Journal of High School Science



Environmental noise, GABA, and the auditory brain across the lifespan: A mechanistic gap analysis

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Submitted: July 27, 2026, Revised: version 1, September 2, 2026, version 2, October 17, 2026
Accepted: October 24, 2026

Abstract
Environmental noise has been associated with altered auditory physiology, impaired speech perception, and adverse developmental outcomes, yet the causal mechanisms connecting these observations remain incompletely established. This review applies the Mechanistic Gap Index (MGI), a quantitative framework for evaluating individual causal transitions, to proposed pathways involving environmental noise, cochlear synaptopathy, GABAergic inhibition, neural encoding, and auditory development. Eight relationships yielded a mean MGI of 0.75, with four critical evidentiary bottlenecks. Application of the same scoring criteria to a more established auditory-training mechanism yielded an MGI of 0.33, providing a preliminary comparison of mechanistic completeness. Beyond identifying missing causal links, we propose extending the MGI in four directions: prioritizing experiments capable of closing specific gaps; investigating long-range causal relationships between apparently disconnected biological observations; identifying overlooked intermediate mechanisms concealed within unsupported causal transitions; and iteratively refining causal pathways as new evidence emerges. Importantly, a high-gap transition may reflect not only insufficient evidence but also an incompletely specified mechanism containing unidentified intermediate processes. Decomposing such transitions could reveal experimentally supported connections and isolate the specific missing steps required for causal closure. Prospective measures of mechanistic gain, longitudinal MGI assessment, and a complementary measure of mechanistic resolution could further support this approach. Although these extensions require independent validation, the proposed advance is to transform the MGI from a descriptive assessment of evidentiary gaps into an iterative framework for experimental prioritization, mechanistic reconstruction, and causal discovery.

Keywords
Environmental noise exposure, Auditory neuroscience, Mechanistic Gap Index, Causal inference, Mechanistic decomposition, Causal discovery, GABAergic inhibition, Cochlear synaptopathy, Frequency-following response, Auditory development

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https://doi.org/10.64337/001c.173225

1. Introduction

The standard audiogram measures the softest pure tones a person can hear. However, it fails to explain why some people struggle when speech competes with background noise. This has led researchers to examine auditory problems that may not appear on a standard hearing test. Possible explanations include: reduced cochlear input, compensatory gain in the central auditory system, weaker cortical inhibition, and less precise neural encoding. Each idea may be reasonable by itself, but separate findings do not automatically prove one connected cause.

That distinction is pertinent when adult and animal findings are applied to adolescents. Auditory listening skills continue to develop through childhood, and children's neural encoding is associated with speech-in-noise outcomes (1) and early literacy measures (2). These studies establish useful relationships, but they did not test environmental noise as the cause of the neural encoding differences. In another part of the literature, sustained noise changed inhibitory markers in rats (3), while human imaging studies linked auditory-cortex GABA with neural distinctiveness and speech-in-noise performance (4, 5). The crucial human noise-to-GABA step is still missing.

The central question of this review is how completely existing evidence connects quantified environmental noise exposure to altered auditory development in humans. To address this question, we evaluate the proposed causal transitions using the Mechanistic Gap Index (MGI), distinguish serial relationships from effect modification, and identify the principal evidentiary bottlenecks. We then investigate a broader methodological question: whether an apparently unsupported causal relationship can be reconstructed into intermediate transitions for which independent evidence already exists. Using the environmental noise–FFR relationship as a worked example, we examine how mechanistic decomposition can generate more specific experimental hypotheses. This approach extends the review from assessing the completeness of an existing causal explanation toward exploring how incomplete mechanisms might be reconstructed and experimentally tested.

2. Scope and search strategy

This is an analytical literature review, not a systematic review or meta-analysis. The initial search was conducted from May through July 2026 with ANARA, Google Scholar, PubMed, publisher pages, and reference-list checking. Search terms combined environmental or lifetime noise exposure with auditory GABA, inhibition, cochlear synaptopathy, auditory brainstem response (ABR), middle ear muscle reflex (MEMR), frequency-following response (FFR), speech-in-noise perception, classroom acoustics, child cognition, and auditory development. A revision search in August 2026 used OpenAI ChatGPT with web search, Google Scholar, PubMed, and publisher pages to target publications from 2023 through August 2026 on synaptopathy, MEMR-based proxies, MRS methods, and FFR source methods.

Peer-reviewed studies were included when they reported evidence about noise exposure, peripheral or central auditory physiology,

GABAergic measures, speech encoding, developmental listening, or child noise-cognition outcomes. Method and framework papers were included when needed to interpret MRS, FFR, causal inference, or the MGI. The current ASA/ANSI classroom acoustic standard was checked separately. Full texts were used when available, and article titles, sample details, numerical claims, years, journals, and DOI records were checked against original articles, PubMed, or publisher records.

The focus is ordinary environmental or lifetime exposure that may occur without a lasting audiometric threshold shift. Immediate masking and reverberation can make speech harder to understand without proving a lasting neural change. In this paper, an altered developmental trajectory means that objectively measured exposure predicts a different pattern of neural encoding or listening growth over time, not simply worse performance while a room is noisy.

3. Analytic framework

3.1 Primary chain and separate modifier

The proposed primary chain is:

Environmental noise exposure → peripheral or neural degradation → altered GABAergic inhibition or central compensation → reduced auditory encoding precision → impaired speech-in-noise processing → altered developmental auditory maturation

A separate possibility is that children who already have atypical auditory encoding may be more vulnerable to this pathway. This is an additional hypothesis because it changes the strength of an exposure effect. For that reason, it is reported separately and is not included in the core MGI report.

3.2 Evaluating the evidentiary completeness of causal mechanisms

The proposed chain is similar to a simplified causal directed acyclic graph, or DAG (7). A full DAG would show confounders, feedback-free parallel paths, and competing explanations. This review instead scores the edges of one stated mechanism so readers can see exactly where a claimed transition has or has not been tested. The MGI's main purpose is to ask whether each arrow in a proposed mechanism was directly measured in the relevant population. It does not score risk of bias, effect size, or the clinical importance of a study.

3.3 Defining edges before scoring

An edge is a proposed connection in which one factor leads to another in a defined population and setting. Before scoring a new application, the analyst should define the starting intervention or exposure, final outcome, intermediate steps, timing of measurements, and full list of edges. A broad process and the measurement used to represent it are not separate causal steps. Multiple harmonics, test conditions, or behavioral tests measuring the same thing stay within one node. A retention node can be included only if the later measurement time is chosen in advance. It must represent a lasting benefit, not a new biological mechanism. All specified transitions remain visible, including ones with little or no support. Splitting, merging, or deleting edges to improve a calculated score is not allowed.

