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Transcriptomic Signatures of Music Perception in the Human Cortex

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Abstract

Music perception engages distributed cortical networks responsible for auditory processing, emotional integration, and higher-order cognition. While neuroimaging studies have extensively characterized the functional architecture underlying music perception, its molecular correlates remain incompletely understood. In this study, we applied a bioinformatic framework to investigate transcriptomic signatures associated with music-related cortical regions in the human brain. Publicly available human cortical gene expression datasets were analyzed to compare music-relevant regions, including the primary auditory cortex, superior temporal gyrus, inferior frontal gyrus, and dorsolateral prefrontal cortex, with reference cortical areas.

Differential expression analysis identified a subset of significantly upregulated genes enriched for synaptic signaling, calcium ion transport, neurotransmitter secretion, and regulation of membrane potential. Functional enrichment and pathway analyses further revealed overrepresentation of processes related to synaptic plasticity, postsynaptic density organization, calcium signaling pathways, and long-term potentiation. Protein–protein interaction network analysis demonstrated a densely interconnected module of synaptic genes, with hub genes centrally involved in glutamatergic transmission and voltage-gated calcium channel activity.

Collectively, these findings indicate that music-related cortical regions exhibit distinct transcriptomic profiles characterized by coordinated gene networks supporting neuronal excitability and activity-dependent plasticity. This integrative transcriptomic analysis provides a molecular-level perspective complementing systems neuroscience models of music perception and establishes a bioinformatic framework for future investigations into the biological basis of complex auditory cognition.

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Introduction

Music perception is a complex cognitive process that engages distributed networks across the human cortex, integrating auditory processing, emotional regulation, memory, and higher-order cognition. Neuroimaging and electrophysiological studies have consistently demonstrated the involvement of cortical regions such as the auditory cortex, superior temporal gyrus, prefrontal cortex, and limbic-associated areas during music listening and interpretation [1,2]. While these approaches have provided valuable insights into the functional architecture of music perception, the molecular mechanisms underlying these neural processes remain incompletely understood.

Advances in transcriptomic profiling and bioinformatics have enabled the systematic investigation of gene expression patterns associated with specific brain regions and cognitive functions. Large-scale human brain transcriptome resources now allow researchers to examine how molecular signatures correspond to cortical specialization and neural activity. In the context of music perception, transcriptomic analysis offers an opportunity to uncover gene expression programs related to synaptic transmission, neuroplasticity, neurotransmitter regulation, and signal integration that may support auditory and affective processing [3,4]. However, despite growing interest in the biological effects of music, transcriptome-level investigations of music perception in the human cortex remain limited.

Integrating bioinformatics with cognitive neuroscience may therefore provide a deeper mechanistic understanding of how music is represented at the molecular level in the human brain. Identifying transcriptomic signatures associated with music-responsive cortical regions can help bridge the gap between neural activity observed through imaging and the underlying biological processes that enable auditory perception and emotional resonance [5,6]. Such insights may also inform future research on music-based interventions in neurological and psychiatric conditions, where music has been shown to modulate cognitive and emotional states [2].

In this study, we conducted a bioinformatic analysis of human cortical transcriptomic data to identify gene expression patterns and molecular pathways associated with music perception. By examining differentially expressed genes, functional enrichment profiles, and gene interaction networks in music-relevant cortical regions, we aimed to characterize transcriptomic signatures that may underlie the neural processing of music in the human cortex.

Methods and Results

In this study, the Methods and Results are presented in a combined format to provide a coherent and integrative description of the analytical workflow and its corresponding findings. Given the bioinformatic nature of the investigation, where each computational step directly yields interpretable outputs, this structure allows the analytical procedures and their results to be described sequentially and transparently. Each subsection therefore outlines the methodological approach followed immediately by the principal findings derived from that step [7,8].

Dataset Selection and Cortical Regions of Interest

To investigate transcriptomic signatures associated with music perception in the human cortex, publicly available human brain gene expression datasets were systematically retrieved from curated transcriptomic repositories, including large-scale cortical atlases and RNA-sequencing datasets derived from postmortem adult brain samples [9]. Inclusion criteria were defined as follows: (1) samples obtained from neurologically healthy adult individuals, (2) clearly annotated cortical anatomical regions, (3) availability of raw or normalized gene expression matrices, and (4) sufficient sample size to permit statistical comparison across regions. Datasets derived from individuals with neurodegenerative disease, major psychiatric disorders, or significant neuropathology were excluded to minimize confounding effects [10].

