide-ranging effects, it is necessary to examine the functional and developmental organization of the auditory brain, which decodes complex sounds and transforms them into perceptual and emotional experiences. In mammals, this system represents an evolutionary refinement of a conserved vertebrate design, allowing exceptional spectral, temporal, and rhythmic resolution suited to communication and social bonding. The human auditory brain is particularly specialized for fine-grained pitch discrimination, rapid temporal tracking, and sensitivity to prosody and rhythm: capacities that support both language and music perception.

The auditory brain is present in all vertebrates, though its degree of complexity varies by species. Even among mammals, evolutionary adaptations yield distinct specializations: for instance, echolocating bats and toothed whales have developed high-frequency processing mechanisms that far exceed the human range. In contrast, humans exhibit extended cortical representation of pitch and harmonic structure, enabling the perception of melody and harmony unique to musical cognition (Masterton et al., 1969). Despite these differences, the general organization of the auditory pathway remains conserved.

Auditory stimuli consist of pressure Waves within species-specific frequency ranges (humans: approximately 0.02–20 kHz). These Waves enter the ear canal and set the tympanic membrane in motion, transmitting mechanical energy via the ossicular chain to the cochlea. Within the cochlea, sensory hair cells convert mechanical displacements into receptor potentials, initiating the neural code for sound. The resulting signals are conveyed by auditory nerve fibers to the brainstem. Unlike vision or somatosensation, the auditory pathway includes multiple relay stations with extensive bilateral projections and cross-talk between hemispheres, providing redundancy and spatial accuracy.

From the cochlea, afferent fibers project to the CNC in the medulla, where parallel processing streams begin. These outputs target the SOC, the first site of binaural integration, and then converge in the IC

of the midbrain. From this hub, ascending fibers reach the MGB of the thalamus and ultimately the AC (**Figure 16**).

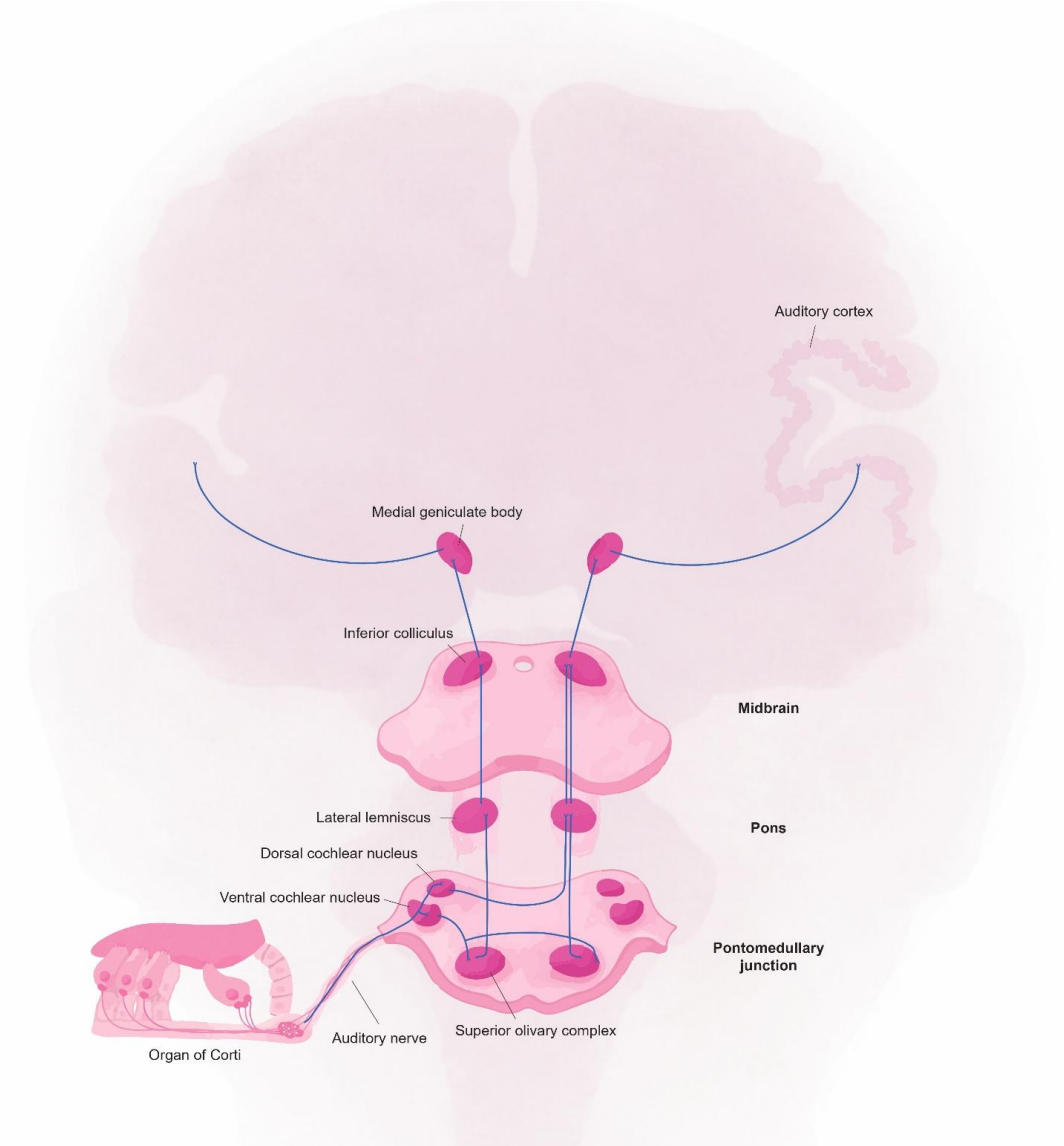


Figure 15. Ascending auditory pathway from cochlea to cortex. Auditory signals are transduced in the organ of Corti containing inner and outer hair cells (left, IHCs; right, OHCs) and transmitted to the cochlear nucleus complex (CNC), superior olivary complex (SOC), lateral lemniscus nuclei (NLL), inferior colliculus (IC), medial geniculate body (MGB), and ultimately the auditory cortex (AC).

5.7. **Systematic Review: Auditory sensitivity in autism: A systematic review of mismatch negativity and mismatch field responses**

Auditory mismatch responses—mismatch negativity (MMN) and mismatch fields (MMF)—are well established electrophysiological markers of pre-attentive auditory discrimination and sensory memory.

These responses, typically elicited using passive oddball paradigms, are increasingly employed to investigate sensory and language development in autism.

This systematic review synthesizes findings from 52 studies comparing MMN and MMF responses in autistic and TD (TD) individuals across childhood, adolescence, and adulthood. Using the SWiM (Synthesis Without Meta-analysis) framework, we identified consistent evidence for attenuated MMN amplitudes and MMF power in autistic children and adolescents, particularly in response to frequency, duration, and speech-based deviants. Prolonged mismatch latencies were also frequently reported and associated with delayed language development and heightened auditory sensitivity.

While some studies suggest developmental normalization of MMN and MMF responses in later childhood or adolescence, atypical right-hemispheric lateralization emerged as a robust finding across both speech and non-speech paradigms, indicating divergent specialization for auditory and language processing in autism. We propose a precision-weighted predictive coding account to explain interindividual and developmental variability in mismatch responses, positing atypical assignment of confidence to sensory prediction errors in autism.

Although study quality was generally fair, methodological heterogeneity, underrepresentation of females, and limited cross-cultural sampling constrain generalizability. Future research should prioritize longitudinal, sex-stratified, and culturally diverse designs, leveraging standardized protocols and collaborative data practices. MMN and MMF responses hold promise as non-invasive translational biomarkers of early-stage sensory prediction and neurodevelopmental divergence in autism.

5.8. **Science communication: the response of the autistic brain to unexpected sounds**

Sensory routines allow us to orient ourselves in everyday life and to adapt to environmental regularities. This study examines how the brain processes repetitive sounds and how it reacts to those that interrupt the auditory routine and alter the sound scene. Using a rat model of autism, the results

show that age and sex modulate these processes and reveal the sensory diversity that exists within the autism spectrum.

From the very first days of life, the brain is immersed in and continuously exposed to a constant flow of sensory stimuli that shape its development. Familiar voices, the sound of the television, or the route to school all form part of the sensory routine of the environment. The developing brain learns from these experiences, extracting regularities in order to build internal models of the world and anticipate what will happen next, allowing it to predict how to act in the future. Over time, these models become increasingly precise and flexible, enabling responses to be adjusted when environmental conditions change.

When something deviates from expectations by breaking the usual regularity, the brain reacts and updates its predictions. In childhood, we respond with curiosity to an unfamiliar voice, with frustration when the television turns off, or with caution when a car horn interrupts the walk to school. This continuous learning process lays the foundation for the development of more complex abilities, such as understanding others' intentions, engaging in social interaction, and acquiring language.

5.8.1. A balance between certainty and surprise

In a neurotypical brain, everyday experience is supported by a balance between certainty and surprise. In divergent brains, such as the autistic brain, this balance appears to operate differently. Some autistic individuals show heightened sensitivity to even subtle changes, while others require greater repetition to recognize environmental regularities. Likewise, everyday experiences may be perceived as unpredictable, uncontrollable, or even overwhelming.

These differences influence how gestures are anticipated, intentions are interpreted, and social situations are navigated. In an autistic brain, the world may be perceived as more changeable, more intense, or less predictable, shaping both sensory experience and interactions with the environment.

5.8.2. Studying neuronal activity using animal models of autism

In our laboratory, we explored how these divergences manifest in auditory processing. We focused on the inferior colliculus, a key region of the auditory brain where the distinction between routine sounds and those that violate expectations begins to emerge. We measured neuronal activity in response to repetitive sounds and to unusual sounds in typical rats and in rat models of autism. To do so, we used a valproate-induced rat model of autism. Valproate is a drug that, when administered during a critical window of embryonic development, produces brain and behavioral alterations comparable to those observed in autism.

In this study, we found that auditory processing in the inferior colliculus differed between typical animals and those exposed to valproate. In typically developing animals, collicular neurons clearly distinguished repetitive sounds from unexpected ones, maintaining a stable balance between adaptation to repetition and responsiveness to novelty. In contrast, in valproate-exposed animals—autism model rats—the balance between adaptation to regularity and response to novelty varied as a function of age and sex. In juvenile animals, sensitivity to repetition was greater and responses to novelty were more unstable, whereas in adults, neuronal activity depended on sex. Females showed a more pronounced neuronal response to surprising sounds, while males exhibited a reduced response.

5.8.3. Divergences that shape everyday experiences

These results reinforce the idea that the autistic brain does not process auditory context in a single, uniform way. Differences across age and sex reflect diverse developmental trajectories within the spectrum. In some cases, this manifests as more rigid behavior in response to change, while in others it appears as heightened sensitivity to novelty. These divergences shape everyday experiences, influencing the ability to anticipate speech sounds, follow conversations in noisy environments, or adapt to disruptions in routine.

For this reason, it is essential to study how the brain builds internal models of sensory routines and how these models are continuously updated based on incoming environmental stimuli. Our results demonstrate that there is no single way of perceiving the world. Each brain develops its own model for anticipation, interpretation, and adaptation to the external environment. Recognizing this diversity broadens our understanding of autism and invites us to value the richness of different ways of experiencing reality.

6. Discussion

Below, we discuss the most relevant findings across each scientific paper; from single-unit recordings of auditory-elicited neural activity to contextual pure tones, to ABRs evoked by pure tones, and behavioral assessments of auditory discrimination by classical oddball presentation.

6.1. Prenatal VPA induces age- and sex-related differences in contextual processing in the inferior colliculus

In this study, we tested how sex, developmental stage, and prenatal VPA exposure shaped predictive processing in the rat IC. We recorded single-unit activity across lemniscal and non-lemniscal IC, and quantified group differences using predictive indices that decomposed neuronal mismatch into repetition suppression and prediction error components. Specifically, we computed normalized indices of neuronal mismatch (iMM), repetition suppression (iRS), and prediction error (iPE) from oddball and cascade control contexts, which allowed us to interpret contextual processing beyond a single mismatch contrast and to isolate the predictive contributions proposed by contemporary predictive-coding frameworks (Friston, 2005; Friston & Kiebel, 2009; Rapaport & Sowman, 2024).

Group-level comparisons in TD controls showed that sex differences in predictive processing emerged in adulthood rather than prepuberty. Adult males exhibited higher iMM and iRS than adult females across IC divisions, consistent with evidence that subcortical auditory processing becomes sexually dimorphic over development (Krizman et al., 2011). This pattern indicated that typical maturation did not simply increase mismatch uniformly across groups; instead, it produced sex-dependent trajectories in how the midbrain suppressed predictable input and, consequently, how strongly it expressed mismatch at the group level.

Prenatal VPA exposure reshaped these developmental patterns and introduced sex-dependent divergence earlier in life. Unlike controls, VPA-exposed prepubertal animals showed sex differences in predictive indices, indicating that prenatal insult shifted the timing and direction of developmental

specialization (Anshu et al., 2022; Chaliha et al., 2020; Nicolini & Fahnestock, 2018). Across groups, these effects supported the idea that autism-relevant phenotypes did not reflect a single uniform deficit, but rather multiple developmental trajectories that differed by sex and age (Lombardo et al., 2019; McFayden et al., 2023; Posserud et al., 2021). Importantly, group-level inference revealed effects that population-level summaries masked, reinforcing the value of modeling sex and age explicitly instead of pooling across them.

The most striking heterogeneity emerged in adult females exposed to VPA. Group-level contrasts indicated that this subgroup expressed increased iMM and iRS alongside reduced iPE relative to other VPA groups, producing a dissociation between enhanced repetition-related suppression and attenuated deviance-related signaling. This profile aligned with predictive-coding interpretations in which overly strong predictions can amplify suppression to repeated input, while reduced precision-weighting of prediction errors can dampen deviance responses without abolishing them (Lawson et al., 2014; Pellicano & Burr, 2012; Rapaport & Sowman, 2024; van de Cruys et al., 2014). In contrast, males and prepubertal females more consistently showed reduced iMM and reduced iRS, a pattern that we interpreted as weaker predictive engagement with repetition structure, consistent with models emphasizing attenuated predictions (hypo-priors) in some autistic phenotypes (Pellicano & Burr, 2012; Rapaport & Sowman, 2024). This group-level split offered a mechanistic route to reconcile why autism research alternately reports attenuated mismatch and atypical repetition effects across cohorts, paradigms, and developmental windows (Ewbank et al., 2017; Lassen et al., 2022; Millin et al., 2018).

Finally, our group-level findings fit with broader evidence that prenatal VPA produces widespread auditory-pathway alterations that could plausibly distort predictive computations already at midbrain stages, including abnormal subcortical structure and atypical responses to complex sounds (Kosmer & Kulesza, 2024; Mansour et al., 2019; Tamaoki et al., 2024; Zimmerman et al., 2020).

By focusing on iMM, iRS, and iPE at the group level, we showed that prenatal VPA did not impose a single "autism-like" signature; instead, it produced sex- and age-dependent predictive phenotypes, with adult females showing a distinctive dissociation between repetition suppression and prediction error that warrants targeted mechanistic follow-up (Kazlauskas et al., 2019; Lacroix et al., 2024; Williams et al., 2025).

6.2. **Sex-divergent organization of predictive indices in the inferior colliculus of two autism-like adult rat models**

In this study, we tested whether biological sex and autism-relevant perturbations reshaped the computational organization of auditory predictive processing in the lemniscal and non-lemniscal IC. We moved beyond descriptive summaries and estimated effects with hierarchical mixed-effects models, which allowed us to quantify model-based contrasts while accounting for subject-level nesting and higher-order interactions in neural datasets (Brehm & Alday, 2022; McCulloch et al., 2008; Yu et al., 2022). We focused on predictive indices that dissociated repetition suppression and prediction error components of neuronal mismatch by comparing responses to standards (STD), deviants (DEV), and cascade controls (CAS) and computing iRS, iPE, and the composite iMM (Friston, 2005; Parras et al., 2017; Pellicano & Burr, 2012; Rapaport & Sowman, 2024; van de Cruys et al., 2014).

First, we examined how control animals organized predictive processing across sex and circuit division under high-intensity stimulation, which reliably elicited contextual modulation and matched the suprathreshold stimulation commonly used in human autism electrophysiology. Control males showed larger iRS than control females in both IC divisions, indicating stronger repetition-based encoding of regularity. In contrast, control females showed larger iPE, indicating stronger prediction-error signaling when sounds violated expected structure. Because iMM integrates these two components, control females expressed lower iMM overall than control males across divisions. This dissociation showed that sex did not simply scale mismatch magnitude; instead, sex biased the balance between repetition suppression and prediction error, consistent with predictive-coding accounts that treat these

computations as separable processes (Friston, 2005; Pellicano & Burr, 2012; Rapaport & Sowman, 2024). These results also aligned with human evidence suggesting sex differences in auditory gain and subcortical response profiles (Krizman et al., 2011; Ruytjens et al., 2007).

Then, we tested how two autism-like conditions—prenatal VPA exposure and heterozygous *Grin2b* deletion—altered predictive indices in a sex- and division-dependent manner. Across models, the strongest effects localized to non-lemniscal circuits, which play a central role in context sensitivity, deviance tracking, and prediction updating along the auditory pathway (Carbajal et al., 2024; Malmierca et al., 2009; Parras et al., 2017). In females, both perturbations increased iMM in the lemniscal IC, indicating heightened mismatch-related signaling at the subcortical entry point of midbrain processing. However, the component profile clarified that this increase did not reflect uniformly enhanced deviance detection. VPA-exposed females showed reduced iPE in the non-lemniscal IC, consistent with weakened prediction-error signaling. *Grin2b*+/– females showed a robust increase in iRS across divisions, and VPA produced a similar increase primarily in the non-lemniscal pathway. Together, these patterns indicated that autism-like perturbations in females increased mismatch sensitivity largely through stronger repetition suppression combined with attenuated prediction-error signaling, especially in non-lemniscal circuits.

In males, atypical predictive processing remained comparatively restricted. Prenatal VPA exposure reduced iMM in the non-lemniscal IC, indicating dampened mismatch sensitivity in circuits most associated with contextual evaluation, while sparing lemniscal responses. Neither VPA nor *Grin2b*+/– altered iRS or iPE in males, and *Grin2b*+/– produced no detectable shifts in predictive indices. This sex-divergent outcome supported the idea that autism-linked perturbations did not impose a uniform change in auditory responsiveness; instead, they reorganized predictive computations differently across sexes and circuits (Rapaport & Sowman, 2024; Sinha et al., 2014; van Boxtel & Lu, 2013; van de Cruys et al., 2014).