For the benchmark, this rule combines altered subcortical processing and enhanced pitch-cue encoding in noise into one physiological node. Pitch-cue encoding is the measurement used to represent that processing, rather than a separate process that comes afterward. The chain fixed before scoring was: auditory training → enhanced neural pitch-cue encoding in noise → improved speech-in-noise performance immediately after training → retained speech-in-noise benefit at follow-up. The follow-up interval is approximately six months in the chosen study. This gives three transitions. The pathway was selected on methodological grounds, not to achieve a target MGI value. No cortical or academic outcome is added to this adult speech-in-noise question.

The original environmental matrix and its eight scores are retained. Its rows cover branch and endpoint claims around the proposed pathway, rather than eight adjacent steps in a single linear chain. Its mean is therefore a summary of that evidence map. The smaller benchmark is a narrower ordered pathway. Their means can illustrate a contrast in evidence gaps, but the two mechanisms differ in complexity, so the scores are not directly equivalent. This distinction also limits claims of validation.

3.4 Scoring, bottlenecks, and averaging

Each link receives a gap score: 0 means the transition was directly demonstrated in the relevant population and system; 0.5 means the support is indirect, associational, or cross-species; and 1 means it is untested or substantially inconsistent. The descriptive mean is MGImean = (sum of gap scores) / N. For the eight proposed links in Table 1, the score is 6/8 = 0.75.

A mean by itself is not enough for a serial chain. Well-supported later links cannot repair a missing exposure link. The analysis therefore also reports MGImax, the largest single gap, and names every bottleneck. Here, MGImax = 1.0, with bottlenecks at links 2, 5, 7, and 8. A score of 1.0 identifies an unsupported transition within the proposed causal architecture. Because the eight relationships include branches and endpoint connections rather than a single serial sequence, the maximum score identifies the largest evidentiary gap but does not, by itself, establish that every possible causal route remains incomplete. The mean is still useful as a short description and for tracking how new evidence changes the whole evidence map. It is never used to let one strong arrow cancel a missing one. A maximum below 1 does not prove the whole chain either, because a 0.5 still marks an indirect connection.

Table 1. Core evidence matrix and bottleneck analysis

Proposed link	Best evidence and main limit	Evidence class	Gap
1. Noise → altered auditory-cortex inhibition or organization	Direct animal experiments show changes in inhibitory markers, tonotopy, tuning, or critical-period maturation. The exposures and species differ from ordinary human classrooms.	Experimental, cross-species	0.5

Proposed link	Best evidence and main limit	Evidence class	Gap
2. Quantified noise → reduced auditory-cortex GABA in humans	Human auditory GABA varies with age and auditory conditions, but no reviewed study tested measured noise as the cause. MRS is also a bulk tissue measure rather than synaptic inhibition.	Not directly tested; bottleneck	1.0
3. Reduced GABA → poorer neural distinctiveness	Auditory GABA covaries with fMRI pattern distinctiveness in older adults. No manipulation or within-person causal test establishes direction.	Human association	0.5
4. Reduced GABA → poorer speech-in-noise performance	Right auditory-cortex GABA predicts speech-in-noise performance in older adults, but the evidence remains observational.	Human association	0.5
5. Noise → cochlear synaptopathy in humans	Studies using ABR, envelope-following, and MEMR proxies report mixed results. Living-human markers remain indirect and show substantial variation between people.	Conflicting proxy evidence; bottleneck	1.0
6. Poor encoding → poorer speech-in-noise in children	Timing, stability, fundamental-frequency encoding, and context effects covary with listening outcomes. Causal direction has not been settled.	Human developmental association	0.5
7. Environmental noise → altered FFR or encoding in children	The FFR is plastic and developmentally useful, but reviewed pediatric studies did not measure ordinary environmental exposure as the cause of an FFR change.	Not directly tested; bottleneck	1.0
8. Environmental noise → altered auditory developmental trajectory	Child noise studies report cognitive or school outcomes, including exposure-response and natural-experiment evidence, but do not track auditory neural maturation.	Neural transition untested; bottleneck	1.0
Core result	**Mean = 6/8 = 0.75; maximum = 1.0; proposed mechanism remains open**	**Bottlenecks: 2, 5, 7, 8**	**0.75**

Note. The mean summarizes the distribution of gaps but does not imply compensation among arrows. MGImax and the bottleneck list control the serial interpretation. Scores describe directness and consistency for the specified transition, not overall study quality.

Table 2. Separate additional hypothesis

Modifier	Current evidence	Status	Gap
Baseline atypical encoding × noise → greater impairment	Atypical encoding is reported in developmental dyslexia, but reviewed studies did not test an exposure-by-baseline interaction.	Untested moderator; excluded from core denominator	1.0

Note. Baseline atypical encoding is treated as a separate effect modifier and is not included in the eight-link core MGI calculation.

4. Evidence at the connecting edges

4.1 Developmental animal evidence and auditory-cortex change

Developmental animal research makes the first link stronger than one young-adult rat study alone. Zhang et al. showed that early acoustic experience can persistently shape rat primary auditory cortex (8). Chang et al. (9) found that continuous moderate-level noise delayed development of adult-like auditory cortical organization. De Villers-Sidani et al. (10) identified a critical-period window for spectral tuning, and Zhou et al. (11) found enduring changes in cortical temporal modulation after structured noise during early development. Together, these studies show that early acoustic environments can alter cortical organization during development.

Kamal et al. (3) provide a different but related experiment in six-month-old young adult rats. The animals heard continuous 65 dB broadband noise for eight weeks. Figure 5 of the original article shows about 30% fewer parvalbumin-positive cells, 20% fewer GABA-positive cells, and 44% lower myelin basic protein staining than young controls. The corresponding age-group reductions were about 25% for parvalbumin and 38% for myelin, while the aged GABA-positive cell-count change was not significant. The noise-exposed rats also had broader tuning, less orderly tonotopic maps, and weaker differentiation between standard and deviant sounds.

Most functional outcomes improved after eight weeks in quiet, and parvalbumin and myelin partly recovered, although tonotopic organization did not fully return to normal. Recovery of the lower GABA-positive count was not reported (3). Together, the developmental and young-adult experiments show that acoustic input can change auditory-cortex development and plasticity in rats. They cannot establish that intermittently mixed classroom sound has the same lasting effect in a child. For that reason, link 1 remains 0.5 rather than 0.

4.2 Human peripheral evidence, null findings, and newer proxies

Human peripheral evidence is much less settled. Bramhall et al. (12) reviewed the search for noise-induced cochlear synaptopathy in humans and found that studies using ABR, envelope-following, and MEMR measures often do not agree. ABR Wave I can have acceptable test-retest reliability but very large differences between people, which weakens it as an individual marker. The review also explains that living-human measures are proxies rather than direct synapse counts.