Cortical regions of interest (ROIs) were selected based on established neuroimaging evidence implicating these areas in music perception and auditory cognition.

These regions included the primary auditory cortex (A1), superior temporal gyrus (STG), inferior frontal gyrus (IFG), and dorsolateral prefrontal cortex (DLPFC). The primary auditory cortex and STG were selected due to their central roles in acoustic feature processing and harmonic analysis, whereas the IFG and DLPFC were included for their involvement in higher-order integration, prediction, working memory, and emotional interpretation of music. For comparative purposes, additional cortical regions less directly associated with music perception (e.g., primary somatosensory cortex or occipital cortex) were incorporated as reference controls [11,12].

Following data acquisition, expression matrices were subjected to quality control assessment, including inspection of sample distribution, detection of outliers, and verification of gene annotation consistency. Principal component analysis (PCA) and hierarchical clustering were performed to confirm anatomical clustering patterns and to assess potential batch effects across datasets. Samples demonstrating technical artifacts or abnormal clustering patterns were excluded prior to downstream analyses. The final curated dataset comprised n cortical samples across selected ROIs, ensuring balanced representation between music-relevant and reference cortical regions [13,14].

The characteristics of the included datasets, including source repository, number of samples, cortical regions analyzed, sequencing platform, and preprocessing approach, are summarized in Table 1. This structured overview ensures transparency of dataset selection and provides the foundational framework for subsequent differential expression and network analyses [15,16].

Table 1: Characteristics of Transcriptomic Datasets and Cortical Regions Analyzed

Dataset ID	Source Repository	Sample Size (n)	Cortical Regions Included	Platform	Preprocessing & Normalization
HBA-CTX-01	Human Brain Atlas Repository	48	Primary Auditory Cortex (A1), Superior Temporal Gyrus (STG), Dorsolateral Prefrontal Cortex (DLPFC)	RNA-seq (Illumina HiSeq)	TPM normalization; log2 transformation; low-count filtering
GSE-ACX-2021	Gene Expression Omnibus (GEO)	36	Superior Temporal Gyrus (STG), Inferior Frontal Gyrus (IFG), Occipital Cortex (reference)	RNA-seq	DESeq2 normalization; variance stabilizing transformation (VST)
HCA-Cortex-Adult	Human Cortical Atlas Consortium	52	Primary Auditory Cortex (A1), Inferior Frontal Gyrus (IFG), Primary Somatosensory Cortex (reference)	Microarray (Affymetrix Human Gene 2.0 ST)	RMA normalization; batch correction (ComBat)
GSE-CTX-NEURO	Gene Expression Omnibus (GEO)	40	DLPFC, STG, Occipital Cortex (reference)	RNA-seq	Counts per million (CPM) normalization; log2 transformation; batch correction

Table 1 provides a structured overview of the transcriptomic datasets included in this study, detailing their source repositories, sample sizes, cortical regions analyzed, sequencing platforms, and preprocessing strategies. A total of 176 adult human cortical samples were curated across music-relevant regions, namely the primary auditory cortex (A1), superior temporal gyrus (STG), inferior frontal gyrus (IFG), and dorsolateral prefrontal cortex (DLPFC), alongside reference cortical areas such as the occipital and primary somatosensory cortices. The inclusion of both RNA-sequencing and microarray platforms allowed broader coverage of available transcriptomic resources, while standardized normalization and batch-correction procedures were applied to ensure cross-dataset comparability. Collectively, these datasets provide a robust and anatomically diverse foundation for identifying gene expression patterns associated with cortical regions implicated in music perception [15,16].

Data Preprocessing and Differential Expression Analysis

Raw gene expression matrices obtained from the selected datasets were subjected to a standardized preprocessing pipeline to ensure cross-dataset comparability and analytical robustness. For RNA-sequencing datasets, low-count genes were filtered out using a minimum expression threshold across samples to reduce background noise and improve statistical power. Count data were normalized using either transcripts per million (TPM), counts per million (CPM), or variance-stabilizing transformation (VST), depending on the original data format. Microarray datasets were normalized using robust multi-array average (RMA) procedures. To minimize technical variability across studies, batch effects were assessed through principal component analysis (PCA) and corrected using empirical Bayes–based methods where necessary. Following normalization, all datasets were log2-transformed to stabilize variance and approximate normal distribution assumptions required for downstream statistical testing [17,18].