Finally, we interpreted the female profile—elevated iRS with reduced iPE—as consistent with overweighted predictions suppressing bottom-up input, yielding mismatch signals driven more by exaggerated adaptation than by deviance-related error signaling (Friston, 2005; Pellicano & Burr, 2012; van de Cruys et al., 2014). We interpreted the male profile—reduced iMM without compensatory increases in iPE—as consistent with under-weighted predictions and reduced contextual constraint on sensory processing (Pellicano & Burr, 2012; van de Cruys et al., 2014).

By comparing teratogenic (VPA) and monogenic (*Grin2b*+/–) models, we showed that distinct etiologies converged on a shared principle: sex strongly shaped how autism-relevant risk factors reweighted predictive components, with the clearest divergence expressed in non-lemniscal IC circuits that have been repeatedly implicated in autism-relevant sensory phenotypes (Gonçalves & Monteiro, 2023; Lee, 2015; Møller et al., 2005; O'connor, 2012).

6.3. **Prenatal VPA induces age- and sex-divergent peak amplitudes of ABRs in rats**

This study tested how sex, age, and prenatal VPA exposure shaped peak amplitudes of click-evoked ABRs across development. In control rats, we observed minimal sex differences before puberty, consistent with evidence that gonadal-hormone modulation becomes functionally relevant after pubertal onset, when steroid signaling begins to shape auditory excitability (Charitidi et al., 2012; Charitidi & Canlon, 2010; Ojeda & Skinner, 2006; Sengupta, 2013). After puberty, adult control females showed larger amplitudes than males in early ABR Waves, particularly Waves I and II, indicating stronger recruitment of early auditory relays.

Age effects complemented these sex differences. Across groups, adults exhibited larger ABR amplitudes than prepubertal animals, consistent with maturation of the auditory pathway through postnatal increases in myelination, synaptic refinement, and improved neural synchrony (Blatchley et al., 1987; Doornaert et al., 2025; Geal-Dor et al., 1993; Zucki et al., 2017). Prior work supports the direction of these effects and the female-biased enhancement observed in adulthood. Human studies

report larger ABR amplitudes in adult women than men (Aloufi et al., 2023; Don et al., 1993; Krizman et al., 2019), and rodent studies report greater auditory sensitivity in adult females (Charlton et al., 2019). Estrogenic modulation likely contributes, as estrogen receptors are expressed across auditory structures and estradiol can enhance auditory responsiveness and plasticity via regulation of inhibitory neurotransmission (Charitidi et al., 2012; Charitidi & Canlon, 2010; Tremere et al., 2009; Tremere & Pinaud, 2011).

Prenatal VPA exposure disrupted these typical amplitude patterns in a sex- and stage-dependent manner. In females, VPA primarily reduced the strength of early brainstem components, with the most pronounced attenuation in Wave II amplitude, suggesting reduced excitability in early relays. In males, VPA effects emerged more strongly at later generators, with reduced amplitudes in later Waves, consistent with dampened recruitment at higher brainstem or midbrain stages. These results supported a sex-specific locus of vulnerability, with VPA reducing early response magnitude in females and later-stage response magnitude in males.

Our amplitude findings aligned with prior work in the VPA model reporting altered subcortical responsiveness and ABR divergences, including reduced early-Wave amplitudes and broader disruptions in auditory encoding, while emphasizing that sex and developmental stage shaped which generators expressed the strongest deficits (Engineer et al., 2014; Favre et al., 2013; Arjun S Malhotra & Kulesza, 2023; Tamaoki et al., 2024). Mechanistically, these sex-divergent amplitude effects likely reflected the interaction between pubertal hormone-dependent tuning of auditory gain and VPA-related teratogenic interference with neurodevelopmental pathways that shape circuit maturation (Charitidi & Canlon, 2010; Crider et al., 2014; Ferri et al., 2018; Kim et al., 2023; Nicolini & Fahnestock, 2018; Tremere & Pinaud, 2011). Overall, the amplitude results showed that prenatal VPA altered typical maturation of ABR response magnitude in a sex-dependent way: females primarily exhibited weaker early responses, whereas males exhibited weaker later responses.

6.4. **Sex-related differences in peak amplitudes of ABRs across two autism-like adult rat models**

In this study, we used click-evoked ABRs to test how sex and autism-relevant etiologies (*Grin2b*+/–+ and prenatal VPA) shaped the magnitude of brainstem responses. Because autism phenotypes reflect both genetic and environmental risk factors (Pugsley et al., 2021) and sex-dependent profiles remain incompletely characterized (Rippon, 2024), we interpreted ABR peak amplitudes as a non-invasive readout of how these factors altered synchronized recruitment along the ascending auditory pathway. This approach also addressed an important translational gap, as most clinical ABR work in autism emphasized supra-threshold responses, while auditory sensitivity in autism spans hypo- to hyper-responsiveness (Marco et al., 2011).

Across Waves, both autism-like models altered peak amplitudes relative to controls, supporting the view that genetic and teratogenic perturbations modified the strength of brainstem synchrony. These amplitude reductions aligned with clinical reports of smaller ABR components in autistic individuals, particularly at later peaks (ElMoazen et al., 2020; Ramezani et al., 2019). Prior work linked such reductions to atypical development of brainstem nuclei, including hypoplasia and cytoarchitectural alterations across early, mid, and late auditory relays (Mansour et al., 2019; Seif et al., 2021; Smith et al., 2019; Zimmerman et al., 2018). In that context, our amplitude effects supported the interpretation that autism-relevant perturbations influenced auditory brainstem response magnitude, which could contribute to broader difficulties in processing complex acoustic environments (Russo et al., 2008; Seif et al., 2021).

Notably, sex differences in peak amplitudes emerged only in controls. Control females showed larger peak amplitudes than control males in Waves I, II, and V, consistent with human evidence that females often exhibit larger click-evoked ABR components (Krizman et al., 2012, 2019; Zakaria et al., 2019). This pattern supported a hormonal and neuromodulatory framework in which estrogen-related mechanisms can enhance auditory responsiveness (McFadden, 2009). Brainstem circuits can locally

generate estradiol via aromatase and show rapid estrogen-dependent modulation of excitatory transmission, including NMDA-receptor-linked mechanisms (Bereiter et al., 2019; Smith & McMahon, 2005; Srivastava et al., 2008). Consistent with that framework, key auditory generators implicated in ABR peaks express estrogen receptors (Charitidi & Canlon, 2010), which may help explain why typical sex differences appeared in controls.

In contrast, *Grin2b*+/–+ and VPA animals showed no sex-related amplitude differences. This loss of sex divergence suggested that autism-like perturbations blunted or reorganized the biological mechanisms that normally differentiate female and male response magnitude. For VPA, the absence of sex effects was consistent with reports of disrupted aromatase expression or estrogen-related signaling in VPA-exposed models (Hameed et al., 2023; Symeonides et al., 2024). Together, these findings supported a model in which autism-relevant genetic and environmental insults not only altered ABR peak amplitudes, but also reduced the typical expression of sex-dependent amplification in brainstem responses.

6.5. **The NMDA receptor antagonist MK-801 disrupts auditory-guided behavior in an operant oddball task**

In this study, we examined how NMDA receptor hypofunction induced by a single dose of MK-801 altered operant auditory discrimination in female rats. In this oddball task, standard tones established a no-go context, whereas deviant tones served as a discriminative cue signaling that a go response would be reinforced. Because animals relied on the predictable repetition of the standard to maintain a stable no-go rule across trials, successful performance depended strongly on response inhibition and on the ability to use recent auditory regularities to regulate behavior.

Schizophrenia involves disruptions in executive functioning, including working memory, cognitive flexibility, and response inhibition, which support context-appropriate control of actions (Diamond, 2013; Friedman & Miyake, 2017; Miyake et al., 2000; Wobrock et al., 2009). In our task, response

inhibition was the primary executive demand. MK-801 selectively impaired this inhibitory control: animals showed more false alarms (FA) and fewer correct rejections (CR), while hit (HIT) and miss (MISS) rates remained stable. This pattern indicated that MK-801 did not markedly compromise deviant detection but instead reduced the capacity to withhold responses when the standard tone signaled the no-go context.

Evidence from other behavioral paradigms supported this interpretation. In differential reinforcement of low-rate responding tasks, MK-801 increased premature responding, consistent with impaired inhibitory control and weakened temporal regulation (Welzl et al., 2013). In peak-interval procedures, MK-801 elevated response rates and broadened temporal response distributions, reflecting reduced suppression of premature actions (Miller et al., 2006). In addition, NMDA receptor antagonists induced hyperlocomotion and stereotyped behaviors that were widely interpreted as disinhibited motor output (Ford et al., 1989; Latysheva & Rayevsky, 2003; Martin et al., 1997; Smith et al., 2011; Svoboda et al., 2015; Whishaw & Auer, 1989). Together, these convergent findings supported the conclusion that NMDA receptor blockade biased behavior toward faster, less regulated responding, consistent with the increased FA observed here.

Beyond inhibitory control, our results also suggested that MK-801 disrupted the use of auditory regularities that stabilized the no-go context. The increase in FA and decrease in CR, together with preserved HIT and MISS rates, implied that the deviant cue remained effective but that the standard-based rule deteriorated. This interpretation aligned with extensive evidence that NMDA receptors supported extraction, maintenance, and updating of short-term auditory regularities. Pharmacological and electrophysiological studies showed that NMDA receptor antagonists reduced mismatch negativity (MMN) amplitude and disrupted auditory sensory memory traces that supported regularity-based predictions (Javitt et al., 1996; Todd et al., 2013; Umbricht et al., 2002; Umbricht & Krljesb, 2005).

Although we did not measure MMN, these results converged on the idea that NMDA-dependent signaling was required to maintain an internal model of the recent acoustic past.

The ISI dependence on the MK-801-induced influence strengthened this conclusion. Longer ISIs increased the demand to maintain the no-go context across temporal gaps, a process linked to NMDA-dependent integration of stimulus history and short-term temporal dynamics (Buonomano & Maass, 2009; Murray et al., 2017). Accordingly, MK-801 produced the clearest disruption at 1.5–2 s ISIs, consistent with a reduced ability to sustain and update internal representations of predictable auditory events over time.

These behavioral effects fit within broader accounts of schizophrenia in which impaired executive control and disrupted early auditory processing jointly contributed to symptoms (American Psychiatric Association, 2022; Javitt & Sweet, 2015). Schizophrenia showed robust reductions in MMN, a pre-attentive deviance response that depended on short-term auditory sensory memory (Näätänen et al., 2010), and MMN was selectively disrupted by NMDA receptor antagonism with converging evidence from animal models (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001). Schizophrenia also showed deficits in 40-Hz auditory steady-state responses, indexing reduced power and phase locking (Vohs et al., 2012), and attenuated stimulus-evoked gamma activity that reflected altered local excitatory–inhibitory dynamics (Carlén et al., 2012; Gonzalez-Burgos et al., 2015; Spencer et al., 2004). Collectively, these abnormalities supported a shared disruption in how auditory circuits represented regularities, encoded sensory evidence, and updated internal models of the environment.

Predictive coding frameworks proposed that hierarchical generative models predicted sensory input and updated these predictions by minimizing prediction errors (Friston, 2005; Rao & Ballard, 1999). Computational accounts of psychosis framed schizophrenia as an instability in this message passing because the system assigned abnormal precision to priors and/or prediction errors, degrading inference from context (Adams et al., 2013; Stephan et al., 2009). Within this framework, NMDA receptor

hypofunction provided a plausible mechanistic contributor because NMDA-dependent synaptic integration and plasticity supported short-term representations and stabilized recurrent computations that shaped the impact of prediction error signaling (Adams et al., 2013; Friston, 2005; Stephan et al., 2009). Although we did not measure neural activity, the selective increase in FA and ISI-dependent loss of contextual stability observed here were consistent with impaired maintenance and updating of auditory expectations over time, a process proposed to be vulnerable in schizophrenia.

6.6. **Book chapter**: **from development to intervention: the auditory-emotional processing of music**

We described auditory development as a continuous process that began in utero and progressed through early childhood, shaped by intrinsic maturation programs and the acoustic environment. We treated music as a structured sensory signal whose rhythmic, harmonic, and dynamic regularities recruited different levels of the ascending auditory pathway in coordinated ways. We noted that peripheral and brainstem structures encoded basic acoustic features early, while midbrain and thalamic relays increasingly integrated temporal and spectral regularities that supported melody and rhythm after birth (Moore & Linthicum, 2007). We also emphasized that auditory cortex hierarchies supported repetition, deviance, and expectation processing that contributed to musical form and meaning (Rauschecker & Scott, 2009; Zatorrea & Salimpoor, 2013).

We argued that early auditory experience acted as an active regulator of maturation rather than a passive backdrop. We summarized evidence that structured auditory environments enriched in predictable rhythmic and melodic patterns supported synaptic refinement, myelination, and coordinated cortical timing, whereas deprivation or chaotic noise exposure delayed maturation and weakened temporal precision (Kraus & Chandrasekaran, 2010; Tierney & Kraus, 2013). We highlighted that even passive musical stimulation promoted plasticity and supported speech–music coupling and affect regulation in infancy and childhood (Putkinen et al., 2014; Trainor & Zatorre, 2008). In preterm neonates, we described gentle rhythmic and melodic interventions, including

lullabies and parental singing, as supporting physiological stability, autonomic balance, and emerging auditory–limbic connectivity (Lordier et al., 2019; Yakobson et al., 2020).

We framed music's emotional power as arising from reciprocal connections between auditory pathways and limbic and reward systems, including the amygdala, hippocampus, nucleus accumbens, and orbitofrontal cortex (Koelsch, 2014; Zatorrea & Salimpoor, 2013). We linked emotionally salient music to dopaminergic reward engagement and autonomic modulation, and we connected these physiological effects to experienced emotion, empathic resonance, and emotional contagion that supported social synchrony (Juslin & Västfjäll, 2008; Stark & Hössinger, 2018). On that basis, we positioned music as a practical bridge between sensory encoding and affective regulation across development and clinical contexts.

We then focused on early developmental windows relevant to intervention. We described late gestation as a period when fetal cochlear and central auditory circuits refined frequency sensitivity, and when maternal sounds and attenuated external speech and music reached the fetus largely through tissue and bone conduction (Alberts & Ronca, 1996; Graven & Browne, 2008). We noted that maternal tissues and amniotic fluid filtered high frequencies, biasing prenatal exposure toward low-frequency rhythmic contours that scaffolded early tuning (Armitage et al., 1980; Gerhardt & Abrams, 2000; Querleu et al., 1988). We contrasted this protected soundscape with the neonatal intensive care unit (NICU), where intermittent mechanical noise often exceeded recommended levels and risked either overstimulation or patterned-input deprivation (Blackburn, 1998; Wachman & Lahav, 2011). We described developmental care approaches that "parentalized" the NICU through skin-to-skin care, infant-directed speech, and live singing to restore biologically familiar rhythmic and prosodic cues (Als et al., 1986; Charpak et al., 2005; Conde-Agudelo et al., 2000). Finally, we summarized evidence that caregiver singing and music therapy supported regulation and bonding in preterm infants and that music-based approaches improved language, executive, and emotional outcomes across development and clinical

populations by engaging auditory–limbic–motor plasticity (Haslbeck et al., 2020; Loewy et al., 2013; Sihvonen et al., 2017; Winkler et al., 2009).

6.7. **Systematic review**: **postnatal development of mismatch responses in typically developing and autistic individuals**

We synthesized 52 MMN/MMF studies in autism and followed SWiM because heterogeneity in age, deviants, modality (EEG/MEG), and analysis prevented meaningful quantitative pooling (Campbell et al., 2020). We therefore compared qualitative "boundary conditions" across development and interpreted findings in relation to core mismatch physiology—regularity formation/maintenance, deviance detection timing, and (for speech) hemispheric weighting (Näätänen et al., 2007, 2011, 2012).

Across the lifespan, three tendencies recurred under specific conditions when autistic groups were compared with TD peers: reduced MMN/MMF amplitude was most commonly reported in childhood; prolonged latency appeared in a subset of studies, often for particular deviants and sometimes within-autism subgroups; and when laterality could be inferred, studies more often described relatively greater right-hemisphere weighting, most clearly for speech paradigms. We interpreted these patterns cautiously because many datasets reported null effects or larger responses in autism and because formal hemispheric contrasts were often not tested.

We interpreted attenuated mismatch amplitude as reduced neural expression of deviance relative to the established regularity, rather than a global deficit in discrimination. Within sensory-memory accounts, MMN/MMF depended on building and briefly maintaining a representation of stimulus regularities and generating a mismatch when input violated that representation (Garrido et al., 2009; Näätänen et al., 2001, 2007). Under this framing, smaller responses in some autistic cohorts plausibly reflected weaker or less stable regularity representations, reduced deviant–regularity contrast, or faster model updating under particular stimulus statistics (Näätänen et al., 2012). The developmental boundary conditions supported this view: attenuation appeared most often in childhood—particularly for non-speech frequency deviants—whereas adolescence and adulthood showed more mixed outcomes that

depended on deviant feature and paradigm structure (Chen et al., 2020; Di Lorenzo et al., 2020; Gomot et al., 2011; Randeniya et al., 2023; Sato et al., 2025; Vlaskamp et al., 2017). Speech paradigms further indicated feature dependence: several studies reported reduced mismatch for phoneme/vowel identity or prosody, whereas pitch-based contrasts sometimes showed preserved or enhanced responses (Fan & Cheng, 2014; Korpilahti et al., 2006; Lepistö et al., 2005, 2006, 2008; Lindström et al., 2016, 2018; Ruiz-Martínez et al., 2020; Schall et al., 2024).

We treated mismatch latency as a constraint on the timing of deviance detection once a regularity was established. Within sensory-memory models, latency indexed how quickly input was compared with the current regularity representation and how rapidly that representation was adjusted following a violation (Näätänen et al., 2001, 2007). Prolonged latency emerged inconsistently across childhood paradigms and appeared more clearly in some within-autism subgroup analyses, including language-stratified MEG datasets, emphasizing phenotype dependence rather than a uniform autism effect (Berman et al., 2016; Gomot et al., 2002; Green et al., 2020; Lassen et al., 2022; Roberts et al., 2011).

Speech-evoked MMN/MMF findings supported a feature- and phenotype-dependent account rather than a single direction of altered speech discrimination. When laterality could be inferred, studies more often described relatively greater right-hemisphere weighting for speech contrasts (e.g., prosody, stress, pitch/phonemic cues), but many EEG studies could not test hemispheric contrasts formally, and effects varied by method and contrast (Jansson-Verkasalo et al., 2005; Korpilahti et al., 2006; Kujala et al., 2005; Lepistö et al., 2006; Ma et al., 2018; Matsuzaki et al., 2019). We treated these findings as suggestive and consistent with broader reports of atypical language-network lateralization and connectivity in autism, while noting that direct links between mismatch laterality and continuous language measures remained rare (Finch et al., 2017; Floris et al., 2016; Herbert et al., 2003; Herringshaw et al., 2016).