Guest et al. (13) illustrate the null side of the disagreement. They studied young adults with normal audiograms and found no relationship among verified speech-in-noise difficulty, lifetime noise exposure, and the tested synaptopathy proxies. The sample was young and much of the exposure was recreational, which limits generalization and may narrow the range of actual neural injury.

Newer MEMR work has not solved the problem. A 2023 review described mixed human MEMR findings and the need for better validation (14). Bramhall et al. (15) reported wide normative ranges for wideband MEMR magnitude and limited diagnostic separation for cochlear deafferentation. The human evidence therefore remains mixed enough that link 5 stays at 1.0. It

also illustrates that ordinary environmental noise has not been connected to verified synapse loss with a living-human marker strong enough to settle the disagreement.

4.3 GABA, neural distinctiveness, and fMRI limitations

Dobri et al. (4) measured auditory-cortex GABA in 19 younger and 19 older adults. Older adults had lower auditory GABA, and right auditory-cortex GABA predicted speech-in-noise performance after audiometric status was considered. Their mediation model suggested that GABA explained part of the age-performance relationship. The study did not manipulate GABA or identify noise as the cause of the individual differences.

Lalwani et al. (5) combined magnetic resonance spectroscopy with fMRI. Older adults showed lower uncorrected auditory GABA and less distinct activation patterns for music and foreign speech. Within the older group, higher auditory GABA related to greater auditory pattern distinctiveness. However, the age difference in GABA was sensitive to tissue-composition correction. This is not a minor technical detail. It means that age-related atrophy and the mix of gray matter, white matter, and cerebrospinal fluid inside the voxel can affect the apparent group difference.

Edited MRS partly measures the wrong level of the proposed mechanism. It estimates bulk GABA concentration in a centimeter-scale tissue voxel rather than synaptic inhibition. The common edited signal at 3 ppm also contains co-edited macromolecules and is usually reported as GABA+ unless a suppression method is used (16). A voxel placed over auditory cortex includes mixed tissue and nearby structures. Therefore, even a careful longitudinal MRS study would measure bulk regional GABA, not synaptic inhibitory tone directly. MRS can support links 2 through 4, especially when paired with physiology and behavior, but it cannot close them by itself.

4.4 FFR sources and pediatric encoding-to-behavior evidence

The FFR is a phase-locked response to periodic sound, but it should not be described as purely subcortical. MEG showed a right-weighted cortical contribution at lower fundamental frequencies along with subcortical sources (17). Other source models found that subcortical generators dominate the scalp-recorded electrical FFR to speech (18). High-density EEG constrained by structural MRI also identified both cortical and subcortical activity for missing-fundamental stimuli (19). Together, these findings support careful source wording and make FFR interpretation method-specific.

Among pre-reading four-year-olds, more stable and accurately timed encoding of consonants in noise is associated with early literacy measures (2). In school-age children, context-dependent encoding relates to speech-in-noise perception and differs in developmental dyslexia (1). These findings support link 6 in humans, but they do not show that environmental noise caused the encoding differences.

4.5 Pediatric noise-cognition evidence and the missing neural transition

A large pediatric environmental-noise literature needs to be part of this review. In the cross-

national RANCH study, 2,844 children aged 9 to 10 years attended 89 schools near major airports. Aircraft noise showed linear exposure-response relationships with poorer reading comprehension and recognition memory after adjustment for major confounders, including socioeconomic factors. The road-traffic results were not the same: road noise was not associated with poorer reading in that analysis and some memory results went in an unexpected direction (20). This detail matters because the findings should not be summarized as every transport noise source having the same effect.

The Munich airport relocation gave researchers a clearer picture of what happened before and after noise exposure changed. Children near the old and new airports were tested before the switchover and at two follow-ups. Reading and long-term-memory differences weakened after the old airport closed and appeared near the new airport after exposure began, with some effects stronger at the later wave (21). Bronzaft's train-noise work found that after rail and classroom noise reduction, the earlier reading difference between noisy-side and quiet-side rooms was no longer present (22). In London primary schools, external and classroom noise related to standardized attainment measures (23). Reviews by Klatte et al. (24) likewise describe effects of chronic and classroom noise on children's learning, especially reading and memory.

These population studies provide important evidence that chronic noise can relate to child cognition and that reducing an exposure can improve educational conditions. It still does not close link 8 as defined here. These studies did not repeat FFR, ABR, auditory-cortex GABA, or another auditory-neural measure across development. Possible routes include speech masking, attention, stress, sleep disruption, teaching interruption, and neural change. Because those routes were not separated, the literature supports an exposure-to-cognitive-outcome relationship but not the claimed exposure-to-altered-auditory-maturation transition.

The 2010 edition of ASA/ANSI S12.60/Part 1, reaffirmed in 2024, specifies the acoustic targets summarized here. For qualifying unoccupied core learning spaces, the maximum background level is 35 dBA. The maximum reverberation time is 0.6 seconds for rooms up to 10,000 cubic feet and 0.7 seconds for rooms from 10,000 to 20,000 cubic feet (25). These values support communication access. They do not by themselves establish lasting GABAergic, synaptic, or subcortical injury.

4.6 Baseline atypical encoding as a separate modifier

Children with developmental dyslexia show atypical context-dependent auditory brainstem encoding (1). This study shows baseline variation in encoding, but it did not test whether the same measured noise exposure produces a larger neural or behavioral change in this group. The proposed vulnerability therefore remains a score of 1.0 as a moderator. A valid test requires a baseline encoding measure, objective exposure data, and a pre-specified exposure-by-baseline interaction.

5. MGI results

The core MGImean is 0.75 and MGImax is 1.0, indicating substantial evidentiary gaps within

the proposed causal architecture, with four transitions classified as bottlenecks. This leads to the review's main result: the literature has many studies at individual nodes, but fewer studies that join those nodes within the same population and time sequence. The four bottlenecks are the transitions from noise to human auditory GABA, noise to verified human synaptopathy, environmental noise to pediatric FFR change, and environmental noise to an altered auditory developmental trajectory.

5.1 Auditory training benchmark

Song et al. (6) randomized 60 normal-hearing adults to training [n=28] or no training [n=32]. Training comprised 20 half-hour LACE sessions over four weeks. Neural pitch encoding in noise and speech-in-noise performance improved. Stronger baseline pitch encoding predicted greater perceptual gain. At approximately six months, 16 trained and 12 control participants returned; the study reported lasting benefits. These findings connect intervention, physiology, and behavior more closely than the environmental evidence does, but do not establish mediation. The control group received no training, and fewer than half of the original participants returned for follow-up. Both points limit what the results can tell us.

