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FROM CORRELATION TO CAUSATION: A CONCEPTUAL FRAMEWORK FOR APPLYING CAUSAL AI TO ADOLESCENT DEPRESSION RESEARCH.

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ABSTRACT: *Adolescent depression is a growing global concern, yet most neuroimaging and machine learning research in this domain remains correlational, limiting understanding and clinical translation. Existing studies predominantly use cross-sectional designs and black-box predictive models that identify associations but cannot determine whether observed brain features represent causes, consequences, or correlates of depressive symptoms. This article proposes a conceptual framework for advancing from correlation to causation by integrating longitudinal multimodal data with modern causal AI techniques. We outline key methodological limitations in current research, including poor reproducibility, lack of temporal resolution, confounding development factors, and limited reproducibility; and describe how causal approaches such as Directed Acyclic Graphs, Granger causality, counterfactual reasoning, Mendelian Randomization, and causal graph neural networks can address these gaps. Building on these tools, we propose a three-phase framework consisting of: (a) Data foundations emphasizing longitudinal neuroimaging, symptom-level phenotyping, and multimodal integration; (b) Causal modeling pipelines using causal discovery, causal GNNs, and counterfactual simulations to identify mechanisms; and (c) translational pathways for Personalized interventions and early-risk prediction grounded in causal pathways. Ethical considerations related to privacy, consent, fairness, and data governance are also examined, especially given adolescents' vulnerability and the sensitivity of neural and digital phenotyping data. Collectively, this framework provides a systematic and feasible roadmap for leveraging causal AI to uncover mechanistic pathways, guide interventions, and strengthen the scientific foundation of adolescent depression research.*

KEYWORDS: Adolescent Depression, Causal-AI, Causal Inference, Mendelian Randomization, Neuroimaging.

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INTRODUCTION

Adolescent mental health problems and depressive disorder have become a major global concern. Large-scale reports and surveillance data show that one in seven adolescents experienced a mental disorder; during the pandemic, there was a pooled prevalence rate for depression that reached 25-29%, and anxiety 20-26% (Kim et al., 2024; Madigan et al., 2023; Pillai et al., 2023) in many countries both self-reported depressive symptoms and antidepressant prescribing among young people have increased substantially.

Research on adolescent depression is largely dominated by cross-sectional correlational designs. Neuroimaging work commonly links symptom severity to activity or connectivity in regions and networks such as the amygdala, prefrontal cortex, default mode network, and reward pathways (Auerbach et al., 2021; Toenders et al., 2019a). Similarly, many machine learning (ML) studies (Ding et al., 2025; Haque et al., 2021) emphasize classification or prediction rather than causal modeling. These approaches reveal what is associated with depression, but they do not establish why that is, which neural mechanisms drive onset, persistence, or remission.

Most of the ML research in adolescent depression is designed to classify or predict depressive symptoms using a wide range of features, demographics, psychological, behavioral, and neuroimaging data, rather than to model causal relationships or mechanisms (*Depression Using Machine Learning*, n.d.; Richter et al., 2025; Xu et al., 2025). These models often achieve high accuracy in identifying at-risk individuals or distinguishing between depression and other conditions, but they primarily reveal associations, not causation.

Recent methodological advances show that ML can move beyond mere association to uncover directional, mechanistic relationships in high-dimensional biomedical data. Such approaches include the use of Mendelian Randomization (MR) as used in (Badsha & Fu, 2019; Z. Lin et al., 2023a; Zuber et al., 2020). These methods use genetic variants as instrumental variables to infer causal effects of exposures and outcomes, helping to distinguish causation from correlation. Another is Causal Discovery Algorithm as used by (Z. Lin et al., 2023b; Sanchez et al., 2022) these algorithms, such as those based on Bayesian networks or graph theory, learn the structure and directionality of relationships among variables, allowing for the identification of potential causal pathways in complex datasets; there is also Causality Aware Graph Neural Network and Casual ML that integrates causal reasoning into ML models, enabling simulation of hypothetical interventions and estimation of treatment effects at both population and individual levels (Chen et al., 2025; Prosperi et al., 2020; Rust & Autexier, 2022) these methods allow researchers to estimate the effects of hypothetical interventions, supporting personalized medicine and targeted therapies. Casal network models can reveal direct and indirect effects among multiple traits or biomarkers, providing a system-level understanding of disease mechanisms (Z. Lin et al., 2023; Yazdani et al., 2022). It further helps with personalized individual treatment, thereby improving decision-making and the development of precision medicine tools (Duong et al., 2024)