Predictive-processing models provided a computational complement to sensory-memory accounts by describing mismatch as prediction-error signaling when deviants violated an internal model of recent acoustic statistics, with precision weighting modulating prediction-error gain (Clark et al., 2018; Friston, 2005; Garrido et al., 2009; Hohwy, 2013). Under this framework, attenuated amplitude and/or prolonged latency could emerge when regularities were represented with lower precision or when prediction errors were down-weighted for specific deviant dimensions, yielding selective (not universal) effects that varied with stimulus statistics and phenotype (Brock, 2012; Lawson et al., 2014; Pellicano & Burr, 2012; van de Cruys et al., 2014).

Overall, the literature supported boundary-condition effects rather than a single MMN/MMF phenotype in autism: developmental stage, deviant feature, paradigm statistics, modality, and within-autism sensory/language profiles jointly determined whether mismatch differences emerged, and in what direction.

7. Conclusions

I. We showed that auditory context processing varied systematically with **sex**, **developmental stage**, and **etiology**, rather than reflecting random inconsistency across autism-related models: female rats exhibited increased neuronal mismatch, whereas male rats showed reduced neuronal mismatch relative to respective controls.

II. Auditory brainstem response amplitudes varied systematically with sex, developmental stage, and autism-relevant etiology, with typical age-related increases and female-biased response magnitudes present in controls but altered or absent in autism-related models.

III. Prenatal valproic acid exposure and Grin2b heterozygous deletion reduced brainstem response amplitudes and reorganized typical sex-dependent patterns, producing sex-specific alterations in the contribution of early versus later auditory generators while preserving auditory detection thresholds.

IV. MK-801 injections induced a selective impairment in standard-based behavioral control during an operant auditory oddball task, increasing false alarms and reducing correct rejections in an inter-stimulus-interval–dependent manner while preserving deviant detection performance.

V. Structured acoustic experience across development, and **music in particular, engaged ascending auditory pathways and auditory–limbic–motor circuits**, supporting the regulation of auditory processing and emotional responses during sensitive developmental windows.

VI. Mismatch negativity and mismatch field responses in autism exhibited context-dependent variation rather than a uniform alteration, with differences in amplitude, latency, and hemispheric weighting depending on developmental stage, deviant feature, paradigm statistics, and participant characteristics.

Efectos del sexo, la edad y la etiología sobre el procesamiento auditivo en dos modelos de rata de autismo: evidencia a partir de respuestas auditivas del tronco encefálico y medidas neurales y conductuales dependientes del contexto

1. Introducción

1.1. Procesamiento distribuido a lo largo de la vía auditiva

El entorno acústico es rico, estructurado y está en constante cambio, y esta complejidad se refleja en la propia organización del sistema auditivo. Para transformar paisajes sonoros dinámicos en representaciones significativas, el procesamiento auditivo se despliega a lo largo de una vía jerárquicamente organizada y densamente interconectada que permite tanto una codificación sensorial precisa como una integración flexible a lo largo del tiempo (**Figura 1**).

La información auditiva entra en el sistema nervioso central a través del nervio auditivo y establece sus primeras sinapsis en el complejo del núcleo coclear (CNC), que distribuye vías ascendentes paralelas especializadas en el procesamiento temporal, espectral y binaural a través del complejo olivar superior (SOC) y los núcleos del lemnisco lateral (NLL) (Cant & Benson, 2003; Winer & Schreiner, 2005). Estas corrientes paralelas convergen en el colículo inferior (IC), un importante centro integrador del mesencéfalo que recibe entradas ascendentes de casi todos los núcleos auditivos inferiores y las integra con extensas proyecciones descendentes, incluidas densas entradas corticofugales procedentes de la corteza auditiva (AC) que se dirigen de forma diferencial a sus subdivisiones (Malmierca et al., 2008; Winer, 2005).

A través de esta convergencia, el IC desempeña un papel central en la integración de características acústicas a lo largo del tiempo y la frecuencia, y en la modulación de las propiedades de respuesta en función de la historia reciente del estímulo. Desde el IC, las señales auditivas se transmiten al cuerpo geniculado medial (MGB) del tálamo, cuyas divisiones ventral, dorsal y medial difieren en conectividad y especialización funcional, y participan en bucles tálamo-corticales recurrentes con campos corticales auditivos primarios y no primarios (Lee & Murray Sherman, 2010; Winer & Schreiner, 2005).

Es importante destacar que la vía auditiva no es estrictamente feed-forward: las proyecciones descendentes córtico-talámicas y córtico-coliculares proporcionan sustratos anatómicos mediante los cuales la información contextual y las expectativas pueden influir en el procesamiento auditivo a múltiples niveles jerárquicos (Malmierca et al., 2019; Winer, 2005).

Esta arquitectura jerárquica y recurrente permite que el procesamiento auditivo vaya más allá de la codificación momento a momento, reteniendo información a corto plazo y sesgando las respuestas en función de la entrada reciente. Como resultado, la actividad neuronal refleja no solo las propiedades físicas inmediatas de los sonidos, sino también la estructura estadística más amplia de las secuencias acústicas, sentando las bases para los mecanismos de procesamiento auditivo dependientes del contexto que se describen a continuación.

1.2. Procesamiento del contexto auditivo en entornos acústicos

Los entornos auditivos se caracterizan por regularidades estadísticas, pero están continuamente interrumpidos por eventos que se desvían de los patrones recientes. El sistema auditivo explota estas regularidades extrayendo estructura de las corrientes sonoras en curso y señalando cuándo los sonidos entrantes violan expectativas establecidas (Garrido et al., 2009; Näätänen et al., 2001, 2011). En esta tesis, definimos el contexto como la estructura probabilística del entorno auditivo, es decir, la repetición y estabilidad de los eventos acústicos que permiten a los oyentes formar predicciones y ajustar de forma flexible el procesamiento sensorial (Barch & Ceaser, 2012; Javitt & Sweet, 2015).

La extracción de regularidades y la detección de desviaciones dependen en gran medida de mecanismos automáticos y preatencionales que mantienen representaciones de corta duración de la entrada sensorial reciente y comparan continuamente los nuevos eventos con estos modelos internos (Näätänen et al., 2011, 2012). La capacidad del sistema auditivo para filtrar automáticamente estímulos predecibles y resaltar sonidos únicos e impredecibles se conoce como detección de la desviación (*deviance detection*) (Escera & Malmierca, 2014; Grimm & Escera, 2012). En otras palabras, la

detección de la desviación es un proceso clave que surge de mecanismos internos finamente ajustados capaces de discriminar entre sonidos familiares y novedosos.

1.2. Autismo y heterogeneidad de las características auditivas en sensibilidad y escenas acústicas complejas

En el trastorno del espectro autista, en adelante denominado *autismo*, propuestas recientes sugieren que las representaciones internas de las regularidades ambientales pueden diferir de las típicas, con consecuencias para las respuestas adaptativas ante eventos inesperados (**Figura 2**) (Kujala et al., 2013; Rapaport & Sowman, 2024). Tanto en personas autistas como en individuos con desarrollo típico, estos mecanismos no son estáticos: la formación de regularidades y la detección de desviaciones continúan madurando a lo largo del desarrollo (Bishop et al., 2011; Millin et al., 2018; Sinha et al., 2014), aunque sigue sin estar claro si y cómo estas trayectorias difieren en función del sexo biológico.

El autismo es una condición del neurodesarrollo caracterizada por diferencias en la comunicación e interacción social, junto con patrones restringidos y repetitivos de comportamiento (American Psychiatric Association, 2022). Las personas autistas informan con frecuencia experiencias sensoriales distintivas, y la percepción auditiva contribuye de manera destacada a esta heterogeneidad (Gonçalves & Monteiro, 2023; Marco et al., 2011).

Dentro del dominio auditivo, los estudios describen una marcada variabilidad en la sensibilidad y la capacidad de respuesta. Los informes abarcan desde una sensibilidad aumentada a sonidos específicos hasta una sensibilidad reducida en función de las características del estímulo y las demandas contextuales (Glod et al., 2015; Gomes et al., 2008; Ha et al., 2015). Otros trabajos documentan dificultades en entornos acústicos complejos que requieren filtrar entradas competidoras y seguir objetivos a lo largo del tiempo, incluidas escenas en las que los sonidos relevantes deben segregarse de fuentes concurrentes (Mansour & Kulesza, 2020; Smith et al., 2019).

En conjunto, estas observaciones motivan un enfoque mecanístico centrado en cómo los oyentes utilizan la historia acústica reciente para formar expectativas estables y detectar desviaciones. El procesamiento del contexto auditivo —la formación de regularidades y la detección de desviaciones bajo estadísticas de estímulo controladas— proporciona así una dimensión abordable para examinar la heterogeneidad en el autismo sin presuponer una única dirección uniforme del efecto a través de los contextos de escucha (Kujala et al., 2013; Orekhova & Stroganova, 2014).

1.3. Etapa del desarrollo y sexo biológico como moduladores estructurados en el autismo

El momento del desarrollo modela el procesamiento del contexto auditivo porque la formación de regularidades y la detección de desviaciones continúan madurando a lo largo de la infancia, la adolescencia y la edad adulta, y las trayectorias dependen de las características del estímulo y del contexto experimental (Bishop et al., 2011; Gaeta et al., 1998; Lindín et al., 2013). En el autismo, la detección de la desviación depende del contexto del estímulo y varía entre individuos y edades, de modo que agrupar amplios rangos de edad puede conducir a interpretaciones poco restringidas (Chen et al., 2020; Gomot et al., 2006; Haesen et al., 2011; Kujala et al., 2013; Marco et al., 2011).

El sexo biológico añade un segundo modulador que con frecuencia no se modela adecuadamente. Estudios epidemiológicos informan que el autismo se diagnostica con mayor frecuencia en varones y muestran que la proporción de diagnóstico varón:mujer disminuye a lo largo del desarrollo, desde aproximadamente 4:1 en la infancia hasta alrededor de 2,6:1 en la edad adulta (Loomes et al., 2017). Las prácticas diagnósticas y la presentación fenotípica probablemente contribuyen al infradiagnóstico en mujeres, y muchos conjuntos de datos infrarepresentan a mujeres autistas, lo que limita la inferencia dependiente del sexo (Dean et al., 2017; Lai et al., 2015; Rippon, 2024). Independientemente del autismo, estudios fisiológicos describen diferencias relacionadas con el sexo en la temporización y sincronía auditivas, lo que convierte al sexo en un determinante plausible de cómo los sistemas

auditivos codifican regularidades y registran desviaciones (Dehan & Jerger, 1990; Michalewski et al., 1980; Møller & Moore, 2000; Zakaria et al., 2019).

En consecuencia, esta tesis examinó explícitamente el procesamiento del contexto auditivo a lo largo de distintas etapas del desarrollo y del sexo biológico, tratando ambos factores como moduladores estructurados de la variación neurodesarrollativa en el autismo.

1.4. Medidas neuronales de la detección de la desviación auditiva

1.4.1. Negatividad por desajuste (MMN) como índice operacional

La detección neural del cambio auditivo se evalúa con mayor frecuencia mediante la negatividad por desajuste (*mismatch negativity*, MMN; **Figura 3**), un potencial relacionado con eventos registrado mediante electroencefalografía (EEG). La MMN es un componente del potencial evocado auditivo que refleja la capacidad del cerebro para detectar cambios en el entorno acústico, es decir, la detección de la desviación. La MMN puede evocarse ante cualquier alteración discriminable de la entrada auditiva utilizando un paradigma clásico *oddball*, en el que estímulos auditivos infrecuentes (desviantes, impredecibles; ~10% de probabilidad) se intercalan aleatoriamente dentro de una secuencia de estímulos regulares (estándar, predecibles; ~90% de probabilidad) (Näätänen, 2018). La amplitud de la MMN refleja la magnitud de la diferencia neural entre las respuestas a tonos estándar y desviantes, y suele alcanzar su máximo aproximadamente entre 100 y 250 ms tras el inicio del estímulo.

Los paradigmas *oddball* pasivos evocan la MMN mediante la presentación de desviantes infrecuentes que violan una regularidad establecida por la repetición de estímulos estándar (Garrido et al., 2009; Näätänen et al., 2001, 2011). Dado que la MMN no requiere una respuesta explícita, permite evaluar la formación de regularidades y la detección de la desviación bajo demandas mínimas de tarea y reduce la sensibilidad a factores de confusión relacionados con la comprensión de instrucciones, las

estrategias de respuesta, la atención sostenida y la selección de respuestas (Chen et al., 2020; Foss-Feig et al., 2012; Kujala et al., 2013).

En el autismo, los estudios de MMN muestran hallazgos heterogéneos, con variaciones en amplitud y latencia en función de la clase de estímulo, la estructura probabilística, la temporización, los rangos de edad y las características de los participantes (Chen et al., 2020; Foss-Feig et al., 2012; Haesen et al., 2011; Schwartz et al., 2018).

1.4.2. MMN durante el desarrollo típico y en el autismo

A lo largo del desarrollo típico, las respuestas de desajuste cambian desde la infancia hasta la adolescencia, pero las trayectorias relacionadas con la edad en amplitud y latencia de la MMN siguen siendo heterogéneas y dependen en gran medida del contexto del estímulo y del diseño experimental (Bishop et al., 2011; Gaeta et al., 1998; Lindín et al., 2013). Algunos paradigmas muestran incrementos o disminuciones de la amplitud con la edad, mientras que otros muestran cambios mínimos, lo que respalda la idea de que las representaciones de regularidades auditivas y la detección del cambio maduran de forma prolongada, en lugar de seguir una trayectoria uniforme única (Bishop et al., 2011; Lindín et al., 2013).

En el autismo, los patrones del desarrollo resultan aún más variables, con cambios dependientes de la edad que divergen entre estudios en lugar de converger en una dirección consistente. Durante la infancia, varios estudios informaron amplitudes de MMN reducidas en comparación con pares con desarrollo típico, mientras que otros describieron respuestas comparables o incluso aumentadas, lo que sugiere que las diferencias en el contexto del estímulo modulan cómo las violaciones de regularidad se expresan en las respuestas neuronales (Abdeltawwab & Baz, 2015; Čeponienė et al., 2004; Ferri et al., 2018; Gomot et al., 2011; Vlaskamp et al., 2017). Evidencia procedente de muestras adolescentes y adultas indicó además que las diferencias entre grupos pueden atenuarse o persistir dependiendo de las características del paradigma, lo que es coherente con trayectorias del desarrollo divergentes más

que con un retraso uniforme (da Silva Mayerle et al., 2023; Fan & Cheng, 2014; Hudac et al., 2018; Kujala et al., 2005; Lassen et al., 2022).

Los hallazgos en latencia fueron igualmente heterogéneos a lo largo del desarrollo, con estudios que informaron tanto adelantos como prolongaciones temporales del desajuste dependiendo de la edad y del paradigma, y con trabajos basados en habla y magnetoencefalografía que mostraron además que las diferencias temporales variaban entre muestras en lugar de aparecer de forma consistente en cohortes autistas (Berman et al., 2016; Gomot et al., 2002; Green et al., 2020; Matsuzaki et al., 2019; Roberts et al., 2011).

En conjunto, estos resultados motivaron enfoques informados por el desarrollo que consideran el contexto del estímulo como un determinante central de la variación relacionada con la edad en la amplitud y latencia de la MMN. En este marco, las interpretaciones cognitivas clásicas de la MMN y los enfoques teóricos más recientes ofrecen perspectivas complementarias para explicar cómo la etapa del desarrollo y el contexto del estímulo moldean la expresión de las respuestas de desajuste a través de paradigmas y poblaciones.

1.4.3. Interpretaciones cognitivas clásicas de la MMN

Se han propuesto diversos modelos para explicar cómo el sistema auditivo genera respuestas de desajuste, y estos marcos teóricos han ayudado a interpretar por qué la amplitud y la latencia de la MMN varían entre paradigmas, etapas del desarrollo y cohortes clínicas. Dos perspectivas influyentes incluyen la hipótesis de la adaptación y la hipótesis de ajuste del modelo o traza de memoria, que enfatizan mecanismos fisiológicos y cognitivos, respectivamente (May & Tiitinen, 2010; Winkler, 2007).

Es importante destacar que la hipótesis de la traza de memoria surgió principalmente a partir de estudios electrofisiológicos en humanos, mientras que las explicaciones basadas en la adaptación se

apoyaron fuertemente en la neurofisiología animal, donde la adaptación específica al estímulo podía medirse directamente (May & Tiitinen, 2010; Näätänen & Michie, 1979; Winkler, 2007).

La *hipótesis de la adaptación* atribuye los efectos tipo desajuste a la adaptación específica al estímulo, mediante la cual la repetición de estímulos estándar reduce la capacidad de respuesta neuronal en la corteza auditiva a través de mecanismos pasivos como la depresión sináptica, mientras que las poblaciones neuronales sintonizadas con el estímulo desviado permanecen relativamente menos adaptadas y responden con mayor intensidad cuando aparece el desviado (Fishman, 2014; Jääskeläinen et al., 2004; May et al., 1999; May & Tiitinen, 2010; Ulanovsky et al., 2003). Este enfoque predice que la magnitud y la temporización del desajuste dependerán de las estadísticas del estímulo y de la estructura de repetición, ya que estos factores controlan la fuerza y la selectividad de la adaptación al estándar (May & Tiitinen, 2010; Fishman, 2014).

En contraste, la *hipótesis de ajuste del modelo* o *traza de memoria* propone que la repetición del estímulo estándar establece una representación sensorial de corta duración, sustentada principalmente por generadores corticales auditivos, y que la actividad de desajuste refleja una discrepancia entre esta representación y la entrada sensorial entrante (Näätänen & Michie, 1979; Nyman et al., 1990; Winkler, 2007; Winkler et al., 1996). Este marco predice una mayor sensibilidad a los factores que alteran la estabilidad o actualización de las representaciones de regularidad, incluidas las demandas de la tarea, la complejidad del estímulo y los perfiles individuales (Winkler, 2007).