Table 3. Fixed benchmark transitions and unchanged gap scores

Fixed transition	Basis for the score	Gap
B1. Training → neural pitch-cue encoding in noise	Randomized training comparison directly tests this intervention-to-neural outcome. Zero describes directness, not absence of bias.	0
B2. Neural pitch-cue encoding → immediate speech-in-noise improvement	The reported predictor was baseline encoding, not experimentally isolated encoding change. Co-improvement does not establish that the neural change caused the perceptual gain.	0.5
B3. Immediate speech-in-noise improvement → retained benefit	Follow-up supports persistence, not a manipulation showing that immediate improvement caused retention. This temporal transition remains indirect.	0.5
Benchmark result	**Mean = (0 + 0.5 + 0.5)/3 = 0.33; maximum = 0.5. No 1.0 bottleneck, but causal closure is not established.**	**0.33**

Note. Scores are this review's application of the existing rules, not values reported by Song et al. (6). The study's Results sections on training effects, relationship to behavior, and six-month retention provide the evidence for B1-B3. Retention is included as an explicitly time-separated outcome, not evidence for a new physiological process. It receives 0.5, not 0, because observed persistence alone does not establish its cause.

The benchmark mean is 1/3, ~ 0.33, compared with 6/8 = 0.75 for environmental noise. Its maximum is 0.5 rather than 1.0. This is a descriptive contrast, not a statistical comparison, a percent of causal proof, or evidence that the MGI has been formally validated. The benchmark has fewer transitions, a different population, and a deliberately selected intervention study. Its lower mean needs to be read alongside the individual connections and their limits.

There are several reasons to be careful about claiming causation. Baseline encoding

predicting learning is not evidence that a training-induced encoding change mediated the gain. Also, a nonsignificant difference between post-training and follow-up scores is not an equivalence test. Benefits above baseline support retention but do not prove the proposed persistence mechanism. The FFR studies also show that scalp FFRs cannot be attributed exclusively to the brainstem. Accordingly, B1 refers to measured neural pitch encoding without assuming an exclusively brainstem origin.

6. Prospective use: experiments with the most information gain

Table 4 asks what each next design can actually achieve. A longitudinal association can improve time order and usually move a 1.0 to 0.5, but reaching 0 normally requires an intervention, a strong natural experiment, or a safe manipulation that directly tests the arrow. A null result does not automatically lower a gap. It may keep the uncertainty, contradict the link, or show that the link should be removed.

Table 4. Prospective tests, achievable scores, and intervention requirements

Link or modifier	Highest-value next design	Best score from that design	Intervention for 0?
1. Noise → cortical inhibition or organization	Repeated human exposure and inhibitory or cortical-organization measures	0.5 observational; 0 after credible exposure change	Yes
2. Noise → auditory GABA	Objective exposure plus repeated auditory-cortex MRS, with tissue correction and paired physiology	0.5 longitudinal; 0 after acoustic intervention or strong natural experiment	Yes
3. GABA → neural distinctiveness	Repeated GABA and encoding measures with temporally linked within-person change	0.5; 0 requires a safe, specific manipulation	Usually
4. GABA → speech-in-noise	Repeated MRS and speech-in-noise testing with planned mediation and specificity checks	0.5; 0 requires safe manipulation or intervention evidence	Usually
5. Noise → human synaptopathy	Prospective exposure study using several validated peripheral markers	0.5 if markers converge; 0 is unlikely without stronger validation and exposure-change evidence	Yes, or a strong natural experiment
6. Encoding → child speech-in-noise	Repeated within-child encoding and listening measures; targeted encoding intervention where feasible	0.5 longitudinal; 0 after a specific intervention changes both in order	Yes for 0
7. Noise → pediatric FFR	Objective exposure plus repeated source-aware FFR measurement	0.5 longitudinal; 0 after classroom acoustic intervention	Yes
8. Noise → auditory developmental trajectory	Multiyear cohort with repeated neural and behavioral outcomes	0.5 cohort; 0 after randomized or stepped-wedge acoustic intervention	Yes
Modifier: baseline encoding × noise	Pre-specified exposure-by-baseline interaction with enough subgroup power	0.5 observational; 0 if the interaction changes under assigned exposure reduction	Yes for causal moderation

Note. A score of 0 requires direct support in the relevant human population. Human exposure should not be experimentally increased to harmful levels. Intervention here mainly means reducing classroom noise or reverberation, or using a credible natural change in exposure.

6.1 Socioeconomic status as the main confounding problem

Socioeconomic status (SES) needs careful attention in any future study. Environmental noise is not randomly distributed. Housing quality, neighborhood traffic, airport or rail location, classroom resources, and the ability to avoid noisy places can all vary with income and education. SES also relates to language exposure, sleep, health care, attention, reading opportunities, and school quality. Neural speech encoding has also been linked to maternal education in children (26). RANCH adjusted for major socioeconomic variables and still found an aircraft-noise relationship with reading and memory, but adjustment cannot prove that all social differences were removed (20).

A strong pediatric study should measure parental education and income, neighborhood deprivation, housing and bedroom location, school resources, language background, home literacy, sleep, air pollution, hearing history, and other noise sources. Children share classrooms and schools, so multilevel models are needed to account for these groupings. Repeated within-child measures would remove stable individual differences, while a randomized or stepped-wedge classroom acoustic intervention would reduce confounding further. Negative-control exposures and outcomes could also help detect remaining bias. Even with these steps, remaining confounding should be treated as a major limitation.

6.2 A practical priority study

The highest-information design would follow children for at least one school year, use personal dosimetry and room acoustic measures, and repeat pure-tone audiometry, ABR or source-aware FFR, and speech-in-noise testing. A carefully selected subgroup could undergo auditory-cortex MRS to examine GABA+, with tissue composition, voxel placement, macromolecule handling, and data quality reported. A classroom acoustic intervention, ideally randomized or rolled out in a stepped-wedge design, would test whether changing exposure changes the trajectory. The baseline encoding interaction should be registered before analysis. This single program could address links 2, 6, 7, 8, and the separate modifier while recognizing that an observational association alone cannot prove each arrow.

This longitudinal study would test whether changes in environmental noise exposure produce sustained changes in auditory physiology and development. A complementary, more focused experiment is considered in the Discussion, where independent manipulation of background noise and attentional demands is proposed to investigate a specific intermediate mechanism underlying bottleneck 7. The two approaches address different questions: whether environmental noise produces lasting neural changes, and whether attentional load contributes to immediate changes in auditory encoding.

