Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

ATTENTION-BASED MODELS FOR BLOOD–BRAIN BARRIER PERMEABILITY PREDICTION USING TRANSPORTER AND CNS PROPERTY FEATURES

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ARTICLE INFO

Received:
02 December 2024
Received in revised form:
19 March 2025
Accepted:
23 March 2025
Available online:
28 April 2025

Keywords: Blood–brain barrier, Graph attention network, P-glycoprotein, CNS drug discovery, logBB, Molecular descriptors

ABSTRACT

Achieving adequate brain exposure remains a central challenge in central nervous system drug discovery. Passive permeability descriptors alone cannot capture the dominant influence of active efflux transporters such as P-glycoprotein on net brain penetration. Existing computational models for blood–brain barrier permeability often emphasize structural or physicochemical correlates without explicitly representing transporter liability. As a result, they may predict whether a compound is likely to penetrate the brain but provide limited mechanistic guidance for medicinal chemistry decisions. This manuscript proposes an attention-based deep learning framework that combines molecular graph representations with predicted transporter liability and CNS-specific molecular descriptors. The goal is to support BBB permeability prediction while highlighting molecular features that could drive poor brain exposure. A graph attention network is used to encode molecular structure, while additional input channels represent P-glycoprotein substrate likelihood and CNS multiparameter optimization descriptors. A molecular-level attention mechanism then weights atom-level and auxiliary feature contributions before a conceptual logBB prediction is generated. Conceptually, the proposed model would be expected to distinguish CNS-penetrant from poorly penetrant compounds by combining passive permeability, transporter liability, and structural context. Its attention maps could identify substructures associated with efflux recognition or favorable brain exposure within chemically related series. This transporter-aware attention framework could support early CNS lead prioritization, guide structural modifications intended to reduce efflux liability, and reduce reliance on late-stage in vivo brain exposure testing. Its value would depend on rigorous validation, transparent feature handling, and prospective use in medicinal chemistry workflows.

To Cite This Article: Amrani FZ, Benali Y. Attention-Based Models for Blood–Brain Barrier Permeability Prediction Using Transporter and CNS Property Features. Pharmacophore. 2025;16(2):12-21. https://doi.org/10.51847/8RCghC7ekQ

Introduction

The blood–brain barrier presents a distinctive obstacle in CNS drug development because molecular potency against a neural target does not guarantee adequate brain exposure. Machine-learning studies of BBB permeability have shown that compounds with similar passive physicochemical properties may still differ in predicted brain penetration when broader molecular representations are considered [1]. Deep-learning approaches have further emphasized that BBB behavior is not reducible to a single descriptor because molecular topology, polarity, and transport-related liabilities jointly shape CNS exposure [2]. Transporter-focused modeling is especially important because P-glycoprotein-mediated efflux can prevent otherwise promising compounds from accumulating in the brain [3].

Traditional computational BBB models have often been framed as QSAR or logBB regression systems, where descriptors and fingerprints are mapped to continuous permeability estimates. Such models can be useful for screening, as demonstrated by machine-learning and resampling strategies for BBB classification and regression [4], but they generally do not explain which molecular region may be responsible for failure. Descriptor-centered analyses can identify global features associated with BBB entry [5], yet they do not directly reveal whether a basic center, aromatic domain, or polar substituent is linked to transporter recognition. This limitation restricts their medicinal chemistry utility because chemists need actionable structural explanations rather than only a permeability label.

Attention-based deep learning offers a way to connect predictive modeling with molecular interpretability. Graph attention mechanisms have been used to improve molecular representation learning by allowing models to focus on chemically relevant

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atoms and bonds [6], while message-passing architectures have shown that attention and edge information can support property prediction across chemical tasks [7]. Molecular transformers extend this concept by using self-attention to model long-range structural dependencies beyond local graph neighborhoods [8]. In BBB modeling, these architectures can be paired with transporter prediction outputs so that active efflux likelihood becomes an explicit prior rather than an implicit hidden correlate. The central thesis of this MDL article is that BBB permeability prediction should be treated as a multimodal learning problem combining passive CNS property features, molecular graph structure, and transporter likelihood. Benchmark resources for molecular machine learning support this type of feature integration by encouraging consistent evaluation across chemically diverse datasets [9]. BBB-specific models such as LightBBB and LogBB_Pred show how machine learning can be specialized for brain penetration prediction [10, 11], while newer comparative studies indicate that classical learning, graph neural networks, and transformer models should be considered within a unified modeling strategy [12]. A transporter-aware attention model would therefore aim not only to predict logBB but also to indicate which molecular motifs may contribute to predicted efflux liability.

Background

Physiology of the Blood–Brain Barrier and Transporters

The BBB is formed by endothelial tight junctions, supporting cells of the neurovascular unit, and transporter systems that regulate exchange between blood and brain. Passive diffusion is only one component of net exposure, because efflux transporters such as P-glycoprotein and BCRP can actively remove substrates from endothelial cells before they reach brain tissue [3]. Machine-learning studies that treat BBB permeability as a molecular property implicitly capture some of these effects when curated logBB or CNS activity labels are used [1, 13]. However, transporter-specific modeling remains necessary because passive molecular descriptors alone cannot fully represent the biological distinction between membrane crossing and retained brain exposure.

CNS-Relevant Molecular Descriptors and Rules

CNS drug design has long relied on descriptors such as topological polar surface area, hydrogen-bond donor count, lipophilicity, rotatable bonds, and CNS multiparameter optimization concepts to guide passive permeability optimization. Descriptor-based machine-learning analyses have shown that these properties can help separate likely BBB-permeable and non-permeable molecules [5], and CNS-focused ensemble models have used such features to formulate interpretable rules for CNS classification [14]. Nevertheless, compounds that satisfy passive diffusion heuristics can still fail because transporter recognition is not fully captured by global polarity or lipophilicity. This is why a BBB model should treat CNS descriptors as necessary but incomplete signals.