En conjunto, estas perspectivas ofrecieron rutas complementarias para explicar la heterogeneidad observada: los modelos centrados en la adaptación predicen variabilidad cuando los paradigmas difieren en repetición y solapamiento espectral, mientras que los modelos de traza de memoria predicen variabilidad cuando los paradigmas difieren en la fortaleza de la formación y mantenimiento de regularidades (May & Tiitinen, 2010; Winkler, 2007). Esta distinción resulta particularmente relevante para el autismo, donde trayectorias del desarrollo divergentes podrían reflejar cambios en el peso

relativo de la adaptación basada en repetición frente a las representaciones internas de regularidad, dando lugar a reducciones, incrementos o efectos nulos dependiendo de las estadísticas del estímulo y de las características de la cohorte.

Al mismo tiempo, varias propiedades empíricas de la MMN motivaron un enfoque teórico más amplio. La MMN emerge bajo escucha pasiva y sin conciencia explícita, y puede reflejar violaciones de regularidades complejas, lo que apoya mecanismos de inferencia automática más allá de la actualización del modelo dependiente de la atención (Winkler, 2007). Además, la adaptación específica al estímulo y la actividad relacionada con el desajuste se han observado a múltiples niveles de la vía auditiva, incluidos niveles subcorticales, lo que sugiere contribuciones distribuidas que no quedan capturadas por un único mecanismo cortical (Koelsch, 2014; Malmierca et al., 2019). En el autismo, esta visión más amplia concuerda con hallazgos no uniformes dependientes de la edad y del contexto en la amplitud y latencia de la MMN, lo que sugiere que la variabilidad puede surgir de cambios en el peso relativo de la entrada sensorial y de las regularidades contextuales. Este conjunto de evidencias motivó el uso de la *codificación predictiva* como marco unificador.

1.4.4. Codificación predictiva: la teoría unificadora

La codificación predictiva concibe la percepción como un proceso inferencial en el que los sistemas neuronales generan expectativas a partir de las regularidades del entorno y actualizan dichas expectativas cuando la entrada sensorial se desvía de lo que el sistema predice (**Figura 4**) (Friston, 2005; Garrido et al., 2009). Dentro de este marco, las respuestas de desajuste se interpretan habitualmente como señales de error de predicción de tipo ascendente (*bottom-up)*, que se generan cuando se violan regularidades previamente establecidas, mientras que la entrada predecible evoca respuestas reducidas en parte porque aporta menos información relevante para la actualización de los modelos internos (Garrido et al., 2009; Näätänen et al., 2012). Una vez que los modelos se actualizan, las predicciones descendentes (*top-down)* se propagan a lo largo de la jerarquía auditiva, suprimiendo

las respuestas a estímulos esperados y modulando la sensibilidad neuronal a desviaciones futuras, integrando así la atenuación asociada a la repetición y el realce asociado a la desviación dentro de un único esquema computacional.

Esta teoría constituye uno de los marcos contemporáneos más influyentes sobre la función neural, en parte porque reformula la percepción y la cognición como procesos inferenciales más que como transformaciones puramente *feed-forward* (Heilbron & Chait, 2018). El respaldo empírico de este marco ha surgido de forma destacada a partir de estudios sobre adaptación específica al estímulo descritos a múltiples niveles de la vía auditiva, incluidas estructuras subcorticales y corticales (Casado-Román et al., 2020; Parras et al., 2017; Sánchez et al., 2025). Estos trabajos introdujeron un cambio metodológico en el estudio de la detección de la desviación al separar explícitamente las respuestas neuronales en componentes relacionados con la repetición y con la desviación, utilizando secuencias de control sin repetición desarrolladas originalmente en la literatura sobre MMN (Jacobsen et al., 2003; Jacobsen & Schröger, 2001; Schröger & Wolff, 1996). En este marco, la diferencia de respuesta entre estímulos desviantes y estándar se conceptualiza como *desajuste neuronal* (nMM), proporcionando una descripción más mecanicista de cómo las regularidades contextuales y sus violaciones se representan a nivel de neurona individual (**Figura 5**).

De forma crucial, la codificación predictiva integra contribuciones de múltiples niveles de procesamiento, permitiendo que tanto respuestas corticales como subcorticales reflejen interacciones entre la evidencia sensorial y las expectativas contextuales. En el autismo, este marco ofrece una interpretación principiada de los hallazgos heterogéneos al proponer que las diferencias en el desarrollo y entre individuos pueden alterar el balance o la precisión relativa de las predicciones y de las señales sensoriales, dando lugar a variabilidad dependiente del contexto, de la edad y, potencialmente, del sexo en la amplitud y la latencia de las respuestas de desajuste, en lugar de desplazamientos uniformes entre paradigmas.

1.5. El colículo inferior como enclave integrador

Los modelos animales permiten la localización y descomposición mecanicista de los cálculos de desajuste a lo largo de la jerarquía auditiva, ya que posibilitan la medición directa de la actividad neuronal sincronizada con el estímulo bajo estadísticas de estimulación estrictamente controladas (Garrido et al., 2009; Näätänen et al., 2012). Dentro de la vía auditiva ascendente, el colículo inferior (IC) constituye una etapa clave de integración a nivel mesencefálico. Recibe entradas ascendentes convergentes procedentes de núcleos auditivos del tronco encefálico inferior, lo que lo posiciona como un candidato para la computación temprana de señales relacionadas con el desajuste (Møller & Moore, 2000; Moore & Kitzes, 1985). Estudios subcorticales han demostrado sensibilidad a la desviación de frecuencia y respuestas relevantes para la discriminación en el IC, respaldando la idea de que la sensibilidad tipo desajuste no se restringe a circuitos corticales (Ayala et al., 2013).

La organización en subdivisiones del IC permite además una especificidad mecanicista. En esta tesis, definimos el núcleo central del colículo inferior como la región lemniscal, que transmite principalmente entrada auditiva ascendente específica de frecuencia. En contraste, nos referimos a las cortezas rostral, lateral y dorsal del IC como regiones no lemniscales, que integran la entrada ascendente con señales corticofugales descendentes y señales contextuales, apoyando influencias moduladoras y predictivas sobre el procesamiento auditivo (Ayala et al., 2013, 2016; Duque et al., 2012, 2016; Parras et al., 2017).

El término “vías auditivas no clásicas”, tal como se utiliza habitualmente en la literatura, hace referencia a las vías auditivas no lemniscales, que se han propuesto como relevantes para la neurobiología del autismo (Møller et al., 2005). Este sistema evolutivamente conservado proyecta no solo a estructuras auditivas, sino también a regiones límbicas, paralímbicas y autonómicas, influyendo en la regulación de la activación, la saliencia emocional y la integración multisensorial (Bartlett et al., 2000; Ibrahim et al., 2023; Lee, 2015; Lee & Murray Sherman, 2010; Macias & Llano, 2023). Durante

el desarrollo típico, la influencia de este sistema disminuye a medida que las jerarquías corticales maduran y se fortalece el control *top-down* (Møller & Rollins, 2002). En el autismo, sin embargo, el sistema no lemniscal puede permanecer hiperactivo o mostrar un retraso en su maduración, contribuyendo a un aumento de la ganancia sensorial, a una mayor reactividad emocional y a dificultades en el filtrado de estímulos irrelevantes (Møller et al., 2005).

De forma coherente con la modulación corticofugal del procesamiento mesencefálico, algunos modelos relacionados con el autismo muestran dismorfología cortical junto con proyecciones córtico-coliculares reducidas, lo que identifica una vía anatómica a través de la cual la variación neurodesarrollativa puede influir en los cálculos contextuales del IC (Kosmer & Kulesza, 2024).

1.6. Ejes etiológicos en modelos animales de autismo: exposición prenatal al ácido valproico y variación genética *Grin2b*+/−

1.6.1. Modelo ambiental: exposición prenatal al ácido valproico

La exposición prenatal al ácido valproico (VPA), un fármaco antiepiléptico y estabilizador del estado de ánimo, constituye un modelo ampliamente utilizado de exposición ambiental para el estudio de fenotipos relacionados con el autismo. Estudios epidemiológicos han vinculado la exposición prenatal al VPA con un mayor riesgo de resultados asociados al autismo, aunque las estimaciones varían en función de los criterios de identificación y definición utilizados (Christensen et al., 2013). En roedores, la exposición prenatal al VPA induce fenotipos del neurodesarrollo que se emplean habitualmente como modelos de características relevantes para el autismo y permite realizar pruebas mecanicistas bajo condiciones sensoriales y de desarrollo estrictamente controladas (Chaliha et al., 2020; Chomiak et al., 2013; Nicolini & Fahnestock, 2018).

Los modelos basados en VPA resultan especialmente relevantes para la neurobiología auditiva, ya que diversos estudios han descrito diferencias anatómicas a lo largo de la vía auditiva, incluidas

alteraciones en la citoarquitectura y la densidad neuronal en núcleos del tronco encefálico y del mesencéfalo (Lukose et al., 2011; Mansour et al., 2021; Zimmerman et al., 2020). Asimismo, trabajos fisiológicos han informado prolongaciones en la latencia de las respuestas auditivas del tronco encefálico (ABRs) y reducciones en su amplitud, consistentes con diferencias en la temporización y la sincronía subcorticales (Arjun S. Malhotra & Kulesza, 2023).

1.6.2. Modelo genético: el modelo de rata *Grin2b*+/− y los mecanismos dependientes del receptor NMDA

Estudios de secuenciación en humanos han implicado variantes *de novo* raras en genes sinápticos en el autismo esporádico, incluidas variantes en GRIN2B, que codifica la subunidad GluN2B del receptor N-metil-D-aspartato (NMDA) (Hu et al., 2016; O'Roak et al., 2011; Pan et al., 2015; Yoo et al., 2012). Los receptores NMDA desempeñan un papel clave en la integración sináptica, la coordinación temporal y la plasticidad dependiente de la experiencia, procesos que plausiblemente influyen en el procesamiento predictivo auditivo al modular cómo los sistemas forman y actualizan representaciones de regularidad bajo estructuras probabilísticas (Garrido et al., 2009; Wang, 2010).

En esta tesis, modelamos este eje genético mediante ratas con deleción heterocigota de *Grin2b* (*Grin2b*+/−), que reducen la dosis génica de *Grin2b* mediante una manipulación genética definida y proporcionan un contraste mecanísticamente específico frente a los modelos de exposición prenatal (Brigman et al., 2010; Lee et al., 2024). Dado que la estructura y la función de la vía auditiva en ratas *Grin2b*+/− permanecen poco caracterizadas, este modelo ofrece una vía dirigida para evaluar si la variación genética relevante para receptores NMDA modifica la temporización subcortical y los cálculos de desajuste bajo estadísticas de estimulación equiparables, en paralelo al modelo de exposición a VPA.

1.7. Puentes traslacionales: ABRs y uso conductual de regularidades bajo antagonismo NMDA

Las ABRs proporcionan un índice traslacional del procesamiento auditivo subcortical. Las ABRs miden una secuencia de deflexiones temporales generadas por la actividad sincrónica a lo largo del nervio auditivo y los núcleos del tronco encefálico, con contribuciones que se extienden hasta generadores mesencefálicos; la latencia y la amplitud reflejan la temporización de la conducción y la sincronía neuronal (Jewett & Williston, 1971; Møller & Moore, 2000; Young et al., 2023). En el autismo, estudios del desarrollo informan con frecuencia latencias más prolongadas y amplitudes reducidas, y un metaanálisis respalda la idea de que las diferencias en latencia son más robustas durante el desarrollo y se atenúan con la edad, lo que destaca la temporización del desarrollo como un modulador clave (Fujihira et al., 2021; Miron et al., 2018; Talge et al., 2018). Las medidas de ABR también varían en función del sexo en muestras neurotípicas, con mujeres que suelen mostrar latencias más cortas y amplitudes mayores que los varones (Dehan & Jerger, 1990; Michalewski et al., 1980; Zakaria et al., 2019).

En animales expuestos a VPA, diversos estudios han informado diferencias anatómicas a lo largo de la vía auditiva (Lukose et al., 2011; Mansour et al., 2021; Zimmerman et al., 2020), así como prolongaciones de latencia y reducciones de amplitud en las ABRs, coherentes con diferencias en la sincronía subcortical (Arjun S. Malhotra & Kulesza, 2023).

Mientras que las ABRs indexan la temporización y la sincronía subcorticales, los paradigmas operantes permiten cuantificar cómo los animales utilizan regularidades auditivas para guiar la conducta bajo contingencias controladas. La investigación en esquizofrenia aporta evidencia mecanicista convergente al vincular alteraciones en el procesamiento contextual con hipofunción de receptores NMDA y al demostrar que el antagonismo de receptores NMDA modifica respuestas tipo desajuste (Javitt & Sweet, 2015; Sullivan et al., 2015; Vohs et al., 2012). La señalización dependiente de NMDA proporciona además una vía mecanística para el uso conductual de regularidades, y este eje

complementa el modelo genético dado que *GRIN2B* codifica una subunidad del receptor NMDA implicada en fenotipos asociados al autismo (Hu et al., 2016; Wang, 2010).

Las tareas operantes de discriminación *oddball* operacionalizan el contexto como estructura probabilística con consecuencias para la selección de la acción: los animales aprenden a suprimir respuestas ante estímulos estándar frecuentes y a responder selectivamente a estímulos desviantes raros cuando estos predicen refuerzo (Barch & Ceaser, 2012; Javitt & Sweet, 2015; Quintela-Vega et al., 2023). En roedores, la administración sistémica de MK-801 (dizocilpina), un antagonista no competitivo de alta afinidad del receptor NMDA, induce una hipofunción aguda de estos receptores y modifica tanto la actividad tipo desajuste como el uso conductual de regularidades, apoyando inferencias causales sobre las contribuciones dependientes de NMDA al uso de regularidades auditivas para la acción (Quintela-Vega et al., 2023; Sullivan et al., 2015; Vohs et al., 2012).

2. Hipótesis

El procesamiento del contexto auditivo depende de la extracción de regularidades probabilísticas y del registro de violaciones de patrones establecidos (Garrido et al., 2009; Näätänen et al., 2001, 2011). En el autismo, las respuestas auditivas y las medidas de desajuste varían de forma sustancial entre individuos y a lo largo del desarrollo, y esta variabilidad se ha vinculado al sexo biológico, la clase de estímulo y las características del paradigma, más que a una inconsistencia aleatoria entre estudios (Chen et al., 2020; Foss-Feig et al., 2012; Gomot et al., 2006; Haesen et al., 2011; Loomes et al., 2017; Kujala et al., 2013; Orekhova & Stroganova, 2014; Rippon, 2024). Los modelos animales ambientales y genéticos proporcionan una vía etiológica para examinar cómo esta variabilidad emerge a partir de diferencias en la temporización del desarrollo y en la computación a nivel de circuito, con los modelos de VPA y *Grin2b*+/− permitiendo evaluar la temporización auditiva subcortical y la sensibilidad neuronal al contexto, y el modelo de MK-801 aislando el uso conductual de regularidades auditivas (Christensen et al., 2013; Hu et al., 2016; Miron et al., 2018; Quintela-Vega et al., 2023).

Con base en este marco, planteamos la hipótesis de que el procesamiento auditivo variaría de forma sistemática en función de la etiología, el sexo biológico y la etapa del desarrollo, en lugar de mostrar alteraciones uniformes entre modelos o edades. Asimismo, planteamos que dicha variación se manifestaría de manera diferente a través de los distintos niveles de análisis, reflejando contribuciones parcialmente disociables de la codificación sensorial temprana, la computación contextual mesencefálica y la explotación conductual de regularidades auditivas.

A nivel del tronco encefálico, se planteó la hipótesis de que la temporización de las ABRs diferiría entre modelos etiológicos y etapas del desarrollo, de forma coherente con alteraciones en la maduración de la codificación auditiva subcortical que podrían condicionar el procesamiento contextual posterior. A nivel neuronal, se planteó que la actividad de unidades individuales en el colículo inferior mostraría diferencias dependientes del sexo y de la edad en los componentes

relacionados con el desajuste bajo paradigmas de sonido contextual, reflejando una participación diferencial de procesos asociados a la repetición y a la desviación en modelos relevantes para el autismo. A nivel conductual, se planteó que el rendimiento en una tarea operante *oddball* diferiría entre modelos, indicando estrategias distintas para el uso de regularidades auditivas más que una reducción uniforme de la sensibilidad a la estructura contextual.

Por último, se planteó la hipótesis de que estos efectos no se alinearían de forma uniforme entre las medidas del tronco encefálico, neuronales y conductuales, sino que revelarían perfiles coordinados pero no idénticos a lo largo de la jerarquía auditiva, apoyando la interpretación de que la variabilidad auditiva asociada al autismo refleja interacciones estructuradas entre desarrollo, sexo y etiología, en lugar de un único mecanismo alterado.

3. Objetivos

Objetivo 1. Caracterizar la temporización y la sincronía auditivas subcorticales mediante ABRs a lo largo de la etapa del desarrollo y del sexo biológico en los modelos ambiental (exposición prenatal a VPA) y genético (*Grin2b*+/−) de autismo.

Objetivo 2. Investigar los mecanismos neuronales del procesamiento del contexto auditivo en el colículo inferior cuantificando respuestas de desajuste a nivel de unidad individual bajo estadísticas de estimulación controladas a través de la etapa del desarrollo (prepuberal y adulta), el sexo biológico (hembra y macho) y el modelo etiológico (exposición prenatal a VPA y *Grin2b*+/−).

Objetivo 3. Evaluar cómo los animales utilizan regularidades auditivas para guiar la conducta cuantificando el rendimiento en tareas de discriminación auditiva probabilística en ratas adultas hembras tratadas con MK-801.

4. Materiales y métodos

4.1. Animales, ética y modelos

Realizamos todos los experimentos en la Universidad de Salamanca en cumplimiento de la normativa europea y española sobre investigación con animales (86/609/EEC, 2003/65/EC, 2010/63/EU; RD 53/2013), con aprobación del Comité de Bioética de la Universidad de Salamanca (USAL-ID-574, USAL-ID-1193, USAL-ID-195). Alojamos ratas Long–Evans en parejas o tríos bajo un ciclo de luz/oscuridad de 12 h con comida y agua *ad libitum*, excepto durante el entrenamiento conductual, cuando mantuvimos el peso corporal al 90–95% del valor basal. Definimos las etapas prepuberal y adulta joven como PND 30–45 y PND 65–120, respectivamente (Sengupta, 2013).

Estudiamos tres condiciones etiológicas: controles TD, exposición prenatal a VPA y deleción heterocigota de *Grin2b* (*Grin2b*+/–). Para VPA, confirmamos el día gestacional 0 mediante citología vaginal, administramos valproato sódico (400 mg/kg, i.p.) en el día gestacional 12.5, destetamos a la descendencia en PND 21–23 y seleccionamos los animales expuestos a VPA que presentaban malformaciones leves de la cola. Para *Grin2b*+/–, cruzamos machos *Grin2b*+/– (Long-Evans-*Grin2bem1Mcwi*) con hembras *wild-type* y confirmamos el genotipo por PCR siguiendo el protocolo del proveedor. Combinamos controles adquiridos comercialmente y controles generados en el laboratorio, incluyendo controles prenatales con salino y camadas *wild-type* de la línea *Grin2b*+/–; verificamos que el origen del control no afectaba a las medidas electrofisiológicas principales y agrupamos los controles dentro de estratos emparejados por sexo y edad (**Figura 6**).