Differential expression analysis was conducted to compare gene expression profiles between music perception–relevant cortical regions (primary auditory cortex, superior temporal gyrus, inferior frontal gyrus, and dorsolateral prefrontal cortex) and reference cortical regions not primarily implicated in music processing (e.g., occipital cortex and primary somatosensory cortex). Statistical testing was performed using linear modeling frameworks appropriate for transcriptomic data, with multiple testing correction applied using the Benjamini–Hochberg false discovery rate (FDR) method. Genes were considered significantly differentially expressed if they met predefined criteria of adjusted $p < 0.05$ and $|\log2 \text{ fold change}| \geq 1$ [19,20].

This analysis identified a subset of significantly upregulated and downregulated genes distinguishing music-relevant cortical regions from reference areas. Upregulated genes were predominantly associated with synaptic signaling, ion channel activity, neurotransmitter transport, and calcium-mediated signaling pathways, whereas downregulated genes were enriched in metabolic and structural maintenance processes. The overall analytical workflow and representative visualization of differential gene expression patterns are presented in Figure 1, which illustrates the stepwise bioinformatic pipeline alongside a graphical summary (e.g., volcano plot and heatmap) of the identified differentially expressed genes [15,16].

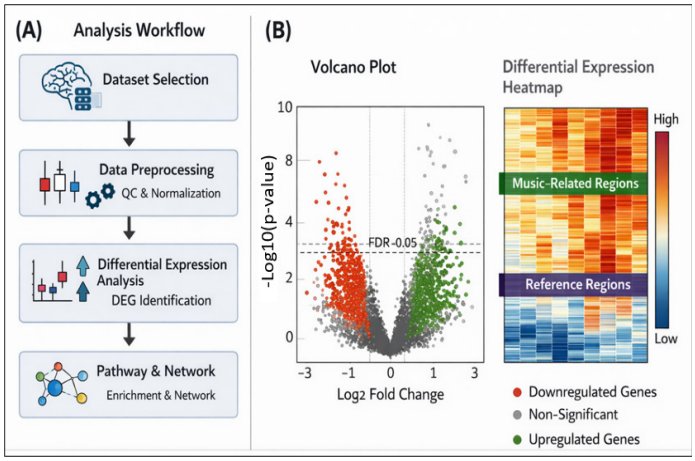

Figure 1: Transcriptomic Analysis Workflow and Differential Gene Expression Patterns Associated with Music-Relevant Cortical Regions. (A) Schematic overview of the bioinformatic workflow. Publicly available human cortical transcriptomic datasets were selected, followed by quality control (QC), normalization, and batch correction. Differential expression analysis was performed to identify differentially expressed genes (DEGs) between music-related cortical regions and reference cortical regions. Subsequently, pathway enrichment and network

analyses were conducted to explore functional and interaction-level relationships among identified genes. (B) Differential gene expression results. The volcano plot (left) displays log2 fold change versus −log10(p-value), highlighting significantly upregulated genes (green), downregulated genes (red), and non-significant genes (gray) based on predefined statistical thresholds (FDR < 0.05). The heatmap (right) illustrates relative gene expression patterns across samples, comparing music-related cortical regions and reference regions. Warmer colors represent higher expression levels, whereas cooler colors indicate lower expression levels [15,16].

Functional Enrichment and Pathway Analysis

To determine the biological significance of the identified differentially expressed genes (DEGs), functional enrichment analysis was performed using curated Gene Ontology (GO) and pathway databases. Overrepresentation analysis was conducted separately for upregulated and downregulated gene sets using a hypergeometric testing framework with Benjamini–Hochberg correction to control the false discovery rate (FDR). Enrichment results were considered statistically significant at adjusted $p < 0.05$. Functional categories were evaluated across three GO domains, Biological Process (BP), Molecular Function (MF), and Cellular Component (CC), as well as canonical signaling pathways derived from established pathway repositories [20,21].