7. Discussion

The principal finding is that the proposed environmental-noise mechanism is supported unevenly across its constituent relationships. This unevenness is scientifically informative: experimental evidence for noise-related cortical changes, human associations involving GABA,

and developmental relationships involving auditory encoding do not necessarily describe successive stages of the same process. The central difficulty is therefore not simply insufficient evidence, but uncertainty about whether findings obtained in different populations and experimental systems can be assembled into one causal explanation. This distinction becomes particularly important when evaluating the four identified bottlenecks and determining whether they reflect genuinely untested relationships or incompletely specified intermediate mechanisms.

The animal-to-child comparison illustrates why the edge specifications are important. Rat pups or young adult rats experienced controlled, continuous or structured noise during defined periods of time. Real classrooms contain speech, HVAC systems, traffic, reverberation, and outdoor equipment that vary in frequency, timing, predictability, and recovery. As a result, animal-based studies themselves cannot prove that everyday classroom noise changes human auditory development.

The same caution applies to cochlear synaptopathy. Human ABR, EFR, and MEMR findings are valuable, but they are merely related without a living-human standard test. A score of 1.0 for link 5 does not mean there is no human connection, rather, noise exposure has not been connected to verified synapse loss with a marker strong enough to settle the continued disagreement.

7.1 Mechanistic decomposition of bottleneck 7: attentional load as an intermediate mechanism

Bottleneck 7 provides a specific opportunity to examine whether the unsupported environmental noise → altered pediatric FFR relationship conceals an intermediate mechanism. Rather than assuming a direct effect of environmental noise on neural encoding, we consider whether increased attentional demands could connect the two observations. This possibility is supported by separate lines of research concerning noise-related listening effort and task-dependent modulation of the FFR.

The original relationship, environmental noise → altered pediatric FFR, was assigned an MGI score of 1.0 because direct evidence connecting these endpoints in the relevant population remains insufficient. However, environmental noise can interfere with ongoing auditory and cognitive activities, increasing listening effort and competing attentional demands (24,27). Separately, experimental studies have demonstrated that performing concurrent auditory or visual tasks can modulate the human FFR. Task-related suppression of FFR pitch strength has been reported during auditory and visual discrimination tasks, while other investigations have demonstrated attentional modulation of auditory brainstem responses (28-30). These findings suggest that attentional load may represent an overlooked intermediate mechanism connecting environmental noise to altered neural encoding. Table 5 decomposes the original causal relationship into two sub-arrows and evaluates the available evidence using the manuscript's existing MGI scoring criteria.

Table 5. Mechanistic decomposition of bottleneck 7: Environmental noise, attentional load, and frequency-following responses

Causal relationship	Supporting evidence	Evidence classification	MGI
Original: Environmental noise → altered pediatric FFR	Direct evidence connecting environmental noise exposure with altered FFR in children remains insufficient.	Unsupported target-population transition	**1.0**
Sub-arrow 1: Environmental noise → increased attentional demands	Background noise can increase listening effort and interfere with concurrent cognitive processing (24,27).	Indirect or associative evidence	**0.5**
Sub-arrow 2: Increased attentional demands → altered FFR	Experimental studies demonstrate task-dependent modulation of human FFR pitch strength and amplitude, although effects vary with task and stimulus characteristics (28-30).	Experimental human evidence; indirect for the pediatric environmental-noise context	**0.5**
Expanded pathway: Environmental noise → attentional demands → altered FFR	Both component relationships have published supporting evidence, but mediation of the complete pathway has not been established in children.	Provisional mechanistic reconstruction	**Mean = 0.50; maximum = 0.50**

Table note: The original MGI score remains 1.0 in the manuscript's principal analysis. The expanded MGI is an exploratory score based on a different causal architecture and should not be interpreted as a directly comparable reduction in evidentiary uncertainty.

The expanded mean MGI is calculated as: MGI_expanded = (0.5 + 0.5)/2 = 0.50. The maximum component score is: MGI_max = max(0.5, 0.5) = 0.50. This analysis provides a concrete example of how mechanistic decomposition can reveal existing evidence within an apparently unsupported causal transition. Whereas the original relationship was assigned an MGI of 1.0, both reconstructed sub-arrows have relevant published support, producing a provisional expanded mean MGI of 0.50 and maximum MGI of 0.50. Importantly, the maximum score is reduced because neither component relationship remains wholly unsupported, rather than merely because additional transitions have been introduced.

Nevertheless, the original and expanded MGI values are not directly comparable as measures of improved causal certainty because their denominators and causal architectures differ. Furthermore, evidence supporting two separate relationships does not establish that attentional load mediates the effect of environmental noise on FFR. The original score of 1.0 should therefore remain unchanged in the principal eight-link MGI analysis, while the expanded score is presented separately as an exploratory mechanistic reconstruction.

An additional distinction concerns whether FFR alterations reflect acute functional modulation or persistent changes in neural encoding. Experimental suppression of FFR during concurrent tasks may represent a reversible response to attentional demands rather than lasting auditory dysfunction. Thus, the proposed intermediate mechanism could explain

immediate noise-related changes in FFR without necessarily accounting for long-term developmental consequences. These possibilities require separate experimental evaluation.

The reconstructed pathway also identifies a specific experiment. A within-participant 2 × 2 factorial design could compare FFR responses under quiet versus controlled background-noise conditions and single-task versus dual-task performance in children. FFR pitch strength, amplitude, neural response consistency, behavioral performance, and listening effort would be measured across all four conditions. If attentional load mediates noise-related FFR alterations, manipulating task demands should systematically modify the noise–FFR relationship. A significant noise-by-task interaction would indicate attentional modulation but would not independently establish mediation; this would require appropriate mediation analysis and controls for acoustic masking, developmental maturation, and peripheral hearing.

The broader methodological contribution is that the MGI can potentially move beyond identifying missing causal evidence to guiding the reconstruction of causal mechanisms. By decomposing high-gap transitions into biologically or functionally plausible intermediate relationships and evaluating each against existing literature, investigators can distinguish genuinely uninvestigated mechanisms from those for which relevant evidence already exists. Bottleneck 7 illustrates this approach and generates a testable hypothesis for future research, although the reconstructed pathway remains provisional until experimentally validated.

8. Strengths and limitations of the MGI

The principal strength of the Mechanistic Gap Index (MGI) is that it provides a structured method for evaluating the completeness of a proposed causal explanation rather than merely the quantity of evidence associated with its constituent observations. Conventional narrative reviews can establish that several biological phenomena have been independently demonstrated without resolving whether they form a continuous causal mechanism. The MGI makes the evidentiary requirements of that mechanism explicit, thereby distinguishing the credibility of individual findings from the completeness of the explanation connecting them.