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Limitations of current neuroimaging and AI approaches

Despite advances in neuroimaging combined with ML and DL in understanding psychiatric disorders, including depression, several important limitations exist; Interpretability remains a major barrier for ML/DL neuroimaging models in depression/psychiatry, limiting mechanistic insight and clinical translation. ML and DL models applied to neuroimaging data for psychiatric diagnosis (for example, like depression, psychosis) often function as "black boxes"; they provide predictions or classifications without clear explanations of which brain features drive those decisions. This lack of interpretability is especially problematic given the high dimensionality of neuroimaging data, where models may latch onto spurious or non-biological patterns, undermining both scientific understanding and clinical trust (Koppe et al., 2021; Smucny et al., 2022)

Cross-sectional neuroimaging and ML studies in MDD can identify associations, but they cannot establish causality, developmental trajectories, or patterns of change over time. Because most neuroimaging and ML studies compare individuals with MDD to controls at a single time point, they reveal correlations between brain features and MDD but cannot determine whether these differences represent causes, consequences, compensatory responses, or unrelated epiphenomena (Toenders et al., 2019b; Tura & Goya-Maldonado, 2023; Wang et al., 2025). Without longitudinal data, it is impossible to infer the directionality or evolution of brain changes in relation to symptom onset, progression, or remission (Gray et al., 2020). While longitudinal studies are rare, systematic reviews and meta-analysis highlight that only a small fraction of neuroimaging studies in MDD are longitudinal, and those that exist often have small sample sizes and heterogeneous methods, limiting their ability to resolve causality or track neurodevelopmental trajectories (Toenders et al., 2019b), where available, longitudinal data suggest that brain abnormalities may fluctuate with symptom changes, but current evidence is insufficient to determine if these changes precede, result from, or co-occur with depressive episodes (Satomura et al., 2019a). Large-scale meta-analysis and reviews consistently note that cross-sectional designs dominate the field and call for more within-participant, longitudinal, and interventional studies to advance mechanistic and prognostic understanding (Dohm et al., 2016).

Confounding variables such as age, puberty, socioeconomic status, and stress significantly complicate brain symptom association in youth, and many studies fail to account for these influences sufficiently. Brain maturity is highly dynamic during childhood and adolescence, with regional and sex-specific trajectories. Failing to account for these can obscure or distort associations between brain structure/function and psychiatric symptoms (Karcher & Barch, 2021; Pfeifer & Allen, 2021; Satomura et al., 2019b). Puberty introduces hormonal and neurobiological changes that interact with social and psychological processes, influencing the risk of mental health problems. Puberty timing and tempo vary widely and can confound brain-symptom relationships if not properly modeled (Dehestani et al., 2023; Kretzer et al., 2024a; Pfeifer & Allen, 2021). Most ML and neuroimaging studies still rely on traditional categorical diagnoses such as comparing individuals with MDD to healthy controls or individuals with schizophrenia to controls .However, these diagnostic labels group together people with widely differing symptom profiles, underlying mechanisms, prognoses, and treatment responses (Bzdok & Meyer-Lindenberg, 2018; Kretzer et al., 2024b). As a result, this approach can obscure important within-diagnosis variability and may overlook brain symptoms relationships that cut diagnostic boundaries (Brossollet et al., 2023; Bzdok & Meyer-Lindenberg, 2018). As

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a result, classification success that is diagnosis versus control may not translate into actionable clinical insights, for example, predicting which patients respond to treatments, or understanding mechanisms underlying specific symptoms such as anhedonia mood swings, rather than broad syndromes (Bzdok & Meyer-Lindenberg, 2018).