Alineamos tres brazos experimentales: ABRs (temporización/sincronía subcortical), registros de unidades individuales en el IC (procesamiento neuronal del contexto) y evaluación conductual bajo antagonismo del receptor NMDA (solo ratas adultas hembras).

4.2. Respuestas auditivas del tronco encefálico (ABRs)

Registramos ABRs en una cámara acústicamente aislada y eléctricamente apantallada utilizando electrodos subdérmicos y clics monaurales en el oído derecho administrados mediante un auricular de campo cerrado (**Figura 7**).

En las cohortes electrofisiológicas anestesiamos a los animales con uretano y mantuvimos la temperatura a 37 ± 1°C. Presentamos clics de 0.1 ms a 21/s en pasos de 10 dB a lo largo del rango de intensidades evaluado, promediamos respuestas a partir de presentaciones repetidas por nivel, adquirimos señales con hardware/software de Tucker-Davis Technologies, filtramos las trazas en banda (100–3000 Hz) y rechazamos artefactos.

En la cohorte conductual registramos ABRs bajo anestesia con ketamina/dexmedetomidina antes y después de la manipulación farmacológica, revertimos la anestesia con atipamezol y utilizamos los mismos parámetros de clic. Los umbrales permanecieron estables y no difirieron entre condiciones salino y MK-801.

Definimos el umbral como la intensidad mínima que evocaba una forma de onda reconocible. Un evaluador entrenado marcó los picos de las formas de onda siguiendo las convenciones estándar de ABR en rata. En los **Artículos 3 y 4** extraímos amplitudes de basal a pico (en adelante, amplitudes de pico) respecto a un basal breve pre-estímulo y, cuando fue pertinente, evaluamos efectos de sexo, edad y etiología mediante pruebas *t* con corrección de Šidák en el **Artículo 3** y comparaciones post hoc Tukey–Kramer (HSD) en el **Artículo 4.**

4.3. Registros de unidades individuales en el colículo inferior

Indujimos anestesia profunda con uretano (con suplementos cuando fue necesario), confirmamos audición mediante ABRs, mantuvimos la temperatura a 37 ± 1°C, monitorizamos la respiración y

estabilizamos la cabeza en un marco estereotáxico. Realizamos una craneotomía sobre el IC izquierdo, retiramos la duramadre y protegimos la superficie con agar.

Registramos actividad extracelular de unidades individuales mediante microelectrodos de alta impedancia en una cámara acústicamente aislada y eléctricamente apantallada. Generamos estímulos de tonos puros con un sistema de sonido programable y los administramos de forma monaural mediante un auricular de campo cerrado calibrado. Digitalizamos y filtramos las señales para detección de espigas y aceptamos unidades individuales cuando las formas de onda permanecieron estables y claramente aisladas.

Para buscar respuestas neuronales evocadas en IC, presentamos ráfagas de ruido blanco y tonos sinusoidales de 75 ms con rampas de subida–bajada de 5 ms, variando manualmente los parámetros para evitar adaptación específica de frecuencia. El protocolo para obtener el área de respuesta en frecuencia consistió en una secuencia de tonos sinusoidales entre 0.7 y 44 kHz, de 75 ms con rampas de 5 ms, presentados a 4 Hz, variando aleatoriamente frecuencia e intensidad (3–5 repeticiones de todos los tonos). Para cada neurona, mapeamos el área de respuesta en frecuencia y seleccionamos 10 tonos espaciados 0.5 octavas (típicamente 10–20 dB por encima del umbral) para las secuencias contextuales. Presentamos (i) secuencias *oddball* (STD 90%, DEV 10%) y (ii) secuencias control en cascada (CAS: escalas ordenadas ascendentes/descendentes sin repetición inmediata), emparejando tasa de estimulación y probabilidad de desviado. Presentamos las secuencias a intensidad fija y, cuando la estabilidad de la unidad lo permitió, a intensidades adicionales. En las secuencias *oddball* requerimos ≥3 STDs antes de cada DEV y analizamos el último STD que precedía a cada DEV.

Cuantificamos respuestas mediante histogramas peri-estímulo representando densidad de potenciales de acción a lo largo del tiempo (potenciales de acción por segundo, Hz) desde −75 a 250 ms alrededor del inicio del estímulo, usando los 40 ensayos disponibles para cada tono y condición. Suavizamos cada histograma peri-estímulo con un núcleo gaussiano de 6 ms (“ksdensity” en Matlab) en pasos de

1 ms para estimar la función de densidad de espigas, y determinamos la tasa basal espontánea como el promedio (Hz) durante los 75 ms previos al estímulo. Retuvimos combinaciones unidad–frecuencia solo cuando al menos una condición evocó actividad significativa (prueba Monte Carlo frente a trenes de Poisson ajustados al basal).

Tratamos el índice de desajuste neuronal (iMM) como un análogo a nivel celular de la MMN, cuantificando *spiking* sincronizado al estímulo bajo contextos que difieren en predictibilidad e historia de repetición (Malmierca et al., 2009; Parras et al., 2017; Ulanovsky et al., 2003). Dado que la elección del control determina de forma crítica la interpretación del desajuste (Ruhnau et al., 2012), los estudios incorporan cada vez más controles predecibles en roedores (Harms et al., 2014). En nuestra implementación, las secuencias *oddball* contrastan eventos DEV y STD, mientras que las secuencias en cascada proporcionan un contexto predecible y ordenado donde los tonos aparecen en series ascendentes o descendentes sin repeticiones inmediatas (Cacciato-Salcedo et al., 2025). En el marco del *predictive coding*, este diseño minimizó confusiones derivadas de la repetición inmediata y permitió disociar supresión por repetición (CAS–STD) de señalización relacionada con la desviación (DEV–CAS), o error de predicción, permitiendo interpretaciones más allá del contraste DEV–STD que típicamente captura la MMN (Garrido et al., 2009; Harms et al., 2014; Näätänen et al., 2012; Ruhnau et al., 2012) (**Figura 8**).

Para comparar neuronas con diferentes escalas de disparo, normalizamos las respuestas DEV/STD/CAS por la norma euclídea $N = \sqrt{(DEV^2 + STD^2 + CAS^2)}$ y calculamos: $iMM = DEV\_N - STD\_N$, $iRS = CAS\_N - STD\_N$ e $iPE = DEV\_N - CAS\_N$. Evaluamos diferencias por edad, sexo y etiología, cuando fue posible, entre estos índices predictivos. Para ello utilizamos dos aproximaciones estadísticas. En el **Artículo 1** realizamos comparaciones pareadas Wilcoxon rank-sum para evaluar diferencias entre grupos directamente a partir de los datos observados. En el **Artículo 2** empleamos modelos jerárquicos lineales generalizados de efectos mixtos y realizamos inferencia sobre medias

marginales estimadas mediante contrastes planificados, permitiendo modelar explícitamente la estructura anidada y probar efectos basados en el modelo (McCulloch et al., 2008; Stroup et al., 2024).

Verificamos posteriormente los sitios de registro histológicamente mediante marcado electrolítico y tinción de Nissl y asignamos los sitios a subdivisiones del IC usando referencias del atlas.

4.4. Evaluación conductual bajo antagonismo del receptor NMDA

Evaluamos el uso conductual de regularidades auditivas en una tarea operante *go/no-go* tras MK-801 (0.1 mg/kg, s.c.) o salino en ratas adultas hembras. Las ratas progresaron desde *shaping* hasta entrenamiento *oddball*, donde los desviantes (10%) aparecían entre estándares (90%); reforzamos aciertos y penalizamos falsas alarmas con *timeouts*. Durante la fase de test variamos el intervalo inter-estímulo (1.0, 1.5, 2.0 s) manteniendo constantes la duración del tono y las rampas de subida/bajada, e incluimos una variante *many-deviant* en la que múltiples frecuencias desviantes compartían la probabilidad total del 10%.

Cuantificamos el rendimiento mediante categorías de respuesta—aciertos (HIT), falsas alarmas (FA), rechazos correctos (CR) y omisiones (MISS) (**Figura 9**).

Para estabilizar estimaciones de tasa aplicamos correcciones estándar para valores extremos, calculando tasas de HIT y FA como (conteo + 0.5)/(N + 1). Posteriormente analizamos estas medidas con modelos lineales de efectos mixtos separados, incluyendo Tratamiento, Condición (pre vs. post) e intervalo inter-estímulo (ISI) como efectos fijos e identidad del animal como intercepto aleatorio, y utilizamos medias marginales estimadas y contrastes planificados para evaluar cambios inducidos por fármaco (**Artículo 5**). Corregimos contrastes con el método de Holm.

4.5. Capítulo de libro y revisión sistemática

Para sintetizar la evidencia humana actual sobre la maduración del sistema auditivo y los cambios relacionados con la edad en respuestas de desajuste en autismo, contribuimos a un capítulo de libro (Book chapter) y realizamos una revisión sistemática (Systematic review).

El protocolo se registró en PROSPERO (CRD42025626806) y siguió las guías PRISMA (Page et al., 2021). Buscamos en Embase, MEDLINE y PsycInfo desde el inicio hasta el 31 de mayo de 2025 e inspeccionamos las listas de referencias de los estudios incluidos.

Incluimos estudios originales con paradigmas *oddball* pasivos que evaluaran amplitud o potencia y latencia de MMN/MMF en participantes autistas y TD a lo largo del desarrollo, requiriendo diagnósticos formales de autismo (DSM-III a DSM-5). Excluimos autismo sindrómico, tareas activas y paradigmas con ruido de fondo. Dos revisores cribaron estudios de forma independiente, extrajeron datos de participantes, estímulos y resultados, y evaluaron calidad metodológica con la escala Newcastle–Ottawa, resolviendo discrepancias por consenso. Cincuenta y dos estudios cumplieron criterios de inclusión (**Figura 10**).

4.6. Comunicación científica

Para reforzar nuestro firme compromiso con la ciencia de alta calidad y la proyección social, realizamos actividades de divulgación científica mediante la difusión de nuestros resultados al público general, incluyendo la publicación de un artículo accesible que resume nuestro trabajo sobre el procesamiento auditivo en el autismo en la plataforma digital de divulgación científica Scientias. Esta actividad de divulgación tuvo como objetivo acercar nuestra investigación a la sociedad y contribuir a una mejor comprensión de las diferencias sensoriales en el autismo.

5. Resultados

5.1. Artículo 1: El procesamiento auditivo contextual en el colículo inferior se ve afectado de forma dependiente del sexo y la edad en el modelo de autismo inducido por ácido valproico

Diversos factores biológicos, incluidos el sexo y la edad, introducen una heterogeneidad sustancial en el procesamiento sensorial en el autismo. Un rasgo central que subyace a esta heterogeneidad es una capacidad alterada para extraer y actualizar información contextual del entorno sensorial. En marcos de *predictive coding*, los sistemas sensoriales forman de manera continua expectativas sobre los estímulos entrantes y señalan desviaciones de estas expectativas cuando se violan las regularidades. Las alteraciones de este proceso perjudican la integración de información contextual y contribuyen a respuestas atípicas ante eventos sensoriales predecibles y novedosos. Aunque la variabilidad dependiente del sexo y la edad se reconoce cada vez más como crítica para comprender estos mecanismos, su contribución al procesamiento predictivo permanece pobremente caracterizada.

Los modelos animales de autismo proporcionan una oportunidad única para investigar el procesamiento contextual a nivel de neurona individual y aislar las computaciones neurales subyacentes al *predictive coding*. En el sistema auditivo, el procesamiento predictivo puede explorarse mediante paradigmas *oddball* que evocan respuestas de desajuste neuronal, el correlato de unidad individual de la negatividad por desajuste. Estas respuestas reflejan la integración de supresión por repetición y señales de error de predicción y se generan tempranamente a lo largo de la jerarquía auditiva, incluido el colículo inferior. Evaluar cómo varían estos componentes con factores biológicos y etapas del desarrollo resulta esencial para entender cómo se configura y cómo se altera el *predictive coding*.

Aquí investigamos el procesamiento predictivo de claves auditivas contextuales en el mesencéfalo auditivo de ratas control y ratas expuestas prenatalmente a VPA, un modelo ambiental bien establecido de autismo. Realizamos registros de unidades individuales en el colículo inferior de animales

prepuberales y adultos, hembras y machos, utilizando un paradigma *oddball* clásico combinado con una secuencia control en cascada sin repetición. Este enfoque permitió cuantificar el desajuste neuronal y disociar sus componentes predictivos—indexando adaptación contextual y error de predicción—a través de sexo, edad y exposición prenatal.

5.1.1. Componentes predictivos del desajuste neuronal

Ajustamos modelos lineales generalizados jerárquicos de efectos mixtos para examinar cómo la división del IC, el nivel sonoro, el sexo, la edad y la exposición prenatal influían en los componentes predictivos del procesamiento de desajuste, indexados por iMM, iRS e iPE. Cada modelo incluyó interceptos y pendientes aleatorias para división, nivel y exposición dentro de los sujetos. Utilizamos una distribución normal con enlace identidad para los tres índices.

Los modelos mostraron un rendimiento sólido para iMM e iRS, con coeficientes de correlación intraclase de 0.856 y 0.681, y errores absolutos medianos de 0.112 y 0.089, respectivamente. En contraste, el modelo de iPE arrojó un coeficiente de correlación intraclase bajo de 0.040, lo cual concuerda con expectativas teóricas. Las regiones subcorticales como el colículo inferior generan señales de error de predicción relativamente pequeñas, especialmente a nivel lemniscal (Cacciato-Salcedo et al., 2025; Parras et al., 2017), y probablemente muestran una variabilidad interindividual mínima explicada por variables experimentales. Nuestros modelos respaldaron esta visión. A pesar del bajo coeficiente de correlación intraclase, el modelo mostró buen ajuste (Criterio de Información de Akaike = –286.792; Criterio de Información Bayesiano = –151.700) y una precisión predictiva aceptable (error absoluto mediano de 0.070), indicando que capturó de manera fiable efectos sistemáticos de división auditiva, nivel sonoro, sexo, edad y exposición prenatal para iPE.

El modelo de iMM reveló efectos principales significativos de división ($p < 0.001$), nivel ($p < 0.001$), sexo ($p = 0.001$), edad ($p = 0.002$) y exposición ($p = 0.003$). También capturó varias interacciones de segundo orden significativas, incluyendo sexo × edad ($p < 0.001$), nivel × exposición ($p = 0.005$), sexo

× exposición ($p = 0.013$) y edad × exposición ($p = 0.005$). Estos resultados, junto con las interacciones de orden superior significativas, indicaron que tanto factores individuales como sus interacciones contribuyeron a modular el desajuste neuronal.

Para iRS, el modelo detectó efectos principales significativos de división ($p < 0.001$), nivel sonoro ($p < 0.001$), sexo ($p < 0.001$), edad ($p < 0.001$) y exposición prenatal ($p = 0.004$). Además, reveló interacciones significativas de división × nivel ($p = 0.001$), nivel × sexo ($p = 0.011$), sexo × edad ($p < 0.001$), sexo × exposición ($p = 0.034$) y edad × exposición ($p = 0.021$). Estos patrones indicaron que los factores experimentales y sus interacciones influyeron conjuntamente en la supresión por repetición.

El modelo de iPE identificó efectos principales significativos de sexo ($p = 0.002$) y una interacción sexo × edad significativa ($p = 0.014$), junto con una interacción marginal nivel × exposición ($p = 0.048$), y efectos de orden superior división × nivel × edad ($p = 0.002$) y división × nivel × exposición ($p = 0.028$). El resto de predictores no alcanzó significación, lo que indicó que las señales de error de predicción estaban moduladas de forma más selectiva.

Las interacciones de orden superior modularon significativamente todos los componentes predictivos, especialmente iMM e iRS, destacando la influencia compleja de sexo, edad y exposición prenatal a través de divisiones del IC y niveles de estimulación. Examinamos estos efectos para cada índice por nivel sonoro y división del IC (**Figura 11**). También caracterizamos estos patrones a nivel de grupo experimental a través de divisiones auditivas y niveles de estimulación (**Figura 11**).

El análisis a nivel de grupo experimental del índice de desajuste neuronal reveló efectos significativos de sexo, edad y exposición, con patrones que variaron entre divisiones del IC y niveles de estimulación (**Figura 11**). En cuanto a diferencias por sexo, las hembras adultas control mostraron valores de iMM significativamente menores que los machos tanto en la división lemniscal ($p < 0.001$, diferencia mediana = –0.092) como en la no lemniscal ($p < 0.001$, diferencia mediana = –0.177) a nivel de

estimulación alto. Este patrón se mantuvo en el grupo VPA, donde las hembras adultas presentaron iMM reducido frente a los machos en la división lemniscal ($p = 0.010$, diferencia mediana = –0.061). Entre los animales prepuberales expuestos a VPA, las hembras también mostraron índices menores que los machos tanto en la división lemniscal ($p = 0.012$, diferencia mediana = –0.079) como en la no lemniscal ($p = 0.029$, diferencia mediana = –0.062) bajo estimulación alta. A nivel sonoro bajo, las hembras adultas control presentaron de nuevo un iMM menor que los machos en la división lemniscal ($p = 0.013$, diferencia mediana = –0.090).

Las comparaciones por edad revelaron efectos robustos del desarrollo que variaron en función del sexo y la exposición (**Figura 11**). En la división lemniscal, las hembras prepuberales control mostraron iMM significativamente mayor que las hembras adultas tanto con estimulación alta ($p < 0.001$, diferencia mediana = 0.125) como baja ($p = 0.020$, diferencia mediana = 0.119). En la división no lemniscal, las hembras prepuberales control también presentaron una puntuación elevada respecto a las adultas bajo estimulación alta ($p < 0.001$, diferencia mediana = 0.182). Sin embargo, entre las hembras expuestas a VPA, la tendencia se invirtió: los animales prepuberales mostraron iMM significativamente atenuado frente a las adultas al mismo nivel sonoro ($p = 0.004$, diferencia mediana = –0.106). Con estimulación baja en la división no lemniscal, las hembras prepuberales VPA también presentaron iMM significativamente menor que las hembras adultas ($p = 0.008$, diferencia mediana = –0.146). Entre los machos, las ratas prepuberales del grupo control mostraron iMM disminuido frente a los adultos en la división no lemniscal con estimulación baja ($p = 0.008$, diferencia mediana = –0.118), patrón que también se observó en machos expuestos a VPA ($p < 0.001$, diferencia mediana = –0.118).