Machine Learning Models for BBB Prediction

BBB prediction has evolved from descriptor-based regression and classification to ensemble learning, graph neural networks, and deep multimodal representations. Recurrent neural networks and deep-learning classifiers have been proposed to learn molecular patterns relevant to BBB penetration from sequence-like encodings [15, 16], while merged molecular representations have been used to combine different structural views of compounds [17]. Relational graph convolutional networks have further shown how graph-based models can encode bond and atom relationships for BBB penetration prediction [18]. Despite this progress, many systems still treat transporter effects as latent correlates rather than explicit input features.

Attention Mechanisms in Molecular Deep Learning

Attention mechanisms are attractive for molecular property prediction because they can assign relative importance to atoms, bonds, or learned molecular tokens. Graph attention networks have demonstrated that attention can improve molecular representation learning for drug discovery tasks [6], and attention-based message-passing networks have incorporated bond context into learned molecular embeddings [7]. Transformer-style models further enable self-attention across molecular representations, supporting the capture of nonlocal relationships that may be important for permeability or transporter recognition [8]. In a BBB setting, attention weights could be projected back to molecular graphs to support chemically interpretable explanations.

Transporter Prediction Models and Their Output as Feature

Transporter prediction models provide a natural auxiliary signal for BBB modeling because they estimate whether a compound is likely to be a substrate or affected by efflux systems. Machine-learning approaches have been applied to P-glycoprotein substrate prediction using molecular dynamics-informed features and learned molecular representations [19]. Ensemble models that predict MDR1 and BCRP efflux activity illustrate how transporter liability can be represented as a computational feature rather than a purely experimental annotation [19]. A downstream BBB attention model could use these predicted transporter probabilities as frozen inputs, allowing the main model to adjust passive permeability estimates according to active efflux risk.

Model Development Overview

High-Level Model Pipeline

The proposed pipeline begins by converting each molecule into a graph whose atoms and bonds are processed by a graph attention encoder. In parallel, a pre-computed P-glycoprotein likelihood score and a CNS descriptor vector are passed through separate embedding layers before being fused with the learned graph representation. This multimodal design follows the broader direction of BBB models that combine multiple molecular representations rather than depending on a single descriptor family [17]. The fused representation then passes to an attention-based readout and regression head that could predict logBB while preserving interpretable feature contributions.

Figure 1 presents the proposed transporter-aware attention architecture for integrating molecular graph structure, P-glycoprotein liability, CNS descriptor features, and interpretable logBB prediction.

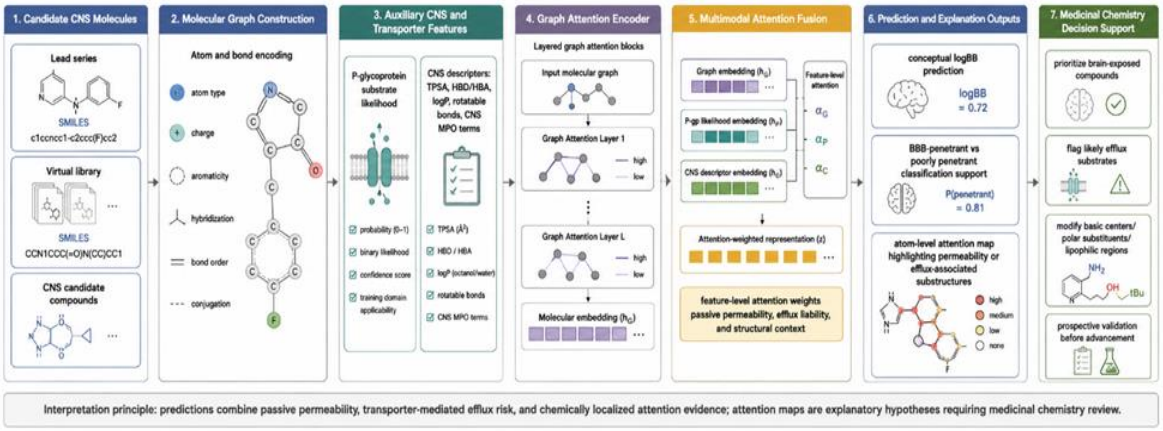

Figure 1. Transporter-Aware Attention Model for Blood–Brain Barrier Permeability Prediction Using Molecular Graphs, P-glycoprotein Liability, and CNS Property Features

Core Input Features

The graph channel would encode atom types, formal charges, hybridization states, aromaticity, and bond-level features such as bond order and conjugation. Auxiliary features would include a scalar P-glycoprotein substrate probability and CNS-relevant descriptors such as polar surface area, hydrogen-bonding capacity, rotatable bonds, and CNS multiparameter optimization terms, reflecting feature families used in CNS classification and BBB prediction studies [14, 20]. Descriptor calculation and molecular standardization should be consistent across training and inference so that the model does not learn artifacts from inconsistent preprocessing. A knowledge-guided molecular pretraining framework could also inform the representation strategy when chemically meaningful priors are available [19].

Design Principles

The model is intended to be multimodal but lightweight, with each feature channel contributing a chemically interpretable signal. Attention is included not merely as an architectural choice but as a mechanism for identifying atom-level and feature-level contributions, consistent with the interpretability motivations of graph attention modeling [6]. Transporter awareness is incorporated from the start by making the P-glycoprotein likelihood a direct input rather than expecting the graph encoder to rediscover efflux liability from limited BBB labels. The training objective would minimize prediction error conceptually while encouraging attention patterns that remain plausible for CNS permeability and transporter recognition.