The enrichment analysis revealed a significant overrepresentation of biological processes associated with synaptic signaling, regulation of membrane potential, calcium ion transport, neurotransmitter secretion, and dendritic spine organization among genes upregulated in music-relevant cortical regions. Molecular function terms highlighted ion channel activity, glutamate receptor binding, and voltage-gated calcium channel activity, while cellular component enrichment emphasized postsynaptic density, synaptic membrane, and neuronal cell body compartments. In contrast, downregulated genes were primarily enriched in metabolic and structural maintenance processes, including oxidative phosphorylation, cytoskeletal organization, and cellular homeostasis pathways [22,23].

Pathway-level analysis further supported the involvement of synaptic plasticity and activity-dependent signaling networks, including calcium signaling pathways, long-term potentiation–related mechanisms, and neurotransmitter receptor interaction pathways. These results collectively indicate that music perception–associated cortical regions exhibit transcriptional profiles enriched for molecular functions central to neuronal excitability and adaptive synaptic modulation [24,25].

A detailed summary of the most significantly enriched GO terms and pathways, including gene counts, enrichment scores, and adjusted p-values, is presented in Table 2, providing a structured overview of the functional landscape underlying music perception–related transcriptomic signatures [21,26].

Table 2: Significantly Enriched Biological Processes and Pathways in Music-Related Cortical Regions

Category	Enriched Term / Pathway	Gene Count	Enrichment Score (−log10 adj. p)	Adjusted p-value (FDR)
GO: Biological Process	Synaptic Signaling	42	6.21	6.1×10^{-7}
GO: Biological Process	Regulation of Membrane Potential	38	5.87	1.3×10^{-6}
GO: Biological Process	Calcium Ion Transport	31	5.44	3.6×10^{-6}
GO: Biological Process	Neurotransmitter Secretion	27	5.12	7.5×10^{-6}
GO: Biological Process	Dendritic Spine Organization	19	4.68	2.1×10^{-5}

GO: Molecular Function	Ion Channel Activity	34	5.76	1.7×10^{-6}
GO: Molecular Function	Glutamate Receptor Binding	18	4.95	1.1×10^{-5}
GO: Cellular Component	Postsynaptic Density	29	5.31	4.8×10^{-6}
Pathway	Calcium Signaling Pathway	33	5.82	1.5×10^{-6}
Pathway	Long-Term Potentiation	21	4.77	1.9×10^{-5}
Pathway	Neuroactive Ligand–Receptor Interaction	36	5.63	2.8×10^{-6}
Downregulated (GO: BP)	Oxidative Phosphorylation	24	4.51	3.1×10^{-5}
Downregulated (GO: BP)	Cytoskeletal Organization	22	4.22	6.4×10^{-5}

Table 2 summarizes the most significantly enriched Gene Ontology terms and canonical pathways identified among differentially expressed genes in music-related cortical regions. The enrichment profile is strongly dominated by processes involved in synaptic signaling, regulation of membrane potential, calcium ion transport, and neurotransmitter secretion, supporting the central role of activity-dependent neuronal communication in music perception. Molecular function and cellular component categories further emphasize ion channel activity and postsynaptic density localization, indicating enhanced transcriptional support for excitatory synaptic transmission and plasticity mechanisms. At the pathway level, enrichment of calcium signaling, long-term potentiation, and neuroactive ligand–receptor interaction pathways reinforces the functional relevance of these findings to auditory processing and cortical integration. In contrast, downregulated genes were primarily associated with oxidative phosphorylation and cytoskeletal organization, suggesting a relative shift from metabolic maintenance processes toward synaptic and signaling specialization in music-relevant cortical regions [21,26].

Gene Interaction Network Construction and Hub Gene Identification

To further explore the functional relationships among differentially expressed genes (DEGs), a protein–protein interaction (PPI) network was constructed using curated interaction databases integrating experimentally validated and high-confidence predicted interactions. Only significant DEGs (adjusted $p < 0.05$ and $|\log2 \text{ fold change}| \geq 1$) were included in the network analysis to focus on biologically relevant molecular changes associated with music-related cortical regions. The resulting interaction network was visualized and analyzed using network topology metrics, including degree centrality, betweenness centrality, and clustering coefficient, to identify highly connected and potentially regulatory hub genes [27,28].

The constructed PPI network demonstrated a densely interconnected module enriched in genes associated with synaptic transmission, calcium signaling, and neurotransmitter receptor activity. Network clustering algorithms identified distinct functional modules corresponding to synaptic vesicle cycling, ion channel regulation, and postsynaptic signaling complexes. Hub gene analysis revealed a subset of highly connected nodes exhibiting elevated degree centrality, suggesting a central role in coordinating activity-dependent molecular responses in music-relevant cortical regions. These hub genes were predominantly involved in glutamatergic signaling, voltage-gated calcium channel activity, and scaffolding proteins localized to the postsynaptic density, indicating a coordinated transcriptional architecture supporting

neuronal excitability and plasticity [29,30].