La exposición prenatal a VPA produjo efectos divergentes según edad y división del IC (**Figura 11**). En hembras adultas, la exposición a VPA incrementó significativamente iMM en comparación con controles en la división no lemniscal bajo estimulación alta ($p = 0.002$, diferencia mediana = –0.153).

De forma distinta, en hembras prepuberales la administración prenatal de VPA disminuyó iMM tanto en la división lemniscal ($p = 0.002$, diferencia mediana = 0.104) como en la no lemniscal ($p < 0.001$, diferencia mediana = 0.136) a nivel sonoro alto. Del mismo modo, entre machos, los animales expuestos a VPA mostraron iMM reducido en prepubertad ($p = 0.004$, diferencia mediana = 0.058) y en adultez ($p = 0.014$, diferencia mediana = 0.054) en esa misma región y nivel sonoro.

El análisis a nivel de grupo experimental del índice de supresión por repetición reveló diferencias robustas por sexo (**Figura 11**). Bajo estimulación alta en la división lemniscal, las hembras adultas control mostraron iRS significativamente menor que los machos ($p = 0.027$, diferencia mediana = –0.133), y lo mismo ocurrió en la división no lemniscal ($p < 0.001$, diferencia mediana = –0.282). Las hembras adultas VPA mantuvieron iRS lemniscal reducido en comparación con los machos ($p < 0.001$, diferencia mediana = –0.130). Con estimulación baja, las hembras adultas control presentaron de nuevo iRS lemniscal menor que los machos ($p = 0.007$, diferencia mediana = –0.121) y también iRS no lemniscal reducido ($p = 0.002$, diferencia mediana = –0.111). En prepubertad bajo VPA, las hembras mostraron iRS no lemniscal mayor que los machos con estimulación alta ($p = 0.016$, diferencia mediana = 0.044).

Las comparaciones por edad revelaron trayectorias del desarrollo divergentes para iRS. En la división lemniscal, las hembras prepuberales control superaron a las adultas tanto con estimulación alta ($p = 0.027$, diferencia mediana = 0.124) como baja ($p = 0.003$, diferencia mediana = 0.167), mientras que los machos prepuberales expuestos a VPA mostraron iRS reducido frente a los adultos VPA bajo estimulación alta ($p = 0.026$, diferencia mediana = –0.117). En la división no lemniscal, las hembras prepuberales control presentaron iRS elevado tanto con estimulación alta ($p < 0.001$, diferencia mediana = 0.282) como baja ($p < 0.001$, diferencia mediana = 0.286). Las hembras prepuberales expuestas a VPA reflejaron aumentos similares (alta: $p = 0.028$, diferencia mediana = 0.032; baja: $p = 0.015$, diferencia mediana = 0.121). Tanto los machos control ($p = 0.001$, diferencia mediana = 0.121)

como los machos VPA ($p = 0.007$, diferencia mediana = 0.065) en prepubertad superaron a los adultos con estimulación no lemniscal baja.

La exposición prenatal a VPA produjo efectos específicos por división y grupo. En la división no lemniscal con estimulación alta, VPA aumentó iRS en hembras adultas ($p < 0.001$, diferencia mediana = –0.228) pero redujo iRS en machos adultos ($p = 0.002$, diferencia mediana = 0.076). En contraste, en prepubertad las hembras control superaron a las hembras VPA en la división lemniscal con estimulación alta ($p = 0.025$, diferencia mediana = 0.059), y los machos control superaron a los machos VPA en la división no lemniscal tanto con estimulación alta ($p = 0.022$, diferencia mediana = 0.030) como baja ($p = 0.042$, diferencia mediana = 0.041). Por último, en estimulación lemniscal baja, los adultos VPA, hembras ($p = 0.019$, diferencia mediana = –0.173) y machos ($p = 0.022$, diferencia mediana = –0.121), mostraron iRS mayor que los controles.

El análisis a nivel de grupo experimental del índice de error de predicción reveló diferencias significativas, con efectos que variaron según división del IC y nivel de estimulación (**Figura 11**). En la división lemniscal con nivel sonoro alto, las hembras adultas expuestas a VPA mostraron iPE significativamente mayor que los machos ($p = 0.042$, diferencia mediana = 0.058). En contraste, la división no lemniscal mostró efectos de sexo más pronunciados. Bajo estimulación alta, las hembras adultas control presentaron iPE significativamente mayor que los machos ($p < 0.001$, diferencia mediana = 0.133). En el grupo VPA, las hembras prepuberales mostraron valores significativamente menores que los machos ($p < 0.001$, diferencia mediana = –0.072).

Observamos influencias robustas del desarrollo sobre iPE en la división no lemniscal (**Figura 11**). Entre las hembras control, las ratas prepuberales presentaron iPE significativamente menor que las adultas tanto con estimulación alta ($p < 0.001$, diferencia mediana = –0.120) como baja ($p < 0.001$, diferencia mediana = –0.356). Las hembras expuestas a VPA mostraron un patrón similar, con valores reducidos en prepubertad tanto a nivel alto ($p < 0.001$, diferencia mediana = –0.119) como bajo ($p <$

0.001, diferencia mediana = –0.284). En machos, los controles prepuberales mostraron una reducción significativa de iPE con estimulación baja ($p < 0.001$, diferencia mediana = –0.224), y los prepuberales VPA también presentaron iPE reducido ($p < 0.001$, diferencia mediana = –0.144) respecto a sus adultos.

La exposición prenatal a VPA moduló significativamente el procesamiento del error de predicción, especialmente en la división no lemniscal de hembras bajo estimulación alta. Las hembras adultas control mostraron valores de iPE mayores que sus contrapartes VPA ($p < 0.001$, diferencia mediana = 0.070), y el mismo patrón emergió entre hembras prepuberales ($p = 0.003$, diferencia mediana = 0.069).

En conjunto, el sexo, la edad y la exposición prenatal a VPA modularon de manera diferenciada los índices de *predictive coding* a través de divisiones del IC y niveles sonoros. Las hembras adultas mostraron de forma consistente iMM e iRS menores que los machos, especialmente en regiones no lemniscales, patrón que se mantuvo en animales expuestos a VPA. En el desarrollo, las hembras prepuberales control mostraron iMM e iRS elevados, mientras que VPA invirtió estas trayectorias. El iPE aumentó tras la pubertad en controles, pero VPA lo redujo en ambas edades, introduciendo diferencias por sexo en prepubertad. A pesar de estas alteraciones, el cambio típico de iPE negativo a positivo en circuitos no lemniscales se mantuvo preservado. El sexo y la edad influyeron en el *predictive coding*, y la exposición prenatal a VPA alteró especialmente estos procesos, en particular en regiones no lemniscales del colículo inferior.

5.2. Artículo 2: Efectos específicos del sexo y de la etiología sobre el procesamiento predictivo en el colículo inferior de dos modelos de rata de autismo

El procesamiento sensorial atípico es una característica común del autismo, pero las computaciones neurales que dan lugar a estas diferencias, particularmente en relación con el sexo biológico y el origen etiológico, siguen sin estar claras. Aquí examinamos el procesamiento auditivo predictivo a nivel de neurona individual en el colículo inferior de dos modelos de rata adultos de autismo: un modelo

genético con deleción heterocigota de *Grin2b* (*Grin2b*+/–) y un modelo ambiental basado en exposición prenatal a ácido valproico. Registramos respuestas neuronales a un paradigma auditivo *oddball* y a una secuencia control en cascada en divisiones lemniscal y no lemniscal del IC bajo estimulación de alta intensidad, lo que permitió derivar índices de supresión por repetición, error de predicción y desajuste neuronal. Mediante modelos lineales generalizados de efectos mixtos que consideraron identidad del animal, división del colículo inferior, sexo y modelo de rata, seguidos de comparaciones jerárquicas a nivel de grupo, identificamos alteraciones robustas del procesamiento predictivo en ambos modelos tipo autismo.

5.2.1. Componentes predictivos del desajuste neuronal

A continuación, examinamos el procesamiento auditivo contextual en el marco de *predictive coding* derivando índices relacionados con el desajuste (iMM, iRS e iPE) a partir de los contrastes correspondientes entre condiciones DEV, CAS y STD.

Ajustamos modelos lineales generalizados de efectos mixtos para cuantificar cómo la división del IC (lemniscal, no lemniscal), el sexo (hembra, macho) y el modelo de rata (Control, *Grin2b*+/–, VPA) explicaban la variabilidad de los componentes predictivos. Para preservar la estructura jerárquica de los datos, incluimos interceptos aleatorios para animales y pendientes aleatorias para división del IC. Cada modelo incorporó 68 observaciones a nivel de división procedentes de 46 animales.

Los modelos proporcionaron buenos ajustes para iMM e iRS, con coeficientes de correlación intraclase de 0.761 y 0.854, respectivamente. En contraste, el modelo de iPE arrojó un coeficiente intraclase menor de 0.060, en línea con expectativas teóricas y con nuestros hallazgos previos. Estructuras subcorticales como el colículo inferior generan señales de error de predicción relativamente pequeñas, especialmente dentro de vías lemniscales, y muestran una variabilidad entre sujetos limitada impulsada por factores experimentales (Parras et al., 2017; Cacciato-Salcedo et al., 2025a).

La validación cruzada confirmó el rendimiento de los modelos, con errores absolutos medianos de 0.037, 0.031 y 0.026 para iMM, iRS e iPE, respectivamente. Estos resultados indicaron que los modelos capturaron con precisión influencias jerárquicas sobre el procesamiento auditivo predictivo a través de divisiones del IC.

Índice de desajuste neuronal. El índice de desajuste neuronal cuantifica la sensibilidad de la neurona a la desviación auditiva comparando sus respuestas al mismo tono cuando se presenta como desviado raro frente a estándar frecuente. Refleja la señal global de desajuste, integrando componentes de adaptación y de procesamiento relacionado con predicción.

El modelo reveló efectos principales significativos de división del IC ($p < 0.001$), sexo ($p = 0.005$) y modelo de rata (*Grin2b*+/–: $p = 0.034$; VPA: $p = 0.030$) sobre iMM. Estos resultados indicaron que iMM varió robustamente entre divisiones anatómicas, con modulación adicional por sexo y por ambas condiciones tipo autismo. La ausencia de términos de interacción significativos sugirió que la deleción heterocigota de *Grin2b* y la exposición prenatal a VPA alteraron las respuestas de desajuste de un modo consistente a través de sexos y divisiones del IC.

Los contrastes post hoc mostraron una modulación clara de iMM dependiente del sexo y de la división. En condiciones control, las hembras generaron valores de iMM significativamente menores que los machos tanto en el IC lemniscal (estimación del contraste = –0.310, $p = 0.003$; Figura 12A) como en el no lemniscal (estimación del contraste = –0.157, $p = 0.007$; Figura 12B), indicando una menor sensibilidad a la desviación auditiva en hembras. Los fenotipos tipo autismo alteraron este patrón de forma específica por sexo. Tanto las hembras *Grin2b*+/– como las hembras expuestas a VPA mostraron iMM mayor que las hembras control en el IC lemniscal (*Grin2b*+/–: estimación del contraste = –0.275, $p = 0.030$; VPA: estimación del contraste = –0.272, $p = 0.026$; Figura 12A). En machos, solo el grupo VPA difirió de los controles, mostrando iMM reducido en el IC no lemniscal (estimación del contraste = 0.140, $p = 0.043$; Figura 12B).

En conjunto, estos resultados mostraron que las hembras control presentaron respuestas de desajuste menores que los machos. La deleción heterocigota de *Grin2b* y la exposición prenatal a VPA incrementaron de forma atípica la actividad de desajuste en hembras dentro del IC lemniscal, mientras que la exposición prenatal a VPA redujo las respuestas de desajuste en machos dentro del IC no lemniscal.

Índice de supresión por repetición. El índice de supresión por repetición cuantifica la adaptación neuronal a la estimulación auditiva repetida comparando respuestas a tonos estándar y en cascada, reflejando el componente adaptativo del *predictive coding* en la vía auditiva.

El modelo reveló efectos principales significativos de división del IC ($p < 0.001$), sexo ($p = 0.004$) y deleción heterocigota de *Grin2b* ($p = 0.010$) sobre iRS. Estos resultados indicaron que iRS varió entre divisiones anatómicas y estuvo modulado independientemente por sexo y por deficiencia heterocigota de *Grin2b*.

Los contrastes post hoc revelaron una modulación fuerte de iRS dependiente del sexo y del modelo, presente en ambas divisiones del IC, con efectos marcadamente mayores en la vía no lemniscal. En el IC lemniscal, las hembras control generaron valores de iRS significativamente menores que los machos control (estimación del contraste = –0.345, $p = 0.003$; Figura 12A). Entre hembras, la deleción heterocigota de *Grin2b* incrementó aún más iRS en comparación con controles (estimación del contraste = –0.368, $p = 0.008$; Figura 12A).

En el IC no lemniscal, el patrón fue más fuerte y extendido. Las hembras control mostraron de nuevo iRS reducido frente a machos (estimación del contraste = –0.248, $p < 0.001$; Figura 12B). Dentro de hembras, tanto *Grin2b*+/– como VPA mostraron iRS notablemente mayor que las hembras control (*Grin2b*+/–: estimación del contraste = –0.259, $p < 0.001$; VPA: estimación del contraste = –0.220, $p < 0.001$; Figura 12B). En contraste, ninguno de los modelos produjo efectos significativos en machos en ninguna de las dos divisiones del IC.

Estos hallazgos mostraron que la supresión neural ante estimulación repetitiva fue consistentemente menor en hembras control que en machos. En los modelos tipo autismo, tanto la deleción heterocigota de *Grin2b* como la exposición prenatal a VPA amplificaron de forma atípica la supresión por repetición en hembras, con los efectos más intensos en circuitos no lemniscales.

Índice de error de predicción. El índice de error de predicción cuantifica la capacidad de una neurona para señalar violaciones de regularidad auditiva aislando el componente de respuesta relacionado con la desviación que no se explica por adaptación.

El modelo identificó efectos principales significativos de sexo ($p = 0.005$) y deleción heterocigota de *Grin2b* ($p = 0.047$) sobre iPE, sin interacciones significativas. Estos resultados indicaron que la señalización de error de predicción en el IC varió modestamente entre sexos y estuvo modulada selectivamente por la deficiencia heterocigota de *Grin2b*.

Los contrastes post hoc mostraron diferencias claras por sexo en iPE bajo condiciones control. Tanto en el IC lemniscal como en el no lemniscal, las hembras control exhibieron valores de iPE significativamente mayores que los machos control (lemniscal: estimación del contraste = 0.095, $p = 0.003$; no lemniscal: estimación del contraste = 0.130, $p = 0.003$; Figura 12A–B).

Los fenotipos tipo autismo produjeron un único efecto significativo, restringido a la vía no lemniscal. Las hembras expuestas prenatalmente a VPA mostraron iPE menor que las hembras control (estimación del contraste = 0.137, $p = 0.006$; Figura 12B), mientras que la deleción heterocigota de *Grin2b* no alteró iPE en ninguno de los sexos ni divisiones del IC.

En conjunto, los resultados mostraron que la codificación de error de predicción fue más fuerte en hembras que en machos bajo condiciones control. La administración prenatal de VPA debilitó efectos específicos de hembras en la señalización de error de predicción dentro del IC no lemniscal, mientras que permaneció estable en machos tipo autismo y no se modificó en vías lemniscales.

5.3. Paper 3: Efectos específicos de sexo y edad sobre las respuestas auditivas del tronco encefálico en el modelo de autismo inducido por ácido valproico

La exposición prenatal a VPA es un modelo roedor bien establecido de autismo, pero sus efectos sobre el procesamiento auditivo a nivel de tronco encefálico siguen sin estar completamente caracterizados a través del sexo y el desarrollo. Registramos ABRs evocados por clics en ratas Long–Evans expuestas prenatalmente a VPA (400 mg/kg, día gestacional 12) y en controles emparejados en etapas prepuberal (días postnatales 30–45) y adulta (65–120) bajo anestesia con uretano. Analizamos amplitudes de pico a través de niveles sonoros. Los umbrales auditivos no difirieron entre grupos.

5.3.1. Amplitud de pico de las formas de onda de ABR

La amplitud de pico refleja la fuerza de la respuesta neural evocada en cada etapa de procesamiento a lo largo de la vía auditiva. Calculamos las amplitudes medias a partir de niveles sonoros promediados por grupo experimental y realizamos comparaciones pareadas mediante pruebas *t* con corrección de Šidák para evaluar diferencias por sexo, edad y exposición a nivel de grupo (Figura 13).

Encontramos que las ondas I (diferencia media = 0.511; $p < 0.023$) y II (diferencia media = 1.224; $p < 0.011$) de hembras adultas control presentaron amplitud media significativamente mayor que las ondas correspondientes en machos (Figura 13A), y una onda III reducida (diferencia media = −0.511; $p < 0.022$), resultado del efecto de enmascaramiento ejercido por la onda II. Las diferencias por exposición aparecieron entre hembras adultas, donde los controles mostraron amplitud media significativamente mayor de la onda II que las ratas expuestas a VPA (diferencia media = 1.12; $p < 0.032$; Figura 4A).

Posteriormente, calculamos amplitudes medias en pasos de 10 dB y ajustamos modelos lineales de efectos mixtos incluyendo sexo, edad, exposición, nivel sonoro y sus interacciones para modelar variabilidad intra-sujeto a través de intensidades y diferencias entre sujetos.

La fiabilidad del modelo aumentó con el nivel sonoro, con coeficientes de correlación intraclase de 0.090 a 30 dB SPL, 0.211 a 40 dB SPL, 0.294 a 50 dB SPL, 0.355 a 60 dB SPL, 0.398 a 70 dB SPL y 0.434 a 80 dB SPL. Extraímos medias marginales estimadas (Figura 13B, recuadros) para ilustrar efectos del modelo.

Para la onda II, las amplitudes aumentaron robustamente con el nivel sonoro ($\beta = 0.069 \pm 0.006$, $p < 0.001$), reflejando un reclutamiento mayor de generadores tempranos del tronco encefálico con estimulación más intensa. Sin embargo, este crecimiento fue menor en machos (Sexo × Intensidad: $\beta = -0.029 \pm 0.009$, $p = 0.001$), en ratas prepuberales (Edad × Intensidad: $\beta = -0.035 \pm 0.009$, $p < 0.001$) y bajo exposición a VPA (Exposición × Intensidad: $\beta = -0.020 \pm 0.008$, $p = 0.015$), indicando menor excitabilidad y un escalado más débil con la intensidad bajo esas condiciones.