Data Sources and Feature Engineering

Curation of BBB Permeability Datasets

BBB permeability data would be curated from literature-derived logBB compilations and external benchmark collections, with quality-control steps used to remove ambiguous, duplicated, or poorly annotated measurements. Curated BBB datasets have highlighted the importance of harmonized chemical structures, consistent permeability labels, and descriptor availability for reproducible modeling [21]. ChEMBL, DrugBank-derived CNS labels, and CNS-focused compound collections could supplement continuous logBB data with broader classification signals, provided label definitions are kept distinct. The resulting dataset would support conceptual training and evaluation without assuming that all sources measure identical biological endpoints.

Generation of Molecular Graphs and CNS Descriptors

SMILES strings would be standardized and converted into molecular graphs using cheminformatics toolkits, with atom and bond features generated for graph attention learning. CNS descriptors such as TPSA, hydrogen-bond donor and acceptor counts, rotatable bonds, lipophilicity-related terms, and molar refractivity would be calculated and normalized before model input, following the descriptor-oriented logic used in BBB and CNS machine-learning studies [5, 14]. Molecular representation studies indicate that graph-based and descriptor-based features can encode complementary information rather than serving as

interchangeable inputs [22]. This supports a feature-engineering strategy in which descriptors provide global physicochemical context while the graph encoder captures local substructure.

Table 1 defines the multimodal input architecture through which molecular graph structure, CNS descriptors, transporter liability, and attention-based explanations contribute distinct but complementary evidence for BBB permeability prediction.

Table 1. Multimodal Input Architecture for Transporter-Aware BBB Permeability Prediction

Model input channel	Primary information captured	Feature examples	Expected contribution to BBB prediction	Mechanistic interpretation for CNS drug design	Key preprocessing or validity concern
Molecular graph channel	Local and relational chemical structure	Atom type, formal charge, aromaticity, hybridization, bond order, conjugation, neighborhood topology	Captures substructural motifs that may influence passive permeability, polarity distribution, steric exposure, or transporter recognition	Identifies chemically localized regions that may explain favorable or unfavorable brain exposure	Requires standardized molecular structures, consistent protonation assumptions, and removal of duplicated or ambiguous compounds
Atom-level attention channel	Relative importance of atoms and bonds within the learned molecular representation	Attention coefficients across graph neighborhoods; highlighted atoms or bonds	Provides localized explanatory evidence for predicted logBB or permeability class	Suggests which structural regions may deserve medicinal chemistry review, such as basic centers, polar substituents, or aromatic domains	Attention weights should be interpreted as explanatory hypotheses rather than direct causal proof
P-glycoprotein likelihood channel	Predicted active efflux liability	Frozen P-glycoprotein substrate probability or calibrated transporter-risk score	Adjusts passive-permeability expectations when compounds are likely efflux substrates	Distinguishes compounds that appear passively permeable from those likely to have reduced net brain exposure due to efflux	Depends on calibration, applicability domain, assay consistency, and scaffold coverage of the external transporter model
CNS descriptor channel	Global physicochemical compatibility with CNS exposure	TPSA, hydrogen-bond donor count, hydrogen-bond acceptor count, logP/logD, rotatable bonds, molar refractivity, CNS MPO terms	Provides interpretable passive-permeability context that complements learned graph features	Supports medicinal chemistry reasoning around polarity, lipophilicity, flexibility, and hydrogen-bonding burden	Descriptor calculation must be harmonized across training, validation, and inference datasets
Feature-level attention fusion channel	Relative weighting of graph, transporter, and descriptor evidence	Learned weights for graph embedding, transporter score, and descriptor embedding	Resolves disagreement among passive permeability, structural motifs, and efflux liability	Clarifies whether a prediction is driven mainly by passive property constraints, transporter risk, or structural context	Fusion weights may shift across chemical series and should be evaluated with ablation studies
Prediction output channel	Final permeability estimate and optional classification support	Continuous logBB prediction; optional CNS-penetrant versus poorly penetrant label	Converts multimodal evidence into a decision-support estimate for screening and prioritization	Supports ranking, triage, and lead optimization rather than autonomous compound selection	Requires external validation, benchmark comparison, uncertainty reporting, and prospective testing
Explanation output channel	Human-interpretable evidence supporting the prediction	Attention map, transporter-aware contrast, descriptor contribution profile	Helps users connect model behavior to actionable molecular design hypotheses	Guides structural modification strategies intended to reduce efflux liability or improve brain exposure	Explanations must be reviewed by medicinal chemists and validated against known transporter or BBB evidence

Transporter Likelihood Score from a Pre-Trained Model

A separate P-glycoprotein substrate prediction model would provide a probability-like transporter liability score for each molecule before the BBB model is trained. The transporter predictor could be based on classical ensemble learning or graph-based architectures, reflecting prior work on P-glycoprotein substrate modeling [8] and MDR1 or BCRP efflux prediction [8]. This score would remain frozen during BBB model training so that the main architecture treats transporter liability as an external biological prior rather than a label to be relearned. Where available, BCRP or other transporter likelihoods could be added as additional auxiliary channels in future versions.

