**Stress–brain metastasis axis in young cancer patients through big data integration and AI modeling**

**Background**

1. **Younger generations are experiencing higher chronic stress exposure**

* There is strong data showing that younger adults today face unprecedented levels of chronic psychosocial stress, linked to modern work patterns, social factors, economic instability, and digital/social media influence.
* Chronic stress contributes to systemic inflammation, neuroendocrine dysregulation, and immunosuppression — all of which can create a fertile ground for tumor progression and metastasis.

1. **Stress-related pathways overlap with suspected drivers of early-onset cancer (<50-year-old)**

* Chronic stress activates the HPA axis, leading to high glucocorticoid levels → immune suppression, increased angiogenesis, and enhanced tumor cell survival.
* Stress-induced neurotransmitter signaling (e.g., serotonin, norepinephrine) can promote brain-tropic metastasis — exactly the mechanisms you’re studying.
* These same pathways may make early-onset cancers in young adults more aggressive or more prone to early dissemination.

1. **Potential synergism with modern lifestyle factors**

* Early-life stress + unhealthy diet + sedentary behavior + disrupted sleep = a pro-metastatic, pro-inflammatory milieu from a young age.
* Your model could integrate these variables to explain why certain cancers in young adults behave aggressively or spread early to the brain.

1. **Unique vulnerabilities of young brains to metastasis?**

* The young adult brain has different immune surveillance, neurovascular characteristics, and neurotransmitter dynamics — which could intersect with your findings on how stress reprograms the brain niche for metastasis.

**Hypothesis**

We hypothesize that chronic stress, increasingly prevalent in younger populations, contributes to the rising incidence and aggressiveness of early-onset cancers ((<50-year-old) --- particularly breast, lung, and GI cancers—by activating stress-responsive pathways (e.g., HTR2B, NR3C1). These pathways reprogram brain-resident cells—astrocytes, microglia, endothelial cells, and pericytes—to form a permissive metastatic niche by disrupting the blood-brain barrier, suppressing neuroimmune responses, and enhancing tumor cell extravasation and colonization. This mechanistic framework may help explain the rising burden of brain metastases in young adults and reveal new therapeutic targets.

**Aim 1: Population-level and molecular association analysis**

**Data sources:** NHANES, UK Biobank

**Analyses:**

* Use multivariable Cox proportional hazards and logistic regression models to assess associations between stress-related variables (e.g., psychiatric diagnoses, cortisol levels, CRP) and early-onset cancer incidence, metastasis site, and survival.
* Stratify models by age group, cancer subtype (e.g., HER2+, TNBC), and metastasis location (brain vs extracranial).
* Apply propensity score matching and inverse probability weighting to adjust for confounders (e.g., smoking, obesity, socioeconomic status).
* Integrate TCGA and METABRIC multi-omics data to compare expression of stress-relevant genes (HTR2B, NR3C1) in early- vs late-onset tumors using differential expression and pathway enrichment analysis.

**AI contribution:**

* Apply ML clustering (e.g., t-SNE, UMAP) to identify molecular subtypes linked to stress signatures.
* Use random forest / gradient boosting models to predict brain metastasis risk based on combined clinical, molecular, and stress data features.
* Develop interpretable SHAP-value models to identify key predictors.

**Aim 2: AI-based modeling of brain metastatic niches**

**Data sources:** Public (e.g., GSE143423, GSE125989), in-house spatial transcriptomic / single-cell data.

**Analyses:**

* Use CCCExplorer and S2C2 to reconstruct spatial cell-cell communication networks in brain metastatic lesions.
* Compare early-onset vs late-onset brain mets for enriched ligand-receptor pairs involving serotonin, glucocorticoid, cytokine, and ECM signaling.
* Identify spatial niches (astrocyte, microglia, tumor, endothelia) showing stress-modulated signaling patterns using unsupervised clustering + spatial correlation analysis.

**AI contribution:**

* Use graph neural networks (GNNs) to model spatially-resolved cell-cell signaling and identify critical hubs (e.g., HTR2B+ niches).
* Apply AI pattern recognition to define niche architectures predictive of stress-driven metastasis.