A second strength is its ability to expose the precise evidentiary burden associated with a scientific claim. Broad mechanistic explanations frequently combine experimental findings, observational associations, cross-species extrapolations, and theoretical inferences within a single narrative. By evaluating the proposed transitions separately, the MGI makes these differences visible and permits readers to determine whether the strength of the overall conclusion is commensurate with the evidence supporting its constituent relationships. This is particularly useful for multidisciplinary hypotheses, where findings from different experimental systems may otherwise acquire an appearance of causal continuity simply through their presentation within a common explanatory framework.

The MGI also improves the transparency and auditability of scientific interpretation. Each score is associated with an explicitly defined relationship and a stated evidentiary basis, allowing readers to challenge individual judgments without necessarily rejecting the entire proposed mechanism. Disagreements can therefore be localized to particular transitions, evidence classifications, or definitions of causal relationships. This makes the framework potentially useful in peer review, where disagreement about the validity of a broad mechanistic claim can be difficult to resolve when the underlying evidentiary assumptions remain implicit.

Another strength is the separation of overall evidentiary completeness from the weakest component of a proposed mechanism. Reporting the mean MGI together with the maximum score and identified bottlenecks prevents extensive support for some transitions from obscuring the absence of evidence for others. The distinction is especially important when interpreting serial mechanisms, because establishing several consecutive relationships does not establish the remaining relationships by implication. Similarly, treating effect modifiers separately from serial transitions preserves the logical distinction between factors that transmit an effect and factors that change its magnitude.

The framework is also adaptable to different levels of biological organization. A proposed mechanism may involve molecular, cellular, physiological, behavioral, or developmental processes, yet the fundamental assessment remains whether the specified transitions have been adequately investigated in the relevant population and experimental system. This permits the same general evaluative logic to be applied across disciplines without requiring all mechanisms to share the same measurements or biological endpoints. Such adaptability is a conceptual strength, although it should not be mistaken for demonstrated comparability of numerical scores across different mechanisms.

These advantages must be considered alongside important limitations. The MGI remains an author-proposed framework without established psychometric properties, independent validation, or demonstrated reproducibility across investigators. Its three-level scoring system compresses several distinct sources of uncertainty—including indirect measurement, observational design, cross-species extrapolation, and inconsistent findings—into the same numerical categories. Consequently, identical scores may represent substantially different evidentiary circumstances. The resulting arithmetic mean is an ordinal summary expressed numerically, not an interval-scale measurement with demonstrated equal distances between categories.

The framework is also sensitive to how causal relationships are defined. Broad transitions can conceal multiple biological processes, whereas narrowly specified pathways may contain more individually assessable relationships. Although explicit edge definitions improve transparency, they do not eliminate investigator judgment concerning the appropriate level of mechanistic detail. Moreover, the equal weighting of transitions is a simplifying assumption rather than an established property of biological causation. Some transitions may be

indispensable to the proposed mechanism, while others may represent one of several possible routes to the same outcome. A mean score cannot capture these differences in causal importance.

Another limitation is that the MGI evaluates evidentiary directness rather than the reliability or magnitude of the underlying findings. A directly tested relationship may receive a favorable gap score even when the supporting experiment is small, imprecise, poorly controlled, or susceptible to bias. Conversely, a relationship supported by several rigorous but indirect studies may retain an intermediate score. The MGI should therefore complement, rather than replace, formal assessments of study quality, consistency, effect size, and causal identification.

The present application has additional limitations arising from its narrative-review design. The literature was not assembled through systematic-review screening, and no formal risk-of-bias assessment, meta-analysis, or independent scoring exercise was conducted. The single selected auditory-training benchmark provides an illustrative comparison rather than evidence of generalizability or external calibration. These constraints limit the precision and reproducibility of the reported scores and preclude interpreting differences between pathways as statistically established differences in mechanistic validity.

Finally, the MGI evaluates a specified causal hypothesis rather than determining whether that hypothesis is the correct explanation of an observed phenomenon. A pathway can receive substantial evidentiary support while competing mechanisms remain viable, and an incomplete pathway may coexist with a well-established endpoint effect. Accordingly, the MGI should be interpreted as a transparent assessment of the evidentiary completeness of a defined causal architecture, not as a probability that the mechanism is true, a measure of biological injury, or an estimate of clinical or developmental risk. Its present value lies in making mechanistic claims more explicit, inspectable, and scientifically accountable; its reliability as a general quantitative framework remains to be established.

9. Perspectives: From mechanistic gap assessment to causal discovery and experimental prioritization

The preceding analysis identifies the evidentiary limits of the proposed environmental-noise mechanism and illustrates, through Table 5, how one unsupported relationship can be reconstructed into more specific intermediate transitions. These findings suggest a broader application of the MGI: using identified gaps to guide the formulation, comparison, and experimental investigation of causal hypotheses. Four related directions follow from this possibility: targeted experimental prioritization, mechanistic decomposition, investigation of long-range causal relationships, and iterative refinement of causal models.

9.1 Targeted experimental prioritization and prospective mechanistic gain

Conventional reviews frequently recommend additional research without specifying which experiments would most effectively advance mechanistic understanding. The MGI can

potentially transform this general recommendation into a targeted experimental strategy by identifying the causal transitions requiring investigation and the interventions capable of testing them.

In the present manuscript, for example, additional observational evidence associating auditory GABA with speech-in-noise performance would not resolve the missing environmental noise → human auditory GABA transition. A longitudinal or controlled acoustic intervention measuring exposure, auditory GABA, neural encoding, and subsequent perceptual outcomes could more directly address that bottleneck. Similarly, repeated associations between neural encoding and speech perception would not establish whether environmental noise causes changes in pediatric neural encoding. The relevant experiment must test the exposure-to-encoding transition itself.

This prospective application can be formalized by distinguishing the descriptive MGI (MGI-D), representing the current evidentiary state of a specified mechanism, from a projected MGI (MGI-P), representing the remaining gaps if a proposed experiment successfully establishes its targeted causal transitions. The potential mechanistic gain is: $\Delta MGI = MGI\text{-}D - MGI\text{-}P$. For a fixed mechanism containing N equally weighted causal links, changing one link from a gap score of 1 to 0 would reduce the mean MGI by 1/N. However, this reduction is conditional on the experiment actually establishing the proposed transition. It is not equivalent to the probability of experimental success, the expected scientific value of the experiment, or the probability that the entire mechanism is correct.

A more developed framework could estimate expected mechanistic gain across possible experimental outcomes, incorporating the likelihood of confirming, rejecting, or revising particular causal transitions. Experimental cost, feasibility, safety, and the potential importance of each transition could also be considered. Importantly, an informative negative result may advance mechanistic understanding even if it does not reduce the original MGI, because it may eliminate an incorrect causal link or require reconstruction of the proposed mechanism.