Attention-Based Architecture for BBB Permeability

Graph Attention Encoder

The graph attention encoder would apply multiple attention-based message-passing layers to produce atom embeddings that reflect local chemical environments and neighboring bond context. Attention coefficients between adjacent atoms would

indicate which structural interactions are most influential for the hidden representation, following the logic of molecular graph attention mechanisms in drug discovery [6]. Residual connections could help preserve lower-level atom identity while deeper layers encode larger substructures relevant to permeability. Compared with descriptor-only BBB models [1], this graph encoder would allow the model to represent motifs that may not be captured by global physicochemical summaries.

Auxiliary Feature Embedding and Fusion

The P-glycoprotein likelihood and CNS descriptor vector would be passed through a compact feed-forward embedding module before fusion with the pooled graph representation. A learnable global attention mechanism would then weight the relative contribution of graph-derived features, transporter likelihood, and CNS descriptors, extending multimodal BBB prediction ideas that combine multiple molecular representations [17]. This fusion step is important because passive descriptor signals and transporter signals may disagree for the same molecule, especially when a compound appears physicochemically compatible with CNS exposure but has high efflux liability. The model could therefore learn whether predicted brain exposure is driven primarily by permeability, transporter risk, or their interaction.

Regression Head and Loss Function

The fused attention-weighted representation would be passed to a fully connected regression head that outputs a conceptual logBB prediction. The principal loss could be mean-squared error for continuous permeability prediction, while an optional auxiliary classification head could distinguish likely CNS-penetrant from poorly penetrant compounds in a multitask framework, consistent with models that consider both regression and classification endpoints for BBB or CNS prediction [14, 23]. This auxiliary task would be used only as a regularizing signal and would not replace mechanistically interpretable transporter-aware modeling. The resulting architecture should be evaluated against classical models, graph neural networks, and transformer-based approaches to determine whether attention and transporter integration provide meaningful added value [12].

Integrating Transporter Likelihood and CNS Descriptors

Transporter Feature as a Bias Correction

The transporter likelihood channel would allow the model to adjust an initial passive-permeability representation according to predicted efflux liability. This is conceptually aligned with BBB modeling studies that use molecular descriptors and fingerprints to estimate permeability while acknowledging that structure-derived properties alone cannot fully explain brain exposure [1, 24]. A P-glycoprotein score could function as an explicit gate, reducing the influence of otherwise favorable passive-permeability features when efflux risk is high. Such bias correction would make the model more transporter-aware than BBB predictors that rely only on global molecular representation or conventional descriptor fusion [25, 26].

Synergy between CNS Descriptors and Transporter Signal

CNS descriptors and transporter likelihood would be expected to interact rather than contribute independently. For molecules with borderline polarity or hydrogen-bonding profiles, the transporter signal could become decisive because passive permeability alone may not clearly separate CNS-penetrant from non-penetrant compounds [14, 27]. For highly polar molecules, passive permeability restrictions may already dominate the prediction, making transporter likelihood less influential in the final attention-weighted representation. This feature synergy is consistent with the broader observation that modern BBB models benefit from combining physicochemical descriptors, molecular graphs, and learned structural representations [28, 29].

Handling Missing Transporter Predictions

Some compounds may fall outside the applicability domain of a pre-trained P-glycoprotein predictor, particularly when they contain rare scaffolds or unusual ionization patterns. In such cases, the BBB model could use a learned default transporter embedding, an uncertainty gate, or a missingness indicator rather than forcing an unreliable probability into the fusion layer [30]. The output should then be interpreted as lower-confidence because transporter uncertainty would propagate into the permeability estimate. Comparative BBB modeling frameworks support this cautious approach because model reliability depends not only on architecture but also on the quality and domain relevance of the input representation [12, 31].

Model Interpretability and Transporter-Aware Explanations

Attention-Weighted Highlighting of Molecular Substructures

The model's atom-level attention weights could be projected onto the molecular graph to highlight substructures associated with predicted BBB permeability. Graph attention models have shown that learned molecular attention can identify chemically meaningful regions for property prediction [6], while molecular representation analyses indicate that learned features can encode information beyond hand-crafted descriptors [32]. In a transporter-aware BBB model, high-attention atoms near a basic nitrogen, lipophilic aromatic region, or polar substituent could suggest a structural basis for predicted efflux liability. These maps should be treated as explanatory hypotheses that require medicinal chemistry review rather than definitive mechanistic proof.

Transporter-Aware Explanation Contrast

A transporter-aware explanation could compare predictions produced with the P-glycoprotein feature active against predictions generated with that feature neutralized. If the predicted permeability shifts substantially and the attention pattern moves toward motifs associated with efflux, the model would provide a clearer account of transporter-mediated liability. Transporter modeling work on P-glycoprotein substrates supports the plausibility of using predicted transporter class or probability as a mechanistic context feature [22]. Efflux prediction models for MDR1 and BCRP further suggest that transporter-specific auxiliary inputs could help distinguish passive permeability failure from active export risk [19].

Integration into CNS Drug Discovery Workflow

High-Throughput Virtual Screening of CNS Candidates

In a discovery workflow, the proposed model could be deployed as a command-line tool or web service that accepts batches of SMILES strings and returns conceptual logBB predictions, uncertainty indicators, and molecular attention maps. Existing BBB prediction tools such as LightBBB illustrate how machine-learning systems can support rapid compound prioritization during early screening [10]. More recent BBB models based on large language models and machine learning also suggest that flexible molecular encoders may be useful when screening chemically diverse libraries [28]. The proposed model would add value by pairing the prediction with transporter-aware interpretability rather than returning only a permeability estimate.