These limitations highlighted above are published ML and neuroimaging findings with limited reproducibility and generalizability, especially when moving to new datasets, populations, or clinical settings (Komeyer et al., 2025). Models may overfit for specific datasets, capturing noise or site-specific patterns rather than robust neurobiological signals. This undermines their reliability for diagnosis, prognosis, or guiding interventions, because of a lack of interpretability and causal inferences; even strong prediction does not guarantee insight into mechanisms. This restricts the potential of findings to inform early detection, prevention, or targeted treatment. Even though neuroimaging, together with ML and DL, has advanced the field, there remains a causal gap, a gap between statistical association and prediction, and mechanistic understanding. Bridging that gap will likely require new approaches like causal modeling, longitudinal designs, and multi-model data integration rather than incremental improvements on standard ML pipelines.

What Causal AI offers

Causal Inference versus Correlation: What is the difference?

Usually, when it is said that two things are correlated, it simply means they tend to change together. For example, activation in the brain region A tends to be higher in people who report a lower mood. But correlation does not specifically tell us the reason this happens, whether A causes low mood, low mood causes A, both are causedby something else, or it's just a coincidence. Causal inference is the set of tools and ideas that help us to move from "this goes with that" to statements like "this influences that" or "if we change A, we would expect B to change". This shift matters because interventions need causal knowledge; you want to change what drives the problem, not what merely accompanies it (Pearl, 2010a)

Directed Acyclic Graphs (DAGs)

A DAG is a simple drawing where nodes are variables (for example, brain region connectivity, sleep quality, socioeconomic status) and arrows show assumed causal directions, like puberty – brain connectivity. DAGs do not prove causation; they explicitly state assumptions about which variables might cause others. The value is twofold. First, they make assumptions transparent so others can critique or test them. Secondly, they let researchers identify which variables must be measured or adjusted to estimate causal effects. It can be said to be a roadmap that tells whether one can safely infer cause-and-effect from data or where one needs more data (Pearl, 2010b)

Counterfactual reasoning – the "what if" question

Counterfactuals ask questions like: "What would this teen's mood have been if their amygdala connectivity were lower, holding everything else the same?" Counterfactual thinking is central to causal claims because it ties a cause (change in A) to a hypothetical outcome (what would have happened to B). In applied research, causal methods try to estimate these counterfactuals from observational data under explicit assumptions and to quantify how confident we can be

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in those estimates. This is the type of reasoning needed to say whether changing a brain circuit would likely improve or worsen symptoms (Bours, 2021)

Granger Causality" measures directed interactions in time series

Granger causality is a practical way to ask whether one time series helps predict another. If past values of region A improve predictions of region B (beyond what B's past alone provides), A is said to "Granger-cause". In neuroscience, this is often applied to EEG or fMRI time series to infer the directed flow of information between regions. Important caveats: Granger causality captures predictive directionality, not ultimate mechanistic cause, and its reliability depends on data quality (sampling rate, preprocessing) and the absence of unmeasured confounders. Still, it's a useful tool for building directed brain network hypotheses that can be tested further (F.-H. Lin et al., 2014a; Stokes & Purdon, 2017)

Mendelian Randomization using genetics as a natural experiment.