9.2 Missing intermediate mechanisms within apparently unsupported causal links

A further extension arises from recognizing that a causal link assigned an MGI of 1.0 may not simply lack experimental evidence. It may have been formulated at an insufficient level of mechanistic resolution. Two biological events may appear causally disconnected because the intermediate processes linking them have not been identified, rather than because no causal relationship exists.

Consider a hypothetical transition: A → D (MGI = 1.0). The absence of direct evidence connecting A and D may prompt investigators to conclude that the relationship is unsupported. However, further investigation might identify a candidate pathway: A → B → C → D. Some intermediate transitions may already have substantial experimental support, while only one remains uncertain. For example, if the respective gap scores were 0, 0.5, and 0, the expanded pathway would have a mean MGI of: $MGI = (0 + 0.5 + 0)/3 = 0.167$

This illustrative result does not demonstrate that

A causes D, nor is the expanded score directly comparable with the original single-link score. The causal architecture and denominator have changed. Its scientific significance is instead that an unexplained relationship has been transformed into a specific, experimentally testable uncertainty: the B → C transition.

This distinction is especially relevant to the present investigation. The environmental noise → human auditory-cortex GABA relationship could conceal intermediate processes involving altered auditory neural activity, activity-dependent inhibitory regulation, and changes in GABA synthesis, metabolism, or cellular distribution. The reduced GABA → poorer neural distinctiveness relationship could involve changes in inhibitory signaling, excitation–inhibition balance, neuronal tuning, and response selectivity. Likewise, the environmental noise → cochlear synaptopathy relationship may involve cochlear metabolic stress, glutamate-mediated excitotoxicity, and synaptic-terminal injury, mechanisms investigated particularly in experimental animal systems.

These examples do not establish that the proposed intermediates operate under ordinary environmental-noise exposure in humans. They demonstrate how broad, unsupported transitions can be decomposed into biologically plausible mechanisms whose individual components may be independently evaluated.

The same approach applies to the remaining links. The reduced GABA → poorer speech-in-noise relationship may involve intermediate changes in neural selectivity and segregation of competing auditory streams. The poor encoding → poorer speech-in-noise relationship may involve degraded temporal or spectral representations and increased perceptual uncertainty. The environmental noise → altered pediatric neural encoding relationship may involve experience-dependent plasticity and changes in neural response synchronization. Finally, the environmental noise → altered auditory developmental trajectory relationship may involve altered auditory learning opportunities, experience-dependent circuit refinement, and persistent developmental adaptation.

The MGI could therefore be extended to treat high-gap links not only as targets for direct experimental testing, but also as candidate locations for previously unrecognized intermediate mechanisms. This would introduce a systematic process of mechanistic decomposition: identify an unsupported transition, investigate plausible intermediates, construct alternative pathways, score their individual transitions, and determine which experiments would distinguish among them.

Crucially, the objective would not be to obtain a numerically lower MGI by introducing additional links. The objective would be to improve the biological specificity and falsifiability of the proposed mechanism. Original and expanded pathways must be reported separately, with their respective edge definitions and scores preserved.

Table 5 provides a specific application of this proposed approach to bottleneck 7. The original environmental noise → altered pediatric FFR

relationship, assigned an MGI of 1.0, is decomposed into environmental noise → increased attentional demands → altered FFR. Published evidence supports both component relationships, although the complete mediated pathway has not been demonstrated in children. The reconstructed pathway therefore has a provisional mean MGI of 0.50 and, more importantly, a maximum component score of 0.50. This example illustrates the distinction between merely increasing the number of causal links and identifying previously overlooked intermediate processes for which independent evidence already exists. The reduction in the maximum component gap indicates that neither reconstructed transition is entirely unsupported, while the original bottleneck score remains unchanged in the primary analysis. Thus, Table 5 demonstrates how mechanistic decomposition can transform an apparently unsupported relationship into a more specific, evidence-informed, and experimentally testable causal hypothesis without claiming that the complete mechanism has been established.

9.3 Long-range causation and apparently weak associations

The identification of intermediate mechanisms has a further implication: biological variables that initially appear unrelated, or only weakly associated, may participate in a longer causal pathway.

In a simplified linear mediation model: A → B → C → D → E. If the respective causal coefficients are a, b, c, and d, the total mediated effect is: $\tau = a \times b \times c \times d$. For illustration, if each standardized transition has a coefficient of 0.5: $\tau = 0.5^4 = 0.0625$. Thus, a sequence containing moderately strong individual causal transitions can produce a relatively small distal effect. Such an effect may be difficult to distinguish statistically from background variability, particularly when measurements are imprecise, sample sizes are limited, or relevant biological processes operate over different timescales.

This observation raises the possibility that some weak or statistically nonsignificant endpoint relationships may reflect long-range causal mechanisms whose intermediate processes have not been identified or measured. However, this interpretation is not automatic. A nonsignificant association may also reflect the absence of a causal effect, inadequate statistical power, confounding, opposing pathways, nonlinear relationships, or measurement error. Moreover, statistical significance of an endpoint association depends on the complete causal structure and study design, not simply on the number of intermediate transitions.

In the present investigation, environmental noise and altered auditory development may be separated by several biological processes, including peripheral auditory changes, central inhibitory adaptation, altered neural encoding, impaired access to speech information, and experience-dependent auditory learning. An endpoint-focused investigation may fail to distinguish among these possibilities. Identification and measurement of intermediate mechanisms could reveal whether a proposed long-range relationship is mediated through a continuous causal sequence, operates through alternative pathways, or is not causal.

This approach could also distinguish biological injury from other explanations of noise-associated developmental outcomes. For example, environmental noise may impair classroom learning through speech masking and reduced intelligibility without producing cochlear synaptopathy or lasting changes in auditory GABA. Stress, sleep disruption, and attention may represent additional pathways. These competing mechanisms should be constructed and evaluated independently rather than incorporated into a single assumed sequence.

The MGI could thereby support the investigation of apparently disconnected biological observations by converting hypothesized long-range relationships into explicit, testable intermediate transitions. Its contribution would be to organize causal discovery and experimental testing, not to infer causation from an association or from a favorable index score alone.

9.4 Mechanistic resolution as a complementary dimension

These considerations suggest that evidentiary completeness and mechanistic resolution are distinct properties of a causal hypothesis.

The present MGI measures the extent to which the specified causal transitions are supported by evidence. However, a pathway may contain broad transitions that conceal several unidentified biological processes. Conversely, a highly detailed mechanistic pathway may contain numerous well-defined but experimentally unverified transitions.