As shown in **Figure 2**, the proposed model could be integrated into an early CNS drug-discovery workflow as a command-line tool or web service that processes batches of SMILES strings and returns conceptual logBB predictions, uncertainty indicators, and molecular attention maps. This setup would support rapid compound prioritization while also helping medicinal chemists identify structural regions potentially associated with transporter recognition, efflux risk, or reduced brain penetration.

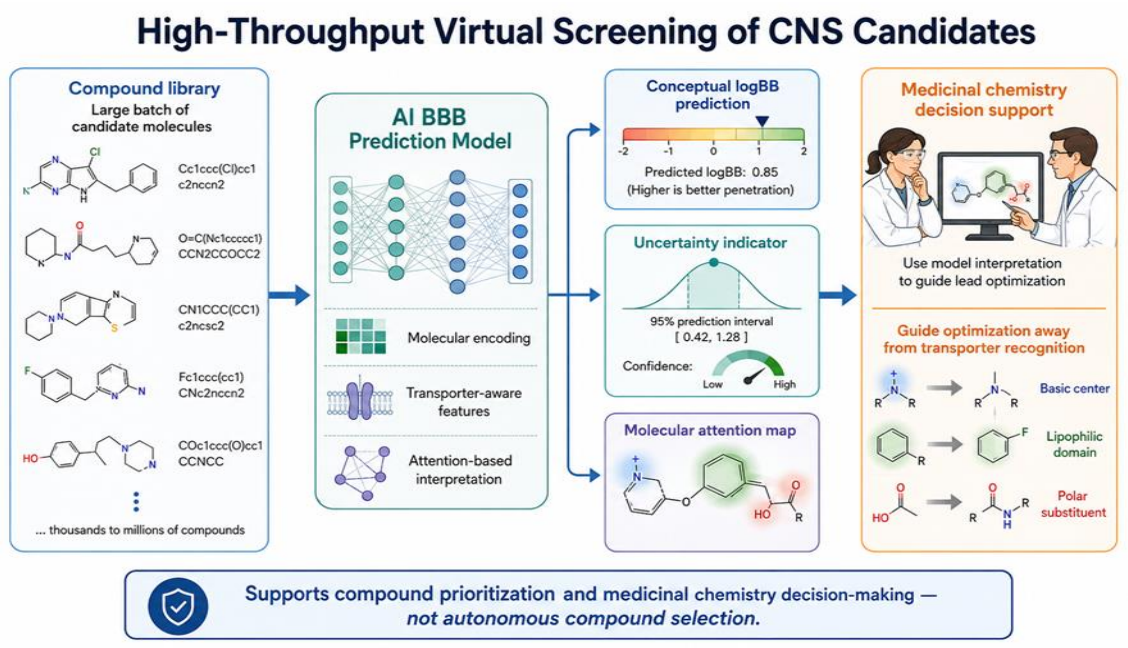

Figure 2. Proposed High-Throughput Workflow for Interpretable CNS Candidate Screening

Guiding Lead Optimization Away from Transporter Recognition

During lead optimization, the attention map could help medicinal chemists identify molecular regions that the model associates with high efflux risk or poor brain penetration. If attention concentrates around a basic center or lipophilic domain while the P-glycoprotein feature suppresses predicted exposure, chemists could consider modifications that alter ionization, steric accessibility, or local polarity. This use case aligns with CNS classification models that emphasize interpretable rules for medicinal chemistry guidance [14] and with BBB modeling approaches that aim to improve chemical decision-making beyond simple classification [33]. The model should therefore be used as a design-support system rather than as an autonomous compound-selection authority.

Evaluation Strategy

Prediction Accuracy

The model should be evaluated conceptually using regression metrics for logBB and classification metrics for CNS-penetrant versus non-penetrant labels, without treating any single benchmark as definitive. Comparisons should include descriptor-based machine learning, random forest or gradient-boosting baselines, standard graph neural networks, and transformer-style molecular encoders, reflecting the range of approaches studied in BBB prediction [4, 12, 18]. DeepBBB-style mixed models

and merged molecular representation methods provide relevant conceptual comparators because they combine learned structural features with broader molecular information [17, 26]. The purpose of evaluation would be to determine whether transporter-aware attention improves decision support, not merely whether it optimizes a benchmark metric.

Ablation Studies to Quantify Feature Contribution

Ablation studies should test whether each model component contributes meaningful information by removing the transporter feature, removing CNS descriptors, replacing attention pooling with simple pooling, or using a graph-only encoder. If removing the transporter score changes predictions most strongly for known or likely efflux substrates, that would support the biological relevance of the auxiliary feature. BBB models based on optimized deep learning and c-RASAR-style reasoning demonstrate that representation choices can materially affect model behavior and should therefore be examined systematically [25, 27]. Ablation should be interpreted cautiously, because removing one feature channel may cause the remaining channels to compensate in chemically indirect ways.

Interpretability Validation

Interpretability should be evaluated by asking whether attention-highlighted atoms and substructures align with known transporter pharmacophores, medicinal chemistry expectations, or independent P-glycoprotein and BCRP annotations. Molecular attention mechanisms can produce useful explanations, but their plausibility must be checked against chemical knowledge and not assumed from the presence of attention weights alone [7, 32]. A validation workflow could compare attention patterns for structurally related compounds with different predicted transporter liabilities and ask whether the explanations support credible lead-optimization hypotheses. Reviews of BBB machine learning for neurological drug development emphasize that such models are most useful when their predictions can be translated into practical design decisions [30].

Table 2 provides an evaluation and deployment framework for determining whether transporter-aware attention improves not only BBB prediction accuracy but also interpretability, applicability-domain control, and medicinal chemistry usefulness.