Para la onda V, los machos mostraron amplitudes globales mayores ($\beta = 0.496 \pm 0.192$, $p = 0.010$), aunque su relación amplitud–intensidad difirió de manera marcada según sexo y exposición. La interacción negativa Sexo × Intensidad ($\beta = -0.014 \pm 0.004$, $p < 0.001$) reveló que la amplitud aumentó de forma menos pronunciada con la intensidad en machos, sugiriendo una ganancia neural reducida a niveles altos. La interacción Sexo × Exposición ($\beta = -0.839 \pm 0.257$, $p = 0.001$) indicó que VPA suprimió amplitudes de forma más notable en machos, mientras que las interacciones de triple vía Sexo × Edad × Intensidad ($\beta = 0.010 \pm 0.005$, $p = 0.046$) y Sexo × Exposición × Intensidad ($\beta = 0.018 \pm 0.005$, $p < 0.001$) sugirieron que estas diferencias específicas de sexo en el escalado con la intensidad se atenuaron en animales más jóvenes y se vieron además moduladas por la exposición teratogénica.

5.4. Artículo 4: Diferencias sexuales en respuestas auditivas del tronco encefálico en dos modelos de rata de autismo: contribuciones ambientales y genéticas a la función auditiva tipo autismo

El autismo es un trastorno del neurodesarrollo de inicio temprano caracterizado por patrones restringidos y repetitivos de conducta y por diferencias en la comunicación e interacción social. Una

proporción considerable de personas autistas experimenta una percepción auditiva divergente, lo que puede interferir con la capacidad de desenvolverse en entornos acústicos cotidianos.

Las respuestas auditivas del tronco encefálico son potenciales electrofisiológicos evocados por estímulos auditivos que evalúan la actividad neural a lo largo del nervio auditivo y el tronco encefálico. De forma importante, las respuestas auditivas del tronco encefálico varían según el sexo, con hembras que típicamente muestran amplitudes mayores y latencias más cortas que los machos. Este perfil neurofisiológico específico por sexo es especialmente relevante en investigación en autismo, donde la razón diagnóstica varón:mujer es aproximadamente 3:1. Por ello, explorar los mecanismos neurobiológicos que subyacen a variaciones específicas por sexo en rasgos autistas resulta esencial. Además, los perfiles sensoriales en autismo pueden variar en función de efectos independientes y combinados de factores ambientales y genéticos.

Para profundizar en esta comprensión, examinamos respuestas auditivas del tronco encefálico en dos modelos de rata de autismo: el modelo de mutación rara GRIN2B y el modelo de inducción prenatal por ácido valproico, junto con animales control.

5.4.1. Amplitud de pico de las formas de onda de ABR

Para capturar diferencias de grupo en amplitudes de pico de ABRs evocados por clic, comparamos grupos de modelos de rata a nivel poblacional (**Figura 14A**) y examinamos diferencias por sexo dentro de cada grupo (**Figura 14C**).

Las comparaciones entre modelos mostraron las siguientes diferencias. Las ratas control exhibieron amplitudes mayores en las ondas I y II que tanto los animales *Grin2b*+/– como los VPA (Onda I: Control vs GRIN2B, diferencia media = 0.477, p = 0.026; Control vs VPA, diferencia media = 0.464, p = 0.028; Onda II: Control vs GRIN2B, diferencia media = 0.845, p = 0.005; Control vs VPA, diferencia media = 0.616, p = 0.044). En la onda III, las ratas *Grin2b*+/– mostraron respuestas más

cercanas al basal que las ratas control (diferencia media = −0.597, $p < 0.001$) y que los animales VPA (diferencia media = 0.375, $p = 0.004$). En la onda IV, las ratas *Grin2b*+/– presentaron amplitudes mayores que los animales VPA (diferencia media = 0.190, $p = 0.020$).

Las diferencias por sexo emergieron únicamente dentro del grupo control: las hembras mostraron amplitudes mayores en las ondas I, II y V (Onda I, diferencia media = 0.985, $p = 0.002$; Onda II, diferencia media = 1.534, $p < 0.001$; Onda V, diferencia media = 0.359, $p = 0.007$), mientras que los machos produjeron respuestas de la onda III más cercanas al basal que las hembras (diferencia media = −0.903, $p < 0.001$).

A continuación, examinamos cómo estos efectos variaron con la intensidad del estímulo (**Figura 14B**). Las hembras exhibieron amplitudes significativamente mayores que los machos en la onda I a 40, 50, 60 y 80 dB SPL (40 dB: diferencia media = 0.302, $p = 0.041$; 50 dB: diferencia media = 0.409, $p = 0.009$; 60 dB: diferencia media = 0.534, $p = 0.001$; 80 dB: diferencia media = 0.505, $p = 0.032$) y en la onda II a 50, 60 y 80 dB SPL (50 dB: diferencia media = 0.463, $p = 0.027$; 60 dB: diferencia media = 0.654, $p = 0.009$; 80 dB: diferencia media = 0.785, $p = 0.035$). En la onda II, los animales control mostraron amplitudes mayores que los animales *Grin2b*+/– en todas las intensidades (30 dB: diferencia media = 0.366, $p = 0.034$; 40 dB: diferencia media = 0.667, $p = 0.003$; 50 dB: diferencia media = 0.650, $p = 0.035$; 60 dB: diferencia media = 0.867, $p = 0.018$; 70 dB: diferencia media = 1.125, $p = 0.008$; 80 dB: diferencia media = 1.394, $p = 0.007$) y superaron a los animales VPA a 30 y 70 dB SPL (30 dB: diferencia media = 0.394, $p = 0.019$; 70 dB: diferencia media = 0.857, $p = 0.049$). La interacción sexo × modelo de rata en la onda II mostró que las hembras control tuvieron las mayores amplitudes entre todos los grupos, superando a hembra-GRIN2B (diferencia media = 1.224, $p < 0.001$), hembra-VPA (diferencia media = 1.390, $p < 0.001$), macho-control (diferencia media = 1.534, $p < 0.001$), macho-GRIN2B (diferencia media = 1.120, $p < 0.001$) y macho-VPA (diferencia media = 1.408, $p < 0.001$).

En la onda III, los animales control produjeron respuestas más negativas que los animales *Grin2b*+/– entre 40 y 80 dB SPL (40 dB: diferencia media = −0.415, p = 0.002; 50 dB: diferencia media = −0.580, p < 0.001; 60 dB: diferencia media = −0.576, p = 0.004; 70 dB: diferencia media = −0.708, p = 0.0010; 80 dB: diferencia media = −1.075, p < 0.001). A 50 dB SPL, los animales *Grin2b*+/– también difirieron de los animales VPA (diferencia media = 0.323, p = 0.006), y este contraste se mantuvo a intensidades más altas (60 dB: diferencia media = 0.465, p = 0.012; 70 dB: diferencia media = 0.556, p = 0.004; 80 dB: diferencia media = 0.701, p = 0.005).

En la onda V, las hembras control generaron amplitudes mayores que los machos control a 60–80 dB SPL (60 dB: diferencia media = 0.413, p = 0.016; 70 dB: diferencia media = 0.404, p = 0.019; 80 dB: diferencia media = 0.608, p = 0.007), mientras que las diferencias por sexo no fueron significativas en los grupos *Grin2b*+/– o VPA.

5.5. Artículo 5: El antagonista del receptor NMDA MK-801 altera la conducta guiada por señales auditivas en una tarea operante *oddball*

La esquizofrenia se asocia con déficits marcados en control cognitivo y conducta guiada por señales sensoriales, pero las consecuencias conductuales de la hipofunción del receptor NMDA para la toma de decisiones auditiva siguen sin estar claras. Examinamos cómo el antagonismo sistémico del receptor NMDA afectó al rendimiento en una tarea operante auditiva *oddball* que requería responder a tonos diferentes en frecuencia (contexto *go*) e inhibir respuestas ante tonos estándar repetitivos o estándar (contexto *no-go*) a través de distintos intervalos inter-estímulo (ISI).

5.5.1. MK-801 modifica patrones de falsas alarmas y rechazos correctos

Cuantificamos cómo inyecciones de salino y MK-801 afectaron a la distribución de resultados conductuales: HIT, CR, FA y MISS, expresados como porcentajes promediados por sesión a intervalo entre estímulos (ISI) de 1, 1.5 y 2 s (**Figura 15**).

Para cada tipo de respuesta, ajustamos modelos lineales de efectos mixtos con Tratamiento (salino vs. MK-801), Condición (pre vs. post) e ISI como efectos fijos y animal como intercepto aleatorio. Los errores absolutos medianos (2.506 para HIT/MISS; 2.326 para CR/FA) indicaron buen ajuste del modelo.

El rendimiento HIT permaneció estable a través de inyecciones, sin efectos principales ni interacciones significativas. Las respuestas MISS reflejaron el mismo patrón, como era esperable por su estructura complementaria.

En contraste, las respuestas FA mostraron un efecto significativo de ISI ($F(2,10) = 9.809$, $p = 0.004$) y una interacción significativa Condición × ISI ($F(2,10) = 4.623$, $p = 0.038$), indicando que el impacto de la inyección difirió entre contextos temporales. Las respuestas CR exhibieron el mismo patrón inferencial, coherente con su relación complementaria con FA.

Para cuantificar efectos específicos por condición, ajustamos modelos lineales de efectos mixtos separados para cada ISI, incluyendo Tratamiento (salino, MK-801) y Condición (pre vs. post) como efectos fijos y animal como intercepto aleatorio. A partir de estos modelos específicos por ISI, calculamos (ΔPorcentaje = Post − Pre) utilizando medias marginales estimadas y aplicamos corrección de Holm a través de ISI.

HIT y MISS no mostraron cambios significativos de ΔPorcentaje bajo ninguno de los tratamientos en ningún ISI. Para las respuestas CR, observamos efectos claros relacionados con la inyección a ISI más largos (Figura 15). A ISI 1.5 s, MK-801 disminuyó el porcentaje de CR (ΔPorcentaje = 30.64, $p = 0.034$), con una reducción similar a ISI 2 s (ΔPorcentaje = 25.06, $p = 0.030$). Las respuestas FA reflejaron estos efectos de CR (Figura 15). MK-801 incrementó de forma marcada la tasa de FA a ISI 1.5 s (ΔPorcentaje = −30.64, $p = 0.034$) e ISI 2 s (ΔPorcentaje = −25.06, $p = 0.030$; Figura 15), indicando respuestas menos controladas o más impulsivas bajo bloqueo del receptor NMDA.

Por último, los contrastes entre tratamientos (MK-801 vs. salino) para ΔPorcentaje no fueron significativos para ningún tipo de respuesta tras el ajuste de Holm, indicando que los cambios asociados al fármaco no difirieron significativamente de las fluctuaciones inducidas por salino a nivel de grupo.

En conjunto, MK-801 alteró selectivamente respuestas al tono estándar al aumentar FA y reducir CR, especialmente a ISI más largos. Estos efectos sugieren un deterioro de la inhibición de respuesta o una precisión conductual reducida que emergió de forma independiente del rendimiento de detección de desviantes, que se mantuvo intacto tras las inyecciones.

5.6. Capítulo de libro: La organización estructural y funcional del sistema auditivo a través del desarrollo: bases para la percepción musical

5.6.1. Organización funcional y evolutiva del cerebro auditivo

Aunque no es esencial para la supervivencia, la música configura de manera profunda la experiencia humana. Presente en todas las culturas, acompaña a las personas desde el desarrollo temprano hasta la vejez, e influye en la conducta, la cognición y la emoción. Sus efectos sobre el cerebro son amplios (Bölte et al., 2011; Ueno & Shimada, 2024), y modifican la actividad y la conectividad neural de formas que fortalecen memoria, atención y control emocional. La música también recluta el sistema motor, coordinando movimiento y temporización tanto si se escucha como si se canta o se baila. Al activar simultáneamente regiones sensoriales, cognitivas, motoras y afectivas, la música se convierte en un modulador potente del pensamiento y de la emoción.

Más allá del movimiento, la música evoca respuestas afectivas intensas, desde placer y recompensa hasta nostalgia o asombro (Trimble & Hesdorffer, 2017; Zatorre et al., 2007). Remodela la actividad del cerebro auditivo e interactúa estrechamente con circuitos límbicos y prefrontales. El potencial terapéutico de la música se reconoce desde hace décadas, pero la creciente accesibilidad de medios

digitales ha intensificado el interés por su uso clínico. Actualmente existe evidencia a favor de intervenciones basadas en música en un espectro amplio de trastornos, desde condiciones psiquiátricas como depresión, ansiedad y trastorno de estrés postraumático, hasta desafíos neurológicos y del neurodesarrollo como demencia, afasia, traumatismo craneoencefálico, parálisis cerebral y enfermedad de Parkinson (Koelsch, 2014; Sihvonen et al., 2017). Dado que la musicoterapia es no invasiva y adaptable, ofrece oportunidades clínicas flexibles, aunque su eficacia depende de manera marcada de factores individuales, contextuales y neurobiológicos.

A pesar de resultados prometedores, muchos estudios aún tienen dificultades para identificar qué mecanismos neurales predicen mejor resultados positivos. Una comprensión más profunda del cerebro auditivo, de su arquitectura, conectividad y desarrollo, resulta esencial para explicar cómo la música influye en la percepción, la cognición y la emoción. La evidencia actual sugiere que las intervenciones basadas en música actúan principalmente a través de circuitos del cerebro auditivo que interfazan con redes motoras, motivacionales y afectivas (Zatorre et al., 2007). Estas interacciones probablemente median mejoras observadas en coordinación motora, regulación del estado de ánimo y resiliencia al estrés. Sin embargo, la integración de entradas auditivas con otros sistemas sensoriales e interoceptivos (como visión, propiocepción y tacto) permanece poco explorada. Cartografiar estas conexiones multimodales podría iluminar nuevas dianas terapéuticas para condiciones como enfermedad de Alzheimer, demencia, disfunción cardiovascular y dolor crónico.

Para entender cómo la música ejerce efectos tan amplios, es necesario examinar la organización funcional y del desarrollo del cerebro auditivo, que descodifica sonidos complejos y los transforma en experiencias perceptivas y emocionales. En mamíferos, este sistema representa un refinamiento evolutivo de un diseño vertebrado conservado, permitiendo una resolución espectral, temporal y rítmica excepcional, adecuada para comunicación y vínculo social. El cerebro auditivo humano está especialmente especializado para discriminación fina de tono, seguimiento temporal rápido y

sensibilidad a prosodia y ritmo, capacidades que sustentan tanto la percepción del lenguaje como de la música.

El cerebro auditivo está presente en todos los vertebrados, aunque su grado de complejidad varía entre especies. Incluso entre mamíferos, adaptaciones evolutivas generan especializaciones distintivas: por ejemplo, murciélagos de ecolocalización y cetáceos odontocetos han desarrollado mecanismos de procesamiento de alta frecuencia que exceden con mucho el rango humano. En contraste, los humanos exhiben una representación cortical extendida de tono y estructura armónica, habilitando percepción de melodía y armonía característica de la cognición musical (Masterton et al., 1969). A pesar de estas diferencias, la organización general de la vía auditiva permanece conservada.

Los estímulos auditivos consisten en ondas de presión dentro de rangos de frecuencia específicos por especie (humanos: aproximadamente 0.02–20 kHz). Estas ondas entran por el conducto auditivo y ponen en movimiento la membrana timpánica, transmitiendo energía mecánica a través de la cadena osicular hacia la cóclea. En la cóclea, las células ciliadas sensoriales convierten desplazamientos mecánicos en potenciales receptores, iniciando el código neural del sonido. Las señales resultantes son conducidas por fibras del nervio auditivo hacia el tronco encefálico. A diferencia de visión o somatosensación, la vía auditiva incluye múltiples estaciones de relevo con proyecciones bilaterales extensas e interacciones entre hemisferios, proporcionando redundancia y precisión espacial.

Desde la cóclea, las fibras aferentes proyectan al complejo del núcleo coclear (CNC) en el bulbo, donde comienzan vías paralelas de procesamiento. Estas salidas alcanzan el complejo olivar superior (SOC), primer sitio de integración binaural, y convergen en el colículo inferior (IC) del mesencéfalo. Desde este nodo, fibras ascendentes llegan al cuerpo geniculado medial (MGB) del tálamo y finalmente a la corteza auditiva (AC) (**Figura 16**).

5.7. Revisión sistemática: Sensibilidad auditiva en autismo: revisión sistemática de respuestas de negatividad por desajuste y campo por desajuste

Las respuestas auditivas de desajuste—negatividad por desajuste (MMN) y campos por desajuste (MMF)—son marcadores electrofisiológicos bien establecidos de discriminación auditiva preatencional y memoria sensorial. Estas respuestas, típicamente evocadas mediante paradigmas pasivos *oddball*, se emplean cada vez más para investigar desarrollo sensorial y del lenguaje en autismo.

Esta revisión sistemática sintetiza hallazgos de 52 estudios que compararon respuestas MMN y MMF entre individuos autistas y con desarrollo típico (TD) a lo largo de infancia, adolescencia y adultez. Utilizando el marco SWiM (*Synthesis Without Meta-analysis*), identificamos evidencia consistente de amplitudes MMN atenuadas y potencia MMF reducida en niños y adolescentes autistas, particularmente ante desviantes de frecuencia, duración y estímulos del habla. También se informaron con frecuencia latencias de desajuste prolongadas, asociadas a un desarrollo del lenguaje más tardío y a una mayor sensibilidad auditiva.

Aunque algunos estudios sugirieron una normalización del desarrollo de respuestas MMN y MMF en etapas posteriores de la infancia o adolescencia, una lateralización atípica hacia el hemisferio derecho emergió como un hallazgo robusto tanto en paradigmas de habla como no habla, indicando una especialización divergente para procesamiento auditivo y del lenguaje en autismo. Proponemos una explicación basada en *predictive coding* ponderado por precisión para dar cuenta de la variabilidad interindividual y del desarrollo en respuestas de desajuste, planteando una asignación atípica de confianza a errores de predicción sensoriales en autismo.

Aunque la calidad de los estudios fue en general moderada (*fair*), la heterogeneidad metodológica, la infrarrepresentación de mujeres y el muestreo transcultural limitado restringen la generalización. Estudios futuros deberían priorizar diseños longitudinales, estratificados por sexo y culturalmente

diversos, aprovechando protocolos estandarizados y prácticas colaborativas de datos. Las respuestas MMN y MMF tienen potencial como biomarcadores traslacionales no invasivos de predicción sensorial temprana y divergencia neurodesarrollativa en autismo.