Mendelian randomization (MR) exploits the fact that genetic variants are assigned at conception and are roughly independent of many environmental confounders. If a genetic variant is robustly associated with a biological trait, and that variant is also associated with depression. MR can provide evidence that the biological trait causally affects depression, assuming a few technical conditions hold. In other words, genetics can sometimes act like a "natural randomized trial" that helps untangle whether brain differences are causes or consequences of symptoms. MR has been used increasingly in neuroimaging and psychiatry to strengthen causal claims (Sanderson et al., 2022; Storm et al., 2020)

All the above could be fitted into a practical research pipeline in 4 main stages; the first is by building clear causal models (DAGs) that list plausible causes, outcomes, and confounders for adolescent mood problems, such as age, puberty, stress, and brain connectivity. DAGs will then make assumptions explicit and guide what to measure (Pearl, 2010b). Afterwards, time-series methods like Ginger and longitudinal designs will be used to recover directional relationships and temporal precedence while checking data quality and sampling rate (Henry & Gates, 2017; F.-H. Lin et al., 2014b). When feasible, genetic approaches such as MR should be used to strengthen causal claims about biological mediators, like structural connectivity. MR offers a robust check against common confounders (Sanderson et al., 2022; Taschler et al., 2022). Since no single method is perfect, strong causal inferences rely on combining complementary approaches and triangulating evidence. These approaches include DAG-guided adjustments, time-series analyses, MR, and targeted experiments where possible. Causal claims are most credible when results are consistent across multiple methods (Pearl, 2010a).

Proposed Conceptual Framework

In this section, we introduce a three-phase conceptual framework designed to guide future research towards a mechanistic, causal understanding of adolescent depression. While neuroimaging and ML studies have generated vast correlational evidence, they have not yet converged on clear, actionable causal pathways. This conceptual framework comprises three major phases: Data foundations, causal modelling pipelines, and translation. This roadmap is intended both as a blueprint for empirical research and as a theoretical contribution, clarifying the requirements, opportunities, and trajectory for future work.

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Phase 1: Data Foundations

1. Longitudinal Neuroimaging: Rather than relying solely on cross-sectional case versus control snapshots, we advocate for repeated neuroimaging across development, like the baseline and follow-ups. Longitudinal data are essential to capture temporal dynamics, neural maturation, and brain changes associated with the onset or course of depressive symptoms. Studies such as the longitudinal multimodal imaging work by the Adolescent Brain Cognitive Development (ABCD) study demonstrate the feasibility and value of prospectively linking baseline brain features to later emergence of depression risk (Gracia-Tabuenca et al., 2024; Pilmeyer et al., 2024)

2. Symptom-level measurement (not just diagnosis): Rather than binary diagnostic categories (depressed versus non-depressed), assessments should target dimensional, symptom-level data like mood swing, anhedonia, sleep problems, and cognitive difficulties. This allows more nuanced modeling of heterogeneity and aligns with efforts to understand subtypes or trajectories rather than a homogeneous disease label. Indeed, recent neurobiological subtyping of adolescent depression leverages multimodal data to parse heterogeneity (*Neurobiological Subtypes of Adolescent Depression*, n.d.)

3. Multi-modal integration (MRI + EEG + behavior + possibly genetics): A single imaging modality like structural MRI alone is often insufficient to capture the complexity of brain processes underlying mental states. Combining structural MRI, functional MRI, EEG (for temporal dynamics), behavioral measures (clinical, cognitive), and, where feasible, genetic or transcriptomic data enhances sensitivity and specificity. Such multimodal integration has already shown promise; combining MRI modalities (structural + functional + diffusion) improved both diagnosis and outcome prediction in depression compared to unimodal models (*Neurobiological Subtypes of Adolescent Depression*, n.d.; Pilmeyer et al., 2024). Similarly, the value of combining EEG with other neuroimaging modalities for biomarker discovery in psychiatry has been emphasized in reviews (*Neurobiological Subtypes of Adolescent Depression*, n.d.).

Invariably, phase one will establish a rich, high-quality, dev dataset, the foundation upon which modeling can be reliably built.