Table 2. Evaluation and Deployment Framework for Transporter-Aware Attention Models in CNS Lead Optimization

Evaluation domain	Main analytical question	Recommended comparison or test	Evidence of added value	Failure mode detected	Practical implication for medicinal chemistry deployment
Predictive accuracy	Does the model predict logBB or BBB class more accurately than established baselines?	Compare against descriptor-only regression, random forest, gradient boosting, standard GNN, graph transformer, and merged-representation models	Improved regression error, classification discrimination, and calibration across chemically diverse test sets	Apparent performance gain caused by data leakage, duplicate scaffolds, or endpoint inconsistency	Use the model only after scaffold-aware validation and endpoint-specific benchmarking
Transporter feature contribution	Does explicit P-glycoprotein likelihood improve prediction beyond passive descriptors and graph structure?	Ablate the P-glycoprotein score and compare prediction shifts in known or likely efflux substrates	Predictions change most strongly for transporter-relevant compounds rather than uniformly across all molecules	Transporter feature behaves as a nonspecific statistical shortcut instead of a biologically meaningful prior	Treat transporter-aware predictions as credible only when effects align with efflux-relevant chemistry
CNS descriptor contribution	Do global CNS property features provide information not captured by graph embeddings?	Remove CNS descriptors or replace them with shuffled descriptors	Model performance and interpretation degrade for compounds near passive-permeability decision boundaries	Descriptor channel adds little because features are redundant, noisy, or inconsistently calculated	Retain only descriptor families that improve decision interpretability and validation performance
Attention interpretability	Do highlighted atoms or substructures support chemically plausible explanations?	Compare attention maps with known transporter pharmacophores, matched molecular pairs, and medicinal chemistry review	Attention concentrates on plausible regions such as basic centers, polar groups, or lipophilic motifs associated with exposure or efflux	Attention highlights unstable, irrelevant, or non-actionable molecular regions	Use attention maps as design hypotheses, not as stand-alone mechanistic evidence
Transporter-aware contrast	Does neutralizing the transporter feature meaningfully change predictions and explanations?	Compare predictions with the P-glycoprotein channel active versus neutralized	Large contrast in predicted logBB for likely efflux substrates, with explanation shifts toward transporter-associated motifs	Transporter channel has no effect or produces implausible prediction reversals	Use contrast analysis to separate passive permeability failure from active efflux liability
Applicability domain	Is the compound chemically similar enough to training and transporter-model	Use scaffold coverage, descriptor-range checks, prediction uncertainty, and transporter-model confidence	Low uncertainty and acceptable domain similarity for prioritized compounds	Rare scaffolds, unusual ionization states, or missing transporter	Flag out-of-domain compounds for experimental testing rather than automated ranking

	domains for reliable inference?			confidence produce unreliable estimates	
Prospective utility	Does model-guided optimization improve lead selection or reduce late-stage BBB failure?	Prospective medicinal chemistry case studies comparing model-guided decisions with standard workflows	Higher enrichment of brain-exposed compounds and more actionable structural modification hypotheses	Model improves retrospective metrics but fails to influence real optimization decisions	Deploy as a decision-support tool embedded in lead optimization review meetings
Governance and transparency	Can users understand how predictions were generated and when they should not be trusted?	Report preprocessing rules, model version, feature provenance, uncertainty, and explanation limitations	Reproducible predictions with transparent feature handling and interpretable outputs	Hidden preprocessing changes, uncalibrated transporter scores, or overconfident predictions	Require documentation, version control, and human approval before using outputs for advancement decisions

Limitations

Dependence on P-glycoprotein Predictor Quality

The proposed model's transporter-aware behavior would depend strongly on the accuracy, calibration, and applicability domain of the external P-glycoprotein predictor. If that predictor is biased toward particular scaffolds or assay conditions, the BBB model may learn spurious associations and present them as biologically meaningful attention patterns [22]. This concern is especially important because BBB datasets and transporter datasets may differ in chemical composition, experimental endpoints, and annotation quality [19, 21]. For this reason, transporter predictions should be accompanied by uncertainty estimates and domain checks whenever the model is used in medicinal chemistry decisions.

Beyond P-glycoprotein: Other Transporters and BBB Biology

The initial model focuses on P-glycoprotein, but BBB exposure can also be influenced by BCRP, OATPs, metabolic stability, plasma protein binding, intracellular sequestration, and biological heterogeneity across disease states. BCRP and MDR1 efflux models indicate that transporter biology is multi-channel rather than reducible to a single efflux score [19]. BBB prediction frameworks that integrate novel molecular parameters and experimental information suggest that broader biological context may improve translational relevance [20]. Future versions should therefore incorporate additional transporter likelihoods and mechanistic context while preserving the interpretability of the attention-based architecture. **Figure 3** shows more information about this context.