A future extension could therefore distinguish two dimensions: Mechanistic assessment = (G, R), where G represents the evidentiary gaps within the specified causal architecture, and R represents its mechanistic resolution: the extent to which relevant intermediate biological processes have been identified and distinguished.

A low evidentiary gap does not necessarily imply high mechanistic resolution. For example, a controlled intervention may establish that changing environmental noise alters a particular auditory outcome without identifying the intervening molecular or neural processes. Conversely, a detailed hypothesis connecting noise exposure to changes in inhibitory regulation and auditory encoding may have high mechanistic resolution but substantial evidentiary gaps.

Mechanistic resolution should not initially be combined with the MGI through arbitrary numerical weighting. Its operational definition, reproducibility, and relationship to experimental informativeness would require independent methodological development. Nevertheless, distinguishing these dimensions could prevent a broadly defined causal transition from being mistaken for a fully elucidated biological mechanism.

9.5 Longitudinal refinement, external calibration, and validation

The MGI should be regarded as an evolving framework rather than a fixed numerical description of a biological mechanism. As new experiments establish, contradict, or refine individual causal transitions, the evidentiary

state of the mechanism can be reassessed.

For a fixed causal architecture, the time-dependent index MGI(t) could describe changes in evidentiary completeness, while: ΔMGI = MGI(before) − MGI(after), could quantify changes associated with new research.

However, discovery of previously unidentified intermediate mechanisms changes the structure of the causal hypothesis itself. Such changes require a separately versioned causal model rather than direct numerical comparison with the original MGI. An increase in the number of unresolved transitions following mechanistic decomposition may represent scientific progress through improved understanding, not deterioration of the evidence base.

External validation should investigate whether MGI-guided prioritization identifies more informative experiments than conventional expert judgment. One approach would reconstruct the evidence available at an earlier date, specify candidate mechanisms and scoring rules without reference to later discoveries, and determine which experiments the MGI would have prioritized. These predictions could then be compared with subsequent experimental findings to assess whether the framework successfully identified consequential causal bottlenecks.

A more demanding test would examine whether high-gap transitions systematically conceal discoverable intermediate mechanisms and whether MGI-guided decomposition produces experimentally useful hypotheses. Independent investigators could construct alternative pathways from the same evidence, score their transitions, and compare the resulting experimental priorities. Such investigations would help establish the reproducibility of pathway construction and the incremental scientific value of the framework.

Calibration against experimentally mature mechanisms would also be valuable. Biological or clinical efficacy may be established despite incomplete documentation of every intermediate causal transition, because the demonstrated therapeutic benefits of interventions that cure disease, alleviate symptoms, or improve quality of life may take precedence over the exhaustive elucidation of the causal mechanisms linking a drug's molecular or physiological actions to its observed clinical efficacy. Consequently, MGI = 0 should represent complete evidentiary support for the specified pathway rather than a prerequisite for demonstrating a functional or therapeutic outcome.

Future validation should also address sensitivity to causal-edge definitions, alternative pathway decompositions, parallel mechanisms, feedback processes, and unequal biological importance of individual transitions. These limitations are especially relevant when extending the framework from scoring prespecified pathways to proposing new causal architectures.

10. Conclusion

This review demonstrates that substantial experimental and observational evidence concerning environmental noise, GABAergic inhibition, cochlear synaptopathy, neural encoding, and auditory development does not

necessarily establish a continuous causal mechanism connecting these phenomena. Applying the Mechanistic Gap Index (MGI) to eight proposed relationships yielded a mean score of 0.75 and a maximum score of 1.0, identifying four critical bottlenecks involving noise-induced changes in human auditory-cortex GABA, cochlear synaptopathy, pediatric frequency-following responses (FFRs), and auditory developmental trajectories. The auditory-training benchmark yielded a lower mean MGI of 0.33, illustrating the framework's capacity to distinguish pathways with different degrees of evidentiary completeness, although this comparison does not constitute formal validation. The central finding is therefore not that environmental noise lacks biological consequences, but that evidence supporting individual observations must be distinguished from evidence establishing the causal transitions connecting them.

The manuscript's more novel contribution is to demonstrate how the MGI can move beyond identifying missing evidence toward reconstructing the mechanisms underlying apparently unsupported causal relationships. Table 5 provides a specific example. The original environmental noise → altered pediatric FFR relationship, assigned an MGI of 1.0, was decomposed into environmental noise → increased attentional demands → altered FFR. Independent published evidence supports both component relationships, producing a provisional expanded mean MGI of 0.50 and, critically, a maximum component score of 0.50. This does not establish that attentional load mediates noise-induced FFR alterations in children, nor does it justify changing the original score in the principal analysis. Rather, it demonstrates that an apparently unsupported causal transition may conceal an intermediate mechanism for which relevant experimental evidence already exists. The resulting hypothesis could be tested by independently manipulating background noise and attentional demands while measuring pediatric FFRs. Such an experiment could establish whether attentional demands contribute to acute noise-related FFR modulation, while appropriate mediation analysis would be required to evaluate the proposed causal pathway. Determining whether these effects persist as developmental changes would require longitudinal measurements.

More generally, the MGI offers a proposed framework for transforming fragmented scientific observations into explicit, experimentally falsifiable causal architectures. Its potential contribution extends beyond quantifying evidentiary gaps to prioritizing experiments, identifying overlooked intermediate processes, investigating long-range causal relationships between apparently disconnected observations, and progressively refining mechanistic explanations as new evidence becomes available. In particular, weak associations between distant biological endpoints need not preclude meaningful intermediate causal relationships, just as strong endpoint associations do not establish the mechanisms producing them. Distinguishing evidentiary completeness from mechanistic resolution could therefore provide a more informative assessment of scientific understanding than either endpoint statistics or mechanistic plausibility alone. Although the

MGI requires independent validation, its broader proposed significance lies in changing the question from whether two phenomena are associated to which sequence of causal processes connects them, which transitions have been established, which remain unsupported, and which experiments can resolve the uncertainty. In this sense, the MGI is proposed not merely as an index of missing evidence, but as a systematic approach to mechanistic reconstruction, experimental prioritization, and causal discovery across scientific disciplines.

Acknowledgement

ANARA AI was used during the initial search to identify potentially relevant publications. OpenAI ChatGPT with web search was used during revision to identify additional candidate publications and to assist with language editing, organization, evidence-matrix formatting, and citation conversion. Google Scholar, PubMed, publisher pages, and original full texts were used to verify citations and numerical details. AI did not generate participant data or reanalyze the original studies. The MGI values are review-level arithmetic summaries, not new statistical analyses of participant data. The author reviewed the manuscript and accepts responsibility for every claim, score, calculation, and citation.

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