Phase 2: Causal Modeling Pipelines

Once data foundations are laid, the framework advances to analytic methodologies designed to move beyond association toward causation. The elements include:

4. Causal Discovery for brain networks: Use of causal network inference algorithms like variants of structural causal modelling, conditional causality measures applied to longitudinal and multimodal neural data to infer directed relationships among brain regions/time-series, beyond simple correlation. For instance, frameworks such as the one described in A graph neural network framework for causal inference in brain networks illustrate how combining structural connectivity (DTI) with functional time-series (fMRI) in a GNN architecture can reveal likely causal interactions (Wein et al., 2021). Similarly, information-theoretic conditional causality measures have been proposed to improve accuracy over classical Granger causality for brain data (Ning & Zalesky, 2024)

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5. Causal Graph Neural Networks (Casual GNNs) for connectivity-based psychiatric analysis: Recent advances, such as CI-GNN- A Grangercausality-inspired graph neural network for interpretable brain network-based psychiatric diagnosis, show that it is possible to build GNN architectures that explicitly aim to learn causally relevant subgraphs (rather than merely correlational ones). CI-GNN disentangles causal versus non-causal connectivity contributions, yielding subgraph-level explanations with theoretically grounded interpretation (Zheng et al., 2024). Also, new frameworks like causal Graphs for brains (CGB) have been proposed to integrate causal discovery, e.g., transfer entropy, with geometric network properties to improve disease classification and causal interpretability (Febrinanto et al., 2025)

6. Counterfactual Simulation for interventions: Once causal structures are inferred, the next step is to simulate "what if" interventions, for example, altering connectivity strength in a putative causal circuit, and estimating the effect on depressive symptom risk or trajectory. This approach, enabled by structural causal models or causal-aware GNNs, provides a bridge between causal discovery and potential therapeutic decision-making. Conceptually, this resembles how interventional methods (e.g., noninvasive brain stimulation) are used to infer causality in cognitive neuroscience (Wein et al., 2021).

What will be achieved in phase two is the operationalization of the core conceptual shift: from association to mechanism, from black-box prediction to an interpretable, causally informed hypothesis.

2. Phase 3: Translation (Prediction, Biomarkers, early detection)

The final phase aims to translate causal insights into clinically or socially actionable outcomes:

1. Predicting who develops severe depression

Using causal models derived in phase two and longitudinal data from phase 1, we can build predictive models that estimate an individual's risk trajectory not simply based on correlational biomarkers, but grounded in inferred causal pathways. This enhances reliability, generalizability, and interpretability of predictions.

2. Informing early or personalized interventions

Ultimately, causal-AI-derived insights may support personalized medicine for adolescent depression: targeted interventions tailored to an individual's neural vulnerability profile; early-warning systems; or circuit-based prevention strategies aligning neuroscience with public health and clinical psychiatry.

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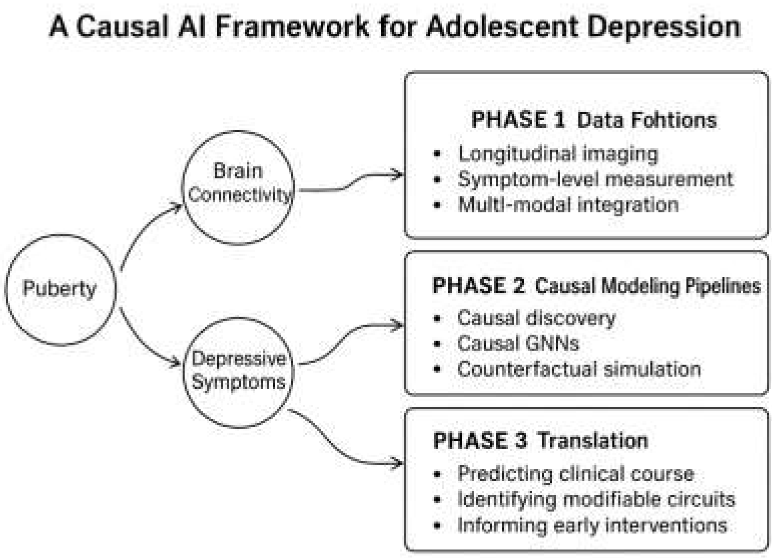
Figure 1: A Causal AI Framework for Adolescent Depression



Why the framework matters

Most existing neuroimaging or AI studies, even when using multimodal data, remain largely correlational or predictive. The proposed framework makes causality central. By integrating longitudinal multimodal data collection with modern causal AI methods, it recognizes brain development's dynamic nature, especially critical in adolescence. Rather than stopping at explanation, the framework envisions intervention: biomarker discovery, risk stratification, and ultimately, neurobiologically informed prevention or treatment. While phases are sequential, the framework allows iteration; for example, new data can inform refined causal models; interventions inspired by counterfactual simulation can feed back into data collection; translational findings can guide future cohort designs.