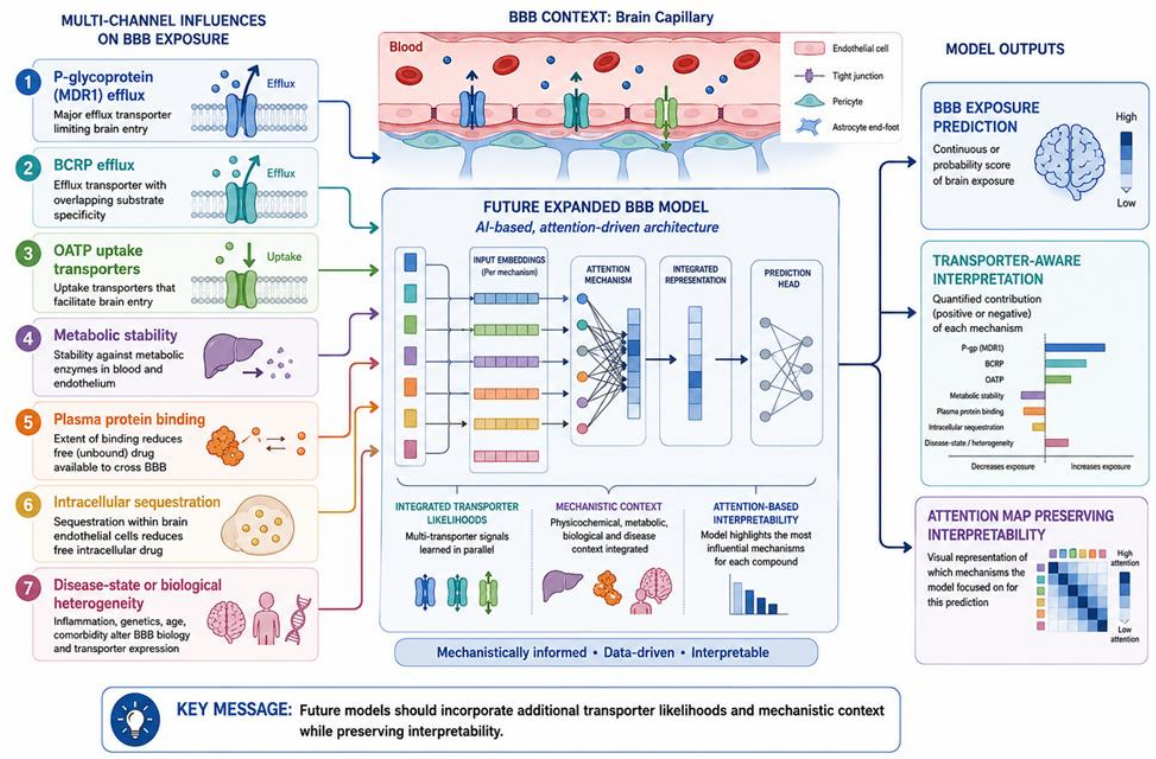

Figure 3. P-glycoprotein and Transporters and BBB Biology

Conclusion

The proposed MDL framework conceptualizes BBB permeability prediction as a transporter-aware multimodal learning task. It combines molecular graph attention, CNS-relevant physicochemical descriptors, and a pre-computed P-glycoprotein

likelihood feature to support logBB prediction. This design recognizes that net brain exposure depends on both passive permeability and active efflux. The model is intended to provide chemically interpretable predictions rather than only categorical screening outputs.

A major strength of the approach is its ability to link predicted BBB behavior to molecular substructures and transporter liability signals. The graph attention encoder could highlight atom-level regions associated with poor exposure, while the auxiliary transporter channel could clarify whether an unfavorable prediction is driven by efflux risk. This would allow medicinal chemists to reason about structural changes that might reduce transporter recognition. The model therefore functions as a design-support tool for CNS lead optimization.

Important challenges remain before such a model could be used prospectively in neuropharmacology programs. Its reliability would depend on the quality of curated BBB measurements, the calibration of the transporter predictor, and the chemical relevance of descriptor preprocessing. The initial focus on P-glycoprotein also leaves other transporters and BBB biological mechanisms incompletely represented. Prospective validation would be needed to determine whether the explanations improve real medicinal chemistry decisions.

Open release of the model architecture, preprocessing workflow, and curated BBB dataset would help accelerate transparent benchmarking. Shared resources would allow researchers to test new molecular encoders, transporter features, and interpretability methods under comparable conditions. Such collaboration could improve the reliability of computational brain-exposure prediction across CNS drug discovery programs. A transporter-aware attention framework therefore represents a promising conceptual direction for interpretable BBB modeling.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Yuan Y, Zheng F, Zhan CG. Improved prediction of blood–brain barrier permeability through machine learning with combined use of molecular property-based descriptors and fingerprints. AAPS J. 2018;20(3):54.
2. Miao R, Xia LY, Chen HH, Huang HH, Liang Y. Improved classification of blood-brain-barrier drugs using deep learning. Sci Rep. 2019;9(1):8802.
3. Jorgensen C, Oliphant E, Barker M, López Martínez E, Thulasi S, Prior H, et al. Simulation and machine learning assessment of P-glycoprotein pharmacology in the blood–brain barrier: inhibition and substrate transport. Int J Mol Sci. 2025;26(18):9050.
4. Wang Z, Yang H, Wu Z, Wang T, Li W, Tang Y, et al. In silico prediction of blood–brain barrier permeability of compounds by machine learning and resampling methods. ChemMedChem. 2018;13(20):2189–201.
5. Majumdar S, Basak SC, Lungu CN, Diudea MV, Grunwald GD. Finding needles in a haystack: determining key molecular descriptors associated with the blood–brain barrier entry of chemical compounds using machine learning. Mol Inform. 2019;38(8-9):1800164.
6. Xiong Z, Wang D, Liu X, Zhong F, Wan X, Li X, et al. Pushing the boundaries of molecular representation for drug discovery with the graph attention mechanism. J Med Chem. 2020;63(16):8749–60.
7. Withnall M, Lindelöf E, Engkvist O, Chen H. Building attention and edge message passing neural networks for bioactivity and physical–chemical property prediction. J Cheminform. 2020;12(1):1.
8. Maziarka Ł, Majchrowski D, Danel T, Gaiński P, Tabor J, Podolak I, et al. Relative molecule self-attention transformer. J Cheminform. 2024;16(1):3.
9. Wu Z, Ramsundar B, Feinberg EN, Gomes J, Geniesse C, Pappu AS, et al. MoleculeNet: a benchmark for molecular machine learning. Chem Sci. 2018;9(2):513–30.
10. Shaker B, Yu MS, Song JS, Ahn S, Ryu JY, Oh KS, et al. LightBBB: computational prediction model of blood–brain-barrier penetration based on LightGBM. Bioinformatics. 2021;37(8):1135–9.
11. Shaker B, Lee J, Lee Y, Yu MS, Lee HM, Lee E, et al. A machine learning-based quantitative model (LogBB_Pred) to predict the blood–brain barrier permeability (logBB value) of drug compounds. Bioinformatics. 2023;39(10):btad577.
12. Grant N, Machado Reyes D, Yang Z, Wan L, Wang C, Yan P. Blood–brain barrier permeability prediction with artificial intelligence and machine learning: a meta-review and future directions. Discov Artif Intell. 2025;5(1):254.
13. Liu L, Zhang L, Feng H, Li S, Liu M, Zhao J, et al. Prediction of the blood–brain barrier permeability of chemicals based on machine-learning and ensemble methods. Chem Res Toxicol. 2021;34(6):1456–67.
14. Yu TH, Su BH, Battalora LC, Liu S, Tseng YJ. Ensemble modeling with machine learning and deep learning to provide interpretable generalized rules for classifying CNS drugs with high prediction power. Brief Bioinform. 2022;23(1):bbab377.

