DOCUMENT SUMMARY

This research paper from Neuron investigates individual differences in the brain's functional connectivity using resting-state fMRI. The authors demonstrate that this variability is not uniform across the brain; it is significantly higher in heteromodal association cortices (areas involved in complex cognition) and lower in unimodal sensory and motor cortices. This functional variability is strongly correlated with evolutionary cortical expansion and anatomical folding patterns, suggesting a deep biological basis for individual differences. A meta-analysis further reveals that brain regions known to predict individual differences in cognitive and behavioral traits are predominantly located in these high-variability zones.

FILENAME

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Related Docs: This paper provides a neurobiological basis for the concepts discussed in speelman_2020 about the ergodic fallacy and the problem of averaging across unique individuals. It also complements yang_2022 by discussing the functional networks involved in higher-order cognition.

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FORMATTED CONTENT

## Summary

The fact that people think or behave differently from one another is rooted in individual differences in brain anatomy and connectivity. Here we used repeated-measurement resting-state functional MRI to explore inter-subject variability in connectivity. Individual differences in functional connectivity were heterogeneous across the cortex, with significantly higher variability in

heteromodal association cortex and lower variability in unimodal cortices[1]. Inter-subject variability in connectivity was significantly correlated with the degree of evolutionary cortical expansion, suggesting a potential evolutionary root of functional variability[2]. The connectivity variability was also related to variability in sulcal depth but not cortical

thickness, positively correlated with the degree of long-range connectivity but negatively correlated with local connectivity[3]. A meta-analysis further revealed that regions predicting individual differences in cognitive domains are predominantly located in regions of high connectivity variability[4]. Our findings have potential implications for understanding brain evolution and development, guiding intervention, and interpreting statistical maps in neuroimaging[5].

## Introduction

The human brain is characterized by striking inter-individual variability in both neuroanatomy and function, which is reflected in the great individual differences in human cognition and behavior[6]. This variability is a joint output of genetic and environmental influences that may impact different brain systems in different ways[7]. Evidence suggests that neural systems for higher-order association and integration are more variable than those for unimodal processing[8].

While structural variability has been extensively studied, individual variability in

functional connectivity has not been systematically investigated[9]. An individual's brain might be best characterized by its

connectome, and intrinsic functional connectivity (measured with resting-state fMRI) can predict individual performance in various cognitive domains[10101010]. Quantifying the spatial distribution of this variability could provide new insights into the neural underpinnings of individual differences and have practical implications for clinical interventions and the interpretation of neuroimaging results[11].

This study uses a unique dataset of 23 healthy subjects, each scanned five times over six months, to assess the spatial distribution of inter-subject functional connectivity variability while controlling for measurement instability[12].

## RESULTS

### Inter-subject Connectivity Variability is Not Uniformly Distributed

The study found that individual differences in functional connectivity are not evenly distributed across the brain[13].

- Highest Variability: The largest differences between individuals were found in the heteromodal association cortex, including the lateral prefrontal lobe and the temporal-parietal junction[14]. When analyzed by functional networks, the

- frontoparietal control and attentional networks demonstrated the highest level of variability[15].
- Lowest Variability: The most consistent connectivity patterns across individuals were found in unimodal sensory and motor cortices[16]. The sensory-motor and visual systems were the least variable networks[17].
- Default Network: The default network demonstrated a moderate level of variability, higher than sensory-motor systems but lower than frontoparietal and attentional networks[18].

**Functional Variability is Highly Correlated with Evolutionary Cortical Expansion**

The brain regions with the highest functional variability are phylogenetically late-developing regions that are essential for complex, human-specific cognitive functions like reasoning and language[19]. To test the hypothesis that this variability has an evolutionary root, the researchers compared their functional variability map to a map of regional

evolutionary cortical expansion (comparing an adult macaque brain to an average human brain).

- Finding: The two maps were significantly correlated (r=0.52), indicating that brain regions that expanded the most during evolution are also the ones that are most variable among individual humans today[20].

**Functional Variability is Associated with Brain Folding, Not Cortical Thickness**

The study then investigated how functional variability relates to anatomical variability.

- Sulcal Depth (Folding): Variability in the brain's folding patterns (sulcal depth) was most pronounced in lateral frontal and temporoparietal regions, consistent with previous findings[21]. This anatomical variability showed a moderate but significant correlation with functional connectivity variability (r=0.30)[22].
- Cortical Thickness: In contrast, variability in cortical thickness showed a very different pattern and was uncorrelated with functional variability[23]. This aligns with the fact that human brain evolution was characterized by a massive surface expansion (leading to more folding) