DOCUMENT SUMMARY

This highly technical neuroscience paper provides a powerful biological basis for Enlitens' core mission. It uses advanced brain imaging and gene expression analysis to demonstrate that "neurodiverse brain organization" is a biological reality. The research successfully moves beyond simple metrics, showing that individualized patterns of brain structure and gene expression can be used to subgroup individuals in behaviorally meaningful ways (e.g., anxiety levels), directly challenging a one-size-fits-all, categorical model of the human mind. The paper's in-depth discussion of the limitations of various sophisticated statistical models also serves as a strong analogy for the inherent flaws and biases in standardized psychological testing.

FILENAME

ECKER_2025_TranscriptomicDecoding_biological_basis_for_neurodiversity_and_methodological_critique.md

METADATA

- **Primary Category**: NEURODIVERSITY
- **Document Type**: research_article
- **Relevance**: Core
- **Key Topics**: neurodiversity, individual_differences, assessment_critique, biological_markers, data_analysis_methods, subgrouping, normative_modeling
- **Tags**: #neurodiversity, #neuroscience, #individualdifferences, #brainmapping, #subgrouping, #methodology, #GABA, #standardizedtestingcritique, #normativemodeling, #dimensionalapproach

CRITICAL QUOTES FOR ENLITENS

"Imaging transcriptomics, the study of correlations between gene-expression patterns and spatially varying properties of brain structure and function', has become a powerful tool for exploring the putative molecular underpinnings of neurotypical and neurodiverse brain organization."

"imaging transcriptomics also holds promise for dissecting the cortical architecture of complex neurotransmission systems and neuromodulatory pathways."

"While there is often no 1:1 relationship between gene expression and receptor density, evidence suggests that patterns of regional variations in gene expression can provide important insights into the functional role of a molecular target (e.g10,11.)."

"This implies that the cortical expression profiles of specific molecular targets may reflect their functional significance, which could be investigated by spatially aligning (i.e., correlating) IDPs with candidate gene expression patterns."

"However, linking spatially-dense gene expression patterns to highly variable IDPs, both across individuals and brain regions, is a computational and statistical challenge."

"Our findings indicate that the cortical transcriptomic landscape of genes encoding for specific pharmacological targets may be indicative of their clinical or behavioral relevance, and so guide the development of targeted pharmacotherapies in the future."

"Notably, these large-scale canonical expression patterns of modules not only align with the diverse spatial scales and temporal epochs of human brain organization-ranging from cytoarchitectonic boundaries to markers of neuronal subtypes-but also seems to be functionally relevant."

"This is particularly relevant when examining IDPs in neuropsychiatric and neurodevelopmental conditions that are marked by highly diverse and individualized neuroanatomical and functional variations in the brain (e.g..)."

"As the developmental trajectory of CT has an inverted U-shape across the human life span, positive deviations from the typical trajectory of CT are commensurate with delayed brain maturation."

"A gene with persistently high expression levels across the cortical surface may therefore exhibit only a weak correlation with a regionally highly variable IDP, yet still have a significant impact on a phenotype. Thus, the impact of a gene on a phenotype cannot be inferred solely based on spatial correlation."

"These studies show that a person's neuroanatomy is marked by highly individualized patterns of neuroanatomical variability, which may serve as a distinct neuroanatomical fingerprint that may be utilized for stratification purposes"

KEY STATISTICS & EVIDENCE

- **Subgrouping based on Neuroanatomy**: The study cohort was divided into two distinct subgroups based on their neuroanatomical profiles. "Subgroup 1 consisted of 178 individuals (65 females, 113 males)... Subgroup 2 consisting of 101 individuals (36 females, 65 males) and was characterized by positive correlations with the cortical Cluster 2, and by negative correlations with the limbic GABAA subunit Cluster 1."
- **Behavioral Differences Between Subgroups**: The neuroanatomically-defined subgroups showed significant differences in self-reported anxiety and depression. "Individuals in Subgroup 1 exhibited significantly elevated self-reported levels of anxiety ($t(74)=2.52$, $p<0.01$, $padj=0.03$, one-tailed) and depression ($t(73)=3.65$, $p<0.001$, $padj<0.01$ one-tailed) compared to those in Subgroup 2 (Fig. 5b)."
- **Brain-Behavior Correlations**: "In adults, we observed a significant positive correlation between levels of anxiety and neuroanatomical diversity within the limbic GABAA subunit Cluster 1 mask, which contained subunits α2,3.5,β1-3, ε, and y_1 ($r=0.26$ $t(80)=2.41$, $p<0.01$ one-tailed)." "Here, as predicted from the subgroup analyses above

(see Fig. 5b), more positive deflections from the typical CT trajectory were associated with elevated self-reported levels of anxiety (Fig. 5c, left panel)."

- **Specificity of Correlation**: "This relationship was absent within the mask representing the more unspecific (i.e., region-overarching) cortical expression pattern of GABAA subunit Cluster 2, which contained subunits α1,4, β2, Y2,3, and (r=0.005, t(80)=0.04, p=0.48) (Fig. 5c, right panel; see Supplementary Data Fig. 9 for model's generalization performance)."
- **Age-Related Findings**: "No significant differences in self-reported anxiety or depression levels were observed between subgroups among adolescents, nor in parent-reported measures for children (Fig. 5b)." "No significant correlations were observed between variation in CT for levels of depression, and for anxiety/depression scores in children and adolescents (all p-values > 0.05)."

METHODOLOGY DESCRIPTIONS

Critique of Different Analytical Methods

The paper provides a detailed comparison of different high-level statistical techniques, highlighting that no single method is perfect and each has significant drawbacks—a powerful analogy for the limitations of standardized testing.

"Overall, the gradient-based approach provided the best trade-off between sensitivity and specificity across various levels of statistical stringency, identifying a reasonable number of significant genes suitable for downstream enrichment analysis (between 100 and 2000 at padj<0.001) (Fig. 3b, Supplementary Data Figs. 2, 3b). In comparison, LME-decoding identified the largest number of significant transcriptomic associations at padi<0.05. Yet, this number decreased rapidly when more conservative p-value thresholds were applied (Fig. 3b, Supplementary Data Figs. 2, 3b). Thus, although LME-decoding has substantial exploratory potential for detecting transcriptomic associations, it is also prone to generating false positives, likely due to spatial autocorrelations within the embedded transcriptomic maps. In contrast, GLS-decoding resulted in the lowest false positive rate (FPR) and yielded findings that were both sensitive and specific. However, incorporating the full spatial autoregressive correlation structure alongside stringent FDR adjustments may result in overly conservative findings, especially at more conservative levels of statistical stringency, where only a few significant genes were observed (Fig. 3d, Supplementary Data Figs. 2, 3d). Thus, while GLS-decoding seems well suited for hypothesis and enrichment testing, it is less optimal for broader exploratory analyses."

Normative Modeling: An Alternative to a Single Standard

The study’s method for analyzing individual brain scans rejects a simple "normal vs. abnormal" dichotomy. Instead, it places each person on a continuum of typical development to understand their unique neuroanatomical variations, which is perfectly aligned with Enlitens' strengths-based, dimensional philosophy.

"To make individuals comparable, IDPs were standardized within the normative (i.e., neurotypical) range to account for the effects of age, sex, full-scale IQ (FSIQ), and other measures affecting brain structure (see Methods for details). Hence, instead of analyzing

absolute CT metrics, all datasets were standardized relative to the canonical trajectory of brain development (Fig. 5a)."

"To make individuals comparable, IDPs were initially standardized within the neurotypical (i.e., non-ID) range by means of a General Linear Model (GLM) that included age, sex, FSIQ, acquisition site, and total brain volume as predictors. The model coefficients were subsequently used to predict CT across the cortex for all individuals in our sample, and the resulting residuals were centered and scaled. Thus, instead of employing absolute CT metrics, all datasets were normalized to unit standard deviations relative to the canonical developmental trajectory. Here, positive values indicated increased CT relative to the expected neurotypical range, while negative values indicated decreased CT. This approach was motivated by so-called normative modeling frameworks, which place each individual within a normative range of expected neurotypical variation. These studies show that a person's neuroanatomy is marked by highly individualized patterns of neuroanatomical variability, which may serve as a distinct neuroanatomical fingerprint that may be utilized for stratification purposes"

Stratifying Individuals Using Hierarchical Clustering

This section details the data-driven method used to group individuals based on their unique brain patterns, providing a practical example of a dimensional and non-categorical approach to understanding human diversity.

"Using hierarchical clustering, IDPs were then stratified according to their spatial similarity (i.e., neuroanatomical affinity) with GABAA subunit classes."

"Across multiple validity indices (see Methods), we discerned an optimal bifurcated clustering solution with a mean bootstrapped Jaccard similarity index of 0.714 for the primary cluster, and of 0.591 for the secondary cluster. Accordingly, our cohort was divided into two neuroanatomically distinct subgroups, each showing a different neuroanatomical association with the limbic and cortical expression signatures of GABAA subunit Clusters 1 and 2 (Fig. 5a)."

"To stratify individuals based on their spatial alignment with GABAA receptor subunit genes, the matrix of spatial correlations was then subjected to hierarchical clustering as outlined above, i.e., using NbClust to identify the optimal number of clusters, and clusterboot to establish their stability. Notably, this approach diverged from using a correlation matrix as input to the clustering algorithm but instead identified consistent patterns of high/low spatial correlations across individuals."

THEORETICAL FRAMEWORKS

The entire study is built on the framework of "imaging transcriptomics," a cutting-edge field that directly supports the idea that our observable brain features are linked to underlying biological diversity. This provides a scientific foundation for rejecting simplistic, purely behavioral labels.

"Imaging transcriptomics has become a power tool for linking imaging-derived phenotypes (IDPs) to genomic mechanisms. Yet, its potential for guiding CNS drug discovery remains underexplored. Here, utilizing spatially-dense representations of the human brain transcriptome, we present an analytical framework for the transcriptomic decoding of high-resolution surface-

based neuroimaging patterns, and for linking IDPs to the transcriptomic landscape of complex neurotransmission systems in vivo."

"Imaging transcriptomics, the study of correlations between gene-expression patterns and spatially varying properties of brain structure and function', has become a powerful tool for exploring the putative molecular underpinnings of neurotypical and neurodiverse brain organization. Here, large open-access repositories featuring genome-wide expression profiles sampled across the brain, e.g., the Allen Human Brain Atlas (AHBA[2]), are used to identify genes with an expression signature that spatially aligns with a structural or functional imaging phenotype."

POPULATION-SPECIFIC FINDINGS

Differences in Findings Between Adults and Children/Adolescents

This section is crucial evidence for Enlitens' argument that assessment tools are not universally applicable. The paper explicitly states that its findings hold for adults but not younger populations and discusses why, highlighting that the very data used to build the model (adult brain atlases) makes it less applicable to other groups. This is a direct parallel to how standardized tests built on one demographic fail others.

"Individuals in Subgroup 1 displayed a pattern of CT variability that positively correlated with the limbic GABAA subunit Cluster 1. IDPs of individuals in Subgroup 2 were positively correlated with the co-expression signatures of cortically-expressed GABAA subunit genes in Cluster 2. As the developmental trajectory of CT has an inverted U-shape across the human life span, positive deviations from the typical trajectory of CT are commensurate with delayed brain maturation. In line with this, individuals - and adults in particular with more atypical CT in the limbic brain circuitry, which was characterized by high expression of the α2- containing GABAA subunit Cluster 1, also had significantly higher levels of anxiety and depression than adults falling into the α1-containing GABAA subunit Cluster 2. Several factors could explain why these correlations were observed in adults but not in children and adolescents. One possibility is a discrepancy between self-reported and parent-reported levels of depression and anxiety, which appears to diminish with age. Additionally, both the AHBA and PET atlas data are derived from adult samples. Thus, transcriptomic associations may be more accurate in adult populations compared to younger age groups."