15. Alsenan S, Al-Turaiki I, Hafez A. A recurrent neural network model to predict blood–brain barrier permeability. Comput Biol Chem. 2020;89:107377.
16. Alsenan S, Al-Turaiki I, Hafez A. A deep learning approach to predict blood-brain barrier permeability. PeerJ Comput Sci. 2021;7:e515.
17. Tang Q, Nie F, Zhao Q, Chen W. A merged molecular representation deep learning method for blood–brain barrier permeability prediction. Brief Bioinform. 2022;23(5):bbac357.
18. Ding Y, Jiang X, Kim Y. Relational graph convolutional networks for predicting blood–brain barrier penetration of drug molecules. Bioinformatics. 2022;38(10):2826–31.
19. Li H, Zhang R, Min Y, Ma D, Zhao D, Zeng J. A knowledge-guided pre-training framework for improving molecular representation learning. Nat Commun. 2023;14(1):7568.
20. Spielvogel CP, Schindler N, Schröder C, Stellnberger SL, Wadsak W, Mitterhauser M, et al. Enhancing blood–brain barrier penetration prediction by machine learning-based integration of novel and existing, in silico and experimental molecular parameters from a standardized database. J Chem Inf Model. 2025;65(6):2773–84.
21. Meng F, Xi Y, Huang J, Ayers PW. A curated diverse molecular database of blood-brain barrier permeability with chemical descriptors. Sci Data. 2021;8(1):289.
22. Jiang D, Wu Z, Hsieh CY, Chen G, Liao B, Wang Z, et al. Could graph neural networks learn better molecular representation for drug discovery? A comparison study of descriptor-based and graph-based models. J Cheminform. 2021;13(1):12.
23. Kumar R, Sharma A, Alexiou A, Bilgrami AL, Kamal MA, Ashraf GM. DeePred-BBB: a blood brain barrier permeability prediction model with improved accuracy. Front Neurosci. 2022;16:858126.
24. Liang L, Liu Z, Yang X, Zhang Y, Liu H, Chen Y. Prediction of blood–brain barrier permeability using machine learning approaches based on various molecular representation. Mol Inform. 2024;43(9):e202300327.
25. Aftab N, Masood F, Ahmad S, Rahim SS, Sanami S, Shaker B, et al. An optimized deep learning approach for blood-brain barrier permeability prediction with ODE integration. Inform Med Unlocked. 2024;48:101526.
26. Cherian Parakkal S, Datta R, Das D. DeepBBBP: high accuracy blood–brain–barrier permeability prediction with a mixed deep learning model. Mol Inform. 2022;41(10):2100315.
27. Kumar V, Banerjee A, Roy K. Breaking the barriers: machine-learning-based c-RASAR approach for accurate blood–brain barrier permeability prediction. J Chem Inf Model. 2024;64(10):4298–309.
28. Huang ET, Yang JS, Liao KY, Tseng WC, Lee CK, Gill M, et al. Predicting blood–brain barrier permeability of molecules with a large language model and machine learning. Sci Rep. 2024;14(1):15844.
29. Vinh T, Le PH, Nguyen BP, Nguyen-Vo TH. Masked graph transformer for blood-brain barrier permeability prediction. J Mol Biol. 2025;437(6):168983.
30. Nabi AE, Pouladvand P, Liu L, Hua Y, Ayubcha C. Machine learning in drug development for neurological diseases: a review of blood brain barrier permeability prediction models. Mol Inform. 2025;44(3):e202400325.
31. Koutroumpa NM, Tsoumanis A, Sarimveis H, Lynch I, Melagraki G, Afantitis A. Prediction of blood–brain barrier and Caco-2 permeability through the Enalos Cloud Platform: combining contrastive learning and atom-attention message passing neural networks. J Cheminform. 2025;17(1):68.
32. Yang K, Swanson K, Jin W, Coley C, Eiden P, Gao H, et al. Analyzing learned molecular representations for property prediction. J Chem Inf Model. 2019;59(8):3370–88.
33. Faramarzi S, Kim MT, Volpe DA, Cross KP, Chakravarti S, Stavitskaya L. Development of QSAR models to predict blood-brain barrier permeability. Front Pharmacol. 2022;13:1040838.