5.8. Comunicación científica: La reacción del cerebro autista frente a sonidos inesperados

Las rutinas sensoriales nos permiten orientarnos en el día a día y adaptarnos a la regularidad ambiental. Este estudio analiza cómo el cerebro procesa los sonidos repetitivos y reacciona ante aquellos que interrumpen la rutina sonora y alteran la escena auditiva. En un modelo de autismo en ratas, los resultados muestran que la edad y el sexo modulan estos procesos y revelan la diversidad sensorial que existe dentro del espectro autista.

Desde los primeros días de vida, el cerebro se ve inmerso y bombardeado por un flujo constante de estímulos sensoriales que moldean su desarrollo. Las voces familiares, el sonido de la televisión o el camino hacia la escuela conforman la rutina sensorial del entorno. El cerebro infantil aprende y extrae regularidades de esas experiencias para construir modelos internos del mundo y anticipar lo que va a ocurrir para así poder predecir cómo actuar en el futuro. Con el tiempo, esos modelos se vuelven más precisos y flexibles, permitiendo ajustar las respuestas ante los cambios ambientales.

Cuando algo se desvía de lo esperado porque rompe la regularidad habitual, el cerebro reacciona y actualiza sus predicciones. En la infancia, respondemos con curiosidad ante una voz desconocida, con frustración cuando la televisión se apaga o con cautela cuando un claxon irrumpe en el camino al colegio. Este aprendizaje continuo sienta las bases del desarrollo de capacidades más complejas, como la comprensión de las intenciones ajenas, la interacción social o la adquisición del lenguaje.

5.8.1. Equilibrio entre certeza y sorpresa

El equilibrio entre certeza y sorpresa sostiene la experiencia cotidiana en un cerebro neurotípico. Sin embargo, en cerebros divergentes como el autista, este equilibrio parece funcionar de forma diferente.

Algunas personas con autismo muestran una sensibilidad elevada ante los cambios más sutiles, mientras que otras necesitan exponerse a una mayor repetición para reconocer una regularidad ambiental. De igual manera, la experiencia más cotidiana puede percibirse como un estímulo impredecible e incontrolable o incluso insoportable.

Estas diferencias influyen en la forma de anticipar gestos, interpretar intenciones o adaptarse a situaciones sociales. En un cerebro autista, el mundo puede percibirse más cambiante, más intenso o menos predecible, y esa diferencia define tanto la experiencia sensorial como la manera de relacionarse con el entorno.

5.8.2. Estudio de la actividad neuronal con animales modelos de autismo

En nuestro laboratorio exploramos cómo se manifiestan estas divergencias en el procesamiento del sonido. Nos centramos en el colículo inferior, una región clave del cerebro auditivo donde se comienza a distinguir entre los sonidos habituales y los que rompen la rutina. Realizamos mediciones de la actividad neuronal ante sonidos repetitivos y ante sonidos inusuales en ratas típicas y modelos de autismo. Para ello, utilizamos un modelo de autismo en ratas inducido por valproato, un fármaco que, administrado durante una ventana crítica del desarrollo embrionario, reproduce alteraciones cerebrales y conductuales comparables a las observadas en el autismo.

En este estudio, encontramos que el procesamiento auditivo en el colículo inferior difería entre los animales típicos y los expuestos al valproato. En los animales típicos, las neuronas coliculares distinguían con nitidez los sonidos repetitivos de los inesperados, manteniendo un equilibrio estable entre adaptación a sonidos repetitivos y respuesta a la novedad. Sin embargo, en los animales expuestos al valproato, en los ratones modelos de autismo, el equilibrio entre adaptación a la regularidad y respuesta a la novedad se alteraba en función de la edad y el sexo. En los animales juveniles, la sensibilidad a la repetición era mayor y la respuesta a la novedad más inestable, pero en los adultos, la actividad neuronal era dependiente del sexo. Las hembras mostraron una respuesta neuronal más

acentuada ante los sonidos sorpresivos, mientras que los machos mostraban una respuesta neuronal menor.

5.8.3. Divergencias que influyen en las experiencias rutinarias

Estos resultados refuerzan la idea de que el cerebro autista no procesa el contexto sonoro de una única forma. Las diferencias entre edades y sexos reflejan trayectorias de desarrollo diversas dentro del espectro. En algunos casos, se manifiesta con una conducta más rígida ante los cambios, mientras que, en otros, se muestra una sensibilidad elevada hacia la novedad. Estas divergencias influyen en las experiencias rutinarias. Modulan la facilidad para anticipar los sonidos del habla, seguir una conversación en entornos ruidosos o adaptarse a rupturas en la rutina.

Por lo tanto, es importante estudiar cómo el cerebro construye modelos internos de la rutina sensorial, y cómo estos se actualizan constantemente según el flujo de estímulos ambientales. Nuestros resultados demuestran que no existe una forma única de percibir el mundo. Cada cerebro desarrolla su propio modelo de anticipación, interpretación y adaptación al mundo exterior. Reconocer esa diversidad amplía nuestro conocimiento sobre el autismo y nos invita a valorar la riqueza de las distintas formas de experimentar la realidad.

6. Conclusiones

I. El procesamiento contextual auditivo varió de manera sistemática en función del sexo, la etapa del desarrollo y la etiología, en lugar de reflejar una inconsistencia aleatoria entre modelos relacionados con el autismo; las ratas hembra mostraron un aumento del desajuste neuronal, mientras que las ratas macho presentaron una reducción del desajuste neuronal en comparación con sus respectivos controles.

II. Las amplitudes de las respuestas auditivas del tronco encefálico variaron sistemáticamente en función del sexo, la etapa del desarrollo y la etiología relevante para el autismo, con incrementos típicos relacionados con la edad y una mayor magnitud de respuesta en hembras presentes en los animales control, pero alterados o ausentes en los modelos relacionados con el autismo.

III. La exposición prenatal al ácido valproico y la deleción heterocigota de *Grin2b* redujeron las amplitudes de las respuestas del tronco encefálico y reorganizaron los patrones típicos dependientes del sexo, produciendo alteraciones específicas por sexo en la contribución de los generadores auditivos tempranos frente a los tardíos, mientras se preservaron los umbrales de detección auditiva.

IV. Las inyecciones de MK-801 indujeron un deterioro selectivo del control conductual basado en estímulos estándar durante una tarea operante de tipo *oddball* auditivo, incrementando las falsas alarmas y reduciendo los rechazos correctos de manera dependiente del intervalo entre estímulos, mientras se preservó el rendimiento en la detección de estímulos desviantes.

V. La experiencia acústica estructurada a lo largo del desarrollo, y la música en particular, activó las vías auditivas ascendentes y los circuitos auditivo–límbico–motores, apoyando la regulación del procesamiento auditivo y de las respuestas emocionales durante ventanas sensibles del desarrollo.

VI. Las respuestas de negatividad por desajuste y los campos de desajuste en el autismo mostraron una variación dependiente del contexto más que una alteración uniforme, con diferencias en amplitud, latencia y lateralización hemisférica en función de la etapa del desarrollo, el tipo de estímulo desviado, las características del paradigma y las particularidades de los participantes.

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Appendix

PLOS Biology

RESEARCH ARTICLE

Contextual auditory processing in the inferior colliculus is affected in a sex- and age-dependent manner in the valproic acid-induced rat model of autism

Sara Cacciato-Salcedo[1,2,3], **Ana B. Lao-Rodríguez**[1,2,3], **Manuel S. Malmierca**[1,2,3]*

1 Cognitive and Auditory Neuroscience Laboratory (CANELAB), Institute of Neuroscience of Castilla y León (INCYL), Salamanca, Spain, **2** Salamanca Institute for Biomedical Research (IBSAL), Salamanca, Spain, **3** Department of Cell Biology and Pathology, Faculty of Medicine, University of Salamanca, Salamanca, Spain

* msm@usal.es

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Abstract

Diverse biological factors, such as sex and age, confer heterogeneity on sensory processing challenges in autism. These factors result in major difficulties in the processing of contextual information in social and non-social situations. To assess divergence in autistic traits, it is critical to consider sex- and age-related variability. Nevertheless, these differences remain largely elusive. Animal models of autism offer the possibility to examine contextual processing at the single-neuron level. Here, we investigated predictive processing of contextual auditory cues in the auditory midbrain of control and prenatally valproic acid-induced rats, a well-established animal model of autism. The rats were prepubertal and adult female and male animals. We performed single-unit recordings in the inferior colliculus of control and prenatally, or *in utero*, exposed rats under the classical oddball paradigm and non-repetitive cascade control sequences to study neuronal mismatch. This is the neuronal correlate of mismatch negativity, the brain's automatic response to interruptions in environmental regularity. When comparing control and exposed rats, our results demonstrated a reduction in neuronal mismatch in rats exposed to valproic acid. However, exposed adult females exhibited an increased neuronal mismatch compared to their control counterparts. With respect to sex distinctions, valproic acid induced sex differences in neuronal mismatch of prepubertal and adult rats that are not observable in control animals. Moreover, we detected an age-dependent refinement in prediction error that is not affected by the drug. But valproic acid altered typical developmental trajectory of neuronal mismatch in both sexes. Such observations support sex- and age-related effects of *in utero* valproic acid exposure in contextual auditory processing at the neural level of the inferior colliculus. In autism, atypical predictive processing of environmental regularities underlies unusual responses to novel experiences. The present study highlights the importance of sex and age, that confer heterogeneity to these challenges.

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Sara Cacciato-Salcedo, Ana B. Lao-Rodriguez & Manuel S. Malmierca

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Sex- and age-specific effects on auditory brainstem responses in the valproic acid-induced rat model of autism

Sara Cacciato-Salcedo [a,b,c], Ana B. Lao-Rodríguez [a,b,c], Manuel S. Malmierca [a,b,c,*]

[a] Cognitive and Auditory Neuroscience Laboratory, Institute of Neuroscience of Castilla y León (INCYL), Salamanca, Spain
[b] Salamanca Institute for Biomedical Research (IBSAL), Salamanca, Spain
[c] Department of Cell Biology and Pathology, Faculty of Medicine, University of Salamanca, Salamanca, Spain

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ABSTRACT

Prenatal exposure to valproic acid (VPA) provides a well-established rodent model of autism, yet its effects on auditory brainstem/midbrain processing across sex and development remain elusive. We recorded click-evoked auditory brainstem responses (ABRs) in Long–Evans rats that received prenatal VPA (400 mg/kg, gestational day 12) and in matched controls at prepubertal (postnatal days 30–45) and adult (65–120) stages under urethane anesthesia. We analyzed peak amplitudes, latencies, inter-peak intervals, and amplitude ratios across sound levels. Auditory thresholds remained comparable among groups. In controls, females showed larger amplitudes for waves I–II, shorter latencies for waves I, II, and IV, and steeper amplitude–intensity slopes for waves II, III, and V than males, indicating stronger level-dependent recruitment. Maturation enhanced early brainstem and midbrain responses by increasing amplitude growth (wave II) and shortening latencies (waves II–V), with effects more pronounced in females. Prenatal VPA exposure reduced wave II amplitude and delayed early peaks (I–III) in females, accompanied by elevated amplitude ratios, whereas in males it mainly affected later responses by reducing amplitudes for waves III–V and prolonging inter-peak latencies (I–III, III–V). These findings show that sex, age, and prenatal VPA exposure distinctly shape auditory brainstem/midbrain function.

1. Introduction

Autism is a spectrum condition characterized by atypical social communication and interaction, together with restricted and repetitive behaviors (American Psychiatric Association, 2022). In the auditory domain, nearly 90% of autistic individuals experience distinctive auditory profiles, marked by hyper- or hypo-sensitivities, atypical perceptual filtering, and altered neural gain (Gonçalves and Monteiro, 2023; Mansour and Kulesza, 2020; Marco et al., 2011; Smith et al., 2019).

Such divergences shape everyday navigation through social and non-social soundscapes (Poulsen et al., 2024). Many autistic individuals report difficulties following speech in noisy environments (Mansour and Kulesza, 2020), reduced adaptation to background regularities, and atypical temporal encoding of auditory information (He et al., 2023; Williams et al., 2021). These sensory differences evolve across development, reflecting neurobiological changes from childhood through adulthood (Poulsen et al., 2024).

A potential neural substrate for these traits lies within early auditory stations. The auditory brainstem response (ABR), a sequence of voltage deflections generated by synchronized activity in the auditory nerve and brainstem nuclei, provides a non-invasive measure of subcortical processing and neural synchrony (Young et al., 2023). Research in children and adolescents with autism reported prolonged absolute and inter-peak latencies, particularly for wave V, and reduced amplitudes across waves I to V, consistent with delayed neural conduction or reduced temporal precision (Azouz et al., 2014; Miron et al., 2018; Ramezani et al., 2019). A meta-analysis confirmed that these latency delays are robust during development but tend to diminish with age (Miron et al., 2018). This likely reflects compensatory maturation, or limited sensitivity of ABR measures to persistent subcortical dysfunction (Fujihira et al., 2021; Miron et al., 2018; Ramezani et al., 2019; Talge et al., 2021). Thus, studies in autistic adults detected no significant differences (Fujihira et al., 2021; Talge et al., 2018), subtle variability or slightly shorter wave V latencies (Miron et al., 2018).

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* Corresponding author at: Cognitive and Auditory Neuroscience Laboratory, Institute of Neuroscience of Castilla y León (INCYL), Salamanca, Spain.
E-mail address: msm@usal.es (M.S. Malmierca).

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Sex Differences in Auditory Brainstem Responses of Two Rat Models of Autism: Environmental and Genetic Contributions to Autism-Like Auditory Function

Sara Cacciato-Salcedo[1,2,3] | Ana B. Lao-Rodríguez[1,2,3] | Manuel S. Malmierca[1,2,3]

[1]Cognitive and Auditory Neuroscience Laboratory, Institute of Neuroscience of Castilla y León (INCYL), Salamanca, Spain | [2]Salamanca Institute for Biomedical Research (IBSAL), Salamanca, Spain | [3]Department of Cell Biology and Pathology, Faculty of Medicine, University of Salamanca, Salamanca, Spain

Correspondence: Manuel S. Malmierca (msm@usal.es)

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Keywords: ABR | auditory | auditory phenotypes | autism | Grin2b gene | sex | valproic acid

ABSTRACT

Autism is an early-onset neurodevelopmental disorder characterized by restricted, repetitive behaviors and atypical patterns of social communication and interaction. A considerable proportion of autistic individuals experience divergent auditory perception, which can interfere with their ability to navigate everyday sound environments. Auditory brainstem responses are electrophysiological potentials elicited by auditory stimuli that evaluate neural activity along the auditory nerve and brainstem. Importantly, the auditory brainstem response varies by sex, with females typically showing higher amplitudes and shorter latencies than males. This sex-specific neurophysiological profile is especially relevant in autism research, where the male-to-female diagnosis ratio is approximately 3:1. Thus, exploring the neurobiological mechanisms underlying sex-specific variations in autistic traits is essential. Furthermore, autism sensory profiles may vary based on the independent and mutual effects of environmental and genetic factors. To deepen this understanding, we examined auditory brainstem responses in two rat models of autism: the GRIN2B rare mutation model and the prenatal valproic acid induction model, alongside control animals. We assessed peak amplitudes and latencies (Waves I through V), inter-peak intervals (I–III, I–V, and III–V), and amplitude ratios (III:I, V:I, and V:III). Female rats generally exhibited greater amplitudes and longer latencies across waveforms. Regarding rat models, control animals consistently showed larger amplitudes and shorter latencies compared to autism-like models. Exploratory analyses further suggested pairwise interactions between sex and rat model, indicating modulation of auditory phenotypes linked to autism. Thus, our findings reveal key insights into the effects of sex and rat model, as well as their interactions.

1 | Introduction

Autism spectrum disorder (hereafter referred to as *autism*) is an early-onset neurodevelopmental condition characterized by restricted, repetitive interests and atypical social communication and interaction (American Psychiatric Association 2022). A substantial proportion of individuals with autism exhibit divergent auditory perception (~90%; Gonçalves and Monteiro 2023; Marco et al. 2011), ranging from hypo- to hyper-sensitivity to specific sounds. This poses a challenge, particularly in listening in noisy

- 10.1002/aur.70125

- https://scientias.net/la-reaccion-del-cerebro-autista-frente-a-sonidos-inesperados/

The Systematic Review is under revision in *Autism Research*, The Book Chapter is under editorial in *Springer Nature*, and the Paper 5 is under revision in *Schizophrenia*.

03th March 2026

Dr. Manuel Sánchez Malmierca, catedrático del Departamento de Biología Celular y Patología de la Universidad de Salamanca.

Dra. Ana Belén Lao Rodríguez, investigadora postdoctoral del Departamento de Biología Celular y Patología de la Universidad de Salamanca.

INFORMAN:

Que los informes de los revisores externos no han solicitado ninguna modificación para la mejora de la memoria de esta Tesis Doctoral.

CERTIFICAN:

Que la tesis doctoral titulada **Sex, age, and etiology effects on auditory processing in two rat models of autism: evidence from auditory brainstem responses and contextual neural and behavioral measures** ha sido redactada en inglés y contiene un resumen en español que describe el trabajo de investigación realizado por Dña. Sara cacciato Salcedo bajo nuestra dirección durante los últimos 4 años.

Esta tesis presenta un estudio exhaustivo de los mecanismos de la codificación predictiva a nivel subcortical en un model animal de autismo. Los resultados expuestos constituyen una contribución original y relevante al campo de la Neurociencia sensorial y de los procesos predictivos en el cerebro.

Por todo ello, consideramos que esta tesis reúne los requisitos necesarios para que sea defendida en la Universidad de Salamanca como parte del procedimiento para optar al grado de Doctora.

Y para que así conste, firmamos el presente certificado en Salamanca, a 03 de Marzo de 2026.

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Fdo: Manuel Sánchez Malmierca

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Sara Cacciato Salcedo, Manuel Sánchez Malmierca y Ana Belén Lao Rodríguez , autora y directores de la Tesis Doctoral titulada "**Sex, age, and etiology effects on auditory processing in two rat models of autism: evidence from auditory brainstem responses and contextual neural and behavioral measures**", declaran el uso de herramientas de inteligencia artificial (IA) únicamente para la corrección de estilo, el perfeccionamiento estilístico y la garantía de coherencia lingüística en la preparación del manuscrito de esta tesis doctoral. El contenido generado por IA fue cuidadosamente revisado y editado. Todas las ideas, los análisis de datos y las interpretaciones científicas son responsabilidad exclusiva del autor.

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Sara Cacciato Salcedo, Manuel Sánchez Malmierca y Ana Belén Lao Rodríguez