Summarily, this proposed conceptual framework lays out a clear, feasible, and innovative roadmap for advancing causal-AI-driven research on adolescent depression. It defines not only what needs to be done but also how to do a systematic, rigorous, and translationally oriented manner.

Ethical and Practical Considerations

Research at the intersection of adolescent neuroimaging, mental-health assessment, and causal AI presents significant opportunities but also raises complex ethical, legal, and practical challenges, especially regarding privacy and data protection for this sensitive population.

Adolescents' neurobiological and digital phenotyping data are highly sensitive, with neural signatures potentially revealing cognitive or emotional states beyond what participants intend to share. The risk is amplified by longitudinal datasets, which can expose developmental vulnerabilities over time (Szoszkiewicz & Yuste, 2025). Current regulations, such as Health Insurance Portability and Accountability Act (HIPAA) in the United State and General Data Protection Regulation (GDPR) in European Union, are often inadequate for protecting neural and digital phenotyping data, especially as these data can be repurposed or sold outside

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healthcare contexts, leading to risks like discrimination or stigmatization (Martinez-Martin et al., 2021; Pavarini et al., 2022). Adolescents themselves express strong privacy concerns, particularly regarding digital data, for example, social media, and are selective about what they are willing to share, emphasizing the need for transparency and choice (Pavarini et al., 2022)

Obtaining meaningful informed consent is challenging due to the complexity of digital phenotyping and neuroimaging findings. Consent procedures must clearly explain what data are collected, potential inferences, risks, and who will access the data, using language appropriate for adolescents and their guardians (Martinez-Martin et al., 2021). Special attention is needed to balance adolescents' autonomy with parental interests, and to ensure that predictive results do not cause psychological harm or undue anxiety.

AI and ML models used in mental health assessment can introduce bias, lack transparency, and may not be equally accurate across all subgroups, raising fairness and accountability concerns (Gooding & Kariotis, 2021; Pavarini et al., 2022; Thakkar et al., 2024). There is a need for robust frameworks to ensure that AI systems are explainable, regularly audited, and that their outputs are communicated understandably to both clinicians and participants (Martinez-Martin et al., 2021; Shen et al., 2024; Thakkar et al., 2024).

Data sharing is essential for scientific progress, but must be balanced with privacy. Adolescents and their families should have the right to opt out of data sharing or secondary uses, and data should not be shared with third parties without explicit consent (Martinez-Martin et al., 2021; Szoszkiewicz & Yuste, 2025). The concept of data solidarity, treating neural data as a shared resource for public good while protecting individual rights, has been proposed as a potential governance model (Szoszkiewicz & Yuste, 2025)

Responsible research in this domain requires robust privacy protections, a transparent consent process, attention to algorithmic fairness, and governance models that respect adolescent autonomy and data rights. Ongoing stakeholder engagement and empirical research are essential to address these evolving challenges.

FUTURE RESEARCH

Building on the proposed causal-AI framework, several testable research directions emerge that can advance mechanistic understanding of adolescent depression and inform targeted intervention strategies. A longitudinal causal Analysis of Limbic Network Development is a worthy research direction, as adolescence is marked by the rapid maturation of Limbic circuits involved in emotion regulation, reward sensitivity, and stress reactivity. So a future study could combine longitudinal fMRI with causal discovery algorithms to identify directed development changes within the amygdala-hippocampal-ventromedial prefrontal cortex network.

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