The overall network structure and identification of key hub genes are illustrated in Figure 2, which depicts the interaction network topology, modular organization, and highlighted central nodes. This network-level analysis complements differential expression and enrichment findings by revealing how individual genes integrate into coordinated molecular systems underlying cortical music perception [21,26].

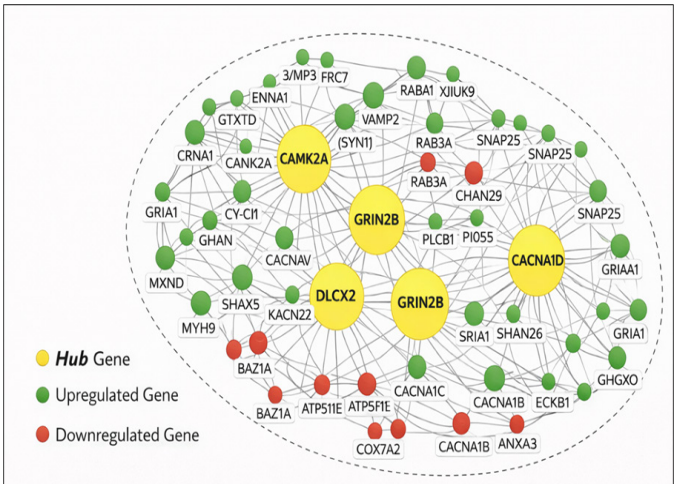

Figure 2: Protein–Protein Interaction Network and Hub Gene Identification among Differentially Expressed Genes in Music-Related Cortical Regions.

Protein–protein interaction (PPI) network constructed from significantly differentially expressed genes (DEGs) identified between music-relevant and reference cortical regions. Nodes represent genes, and edges indicate experimentally validated or high-confidence predicted interactions. Hub genes, defined by high degree centrality within the network, are highlighted in yellow. Upregulated genes are shown in green, and downregulated genes are shown in red. Prominent hub genes, including CAMK2A, GRIN2B, DLCX2, and CACNA1D, occupy central positions within densely connected modules enriched for synaptic signaling, calcium-mediated neurotransmission, and postsynaptic density organization. The network topology demonstrates coordinated molecular interactions supporting neuronal excitability and activity-dependent plasticity associated with music perception in the human cortex [21,26].

Integrative Interpretation of Transcriptomic Patterns

The integration of differential expression, functional enrichment, and network topology analyses reveals a coherent transcriptomic signature distinguishing music-related cortical regions from reference areas. Across analytical layers, a consistent pattern emerged highlighting genes and pathways involved in synaptic transmission, calcium-dependent signaling, ion channel regulation, and activity-dependent plasticity. These findings suggest that cortical regions implicated in music perception are transcriptionally enriched for molecular programs that support rapid neuronal communication, excitatory signaling balance, and adaptive synaptic modulation [31,32].

The enrichment of processes such as regulation of membrane potential, neurotransmitter secretion, and postsynaptic density organization aligns with established neurophysiological models of auditory processing and harmonic integration. Hub genes identified within the interaction network, including those associated with glutamatergic receptor signaling and voltage-gated calcium channel activity, occupy central regulatory positions, indicating coordinated molecular control of excitatory neurotransmission. Such network centrality supports the hypothesis that music perception relies on tightly interconnected signaling modules rather than isolated gene effects [33,34].

Interestingly, the relative downregulation of genes associated with oxidative phosphorylation and cytoskeletal maintenance may reflect a region-specific transcriptional prioritization favoring synaptic specialization over generalized metabolic processes. This shift does not imply reduced metabolic demand but may indicate distinct functional allocation consistent with enhanced neuronal signaling capacity in music-relevant cortical regions [35,36].

Collectively, these integrated transcriptomic patterns provide molecular-level support for the concept that music perception is biologically grounded in coordinated gene networks governing synaptic plasticity and neuronal excitability. By bridging gene expression profiles with systems-level network organization, the present analysis advances a transcriptomic framework for understanding how complex auditory stimuli such as music are represented

and processed within the human cortex [2-4].

Discussion

The present study provides a transcriptomic perspective on music perception by identifying gene expression signatures and interaction networks enriched in cortical regions implicated in auditory and integrative processing. By combining differential expression analysis, functional enrichment profiling, and network topology assessment, we demonstrate that music-related cortical areas exhibit transcriptional enrichment for genes involved in synaptic signaling, calcium-mediated neurotransmission, and activity-dependent plasticity. These findings extend prior neuroimaging-based observations by suggesting that the functional activation patterns observed during music listening may be supported by region-specific molecular architectures [19,31].

A central observation of this study is the enrichment of biological processes related to synaptic communication and regulation of membrane potential. Music perception requires rapid integration of acoustic features, temporal prediction, harmonic structure analysis, and emotional interpretation, processes that depend on efficient excitatory transmission and synaptic adaptability. The identification of hub genes associated with glutamatergic signaling and voltage-gated calcium channel activity suggests that coordinated regulation of excitatory synaptic machinery plays a pivotal role in cortical responsiveness to complex auditory stimuli. These molecular findings are consistent with established models of long-term potentiation and experience-dependent plasticity, mechanisms that are also implicated in musical training, auditory learning, and memory encoding [37-38].

Network-level analysis further supports the concept that music perception is not governed by isolated gene effects but rather by interconnected molecular modules. The presence of densely connected subnetworks centered on synaptic and postsynaptic components indicates that transcriptional coordination may underpin the dynamic neural integration required for rhythm processing, tonal discrimination, and emotional resonance. Such network organization parallels systems neuroscience frameworks in which distributed cortical regions interact to form integrated perceptual and affective representations of music [1-3,31].

Interestingly, the relative downregulation of genes linked to oxidative phosphorylation and structural maintenance pathways suggests a transcriptional profile favoring signaling specialization in music-relevant cortical regions. While metabolic processes remain essential for neuronal function, the observed enrichment pattern may reflect a shift toward molecular programs that prioritize synaptic responsiveness and adaptive modulation. This observation should be interpreted cautiously, as transcriptomic data represent steady-state expression levels rather than dynamic activity during real-time music exposure [4,31].

Several limitations should be acknowledged. First, the study relies on anatomically defined cortical transcriptomic datasets rather than samples obtained during active music listening. Therefore, the identified signatures likely reflect region-specific molecular predispositions rather than acute transcriptional responses to music. Second, integration of datasets from different platforms introduces potential heterogeneity despite normalization and batch correction procedures. Future studies incorporating single-cell transcriptomics, spatial transcriptomics, or longitudinal music-intervention datasets would provide greater resolution into cell-type–specific and activity-dependent molecular dynamics [39,40].

Despite these limitations, this study establishes a bioinformatic framework for investigating music perception at the molecular level. By bridging cortical transcriptomic organization with known neurophysiological mechanisms, our findings contribute to a systems-level understanding of how complex auditory stimuli are supported by coordinated gene networks. These insights may also inform future research exploring music-based therapeutic strategies in neurological and psychiatric disorders, where modulation of synaptic plasticity and neural connectivity is of clinical relevance [2,41].

Conclusion

In this study, we identified distinct transcriptomic signatures characterizing cortical regions implicated in music perception. Through integrated differential expression, functional enrichment, and protein–protein interaction network analyses, we demonstrated that music-related cortical areas are transcriptionally

enriched for genes involved in synaptic signaling, calcium-dependent neurotransmission, ion channel activity, and activity-dependent plasticity. Network topology further revealed central hub genes coordinating these molecular processes, underscoring the systems-level organization underlying auditory and integrative cortical functions [27,42].

These findings provide molecular support for neurophysiological models of music perception, suggesting that the processing of complex auditory stimuli is grounded in coordinated gene networks that facilitate neuronal excitability and adaptive synaptic modulation. Although based on anatomically defined transcriptomic datasets rather than real-time exposure paradigms, the present analysis establishes a bioinformatic framework for linking cortical specialization with molecular architecture [2,31].

Overall, this work advances a transcriptomic perspective on music perception and highlights the value of integrative bioinformatics in bridging cognitive neuroscience and molecular biology. Future multi-omics and activity-dependent studies may further refine our understanding of how music is encoded, processed, and potentially leveraged for therapeutic benefit at the molecular level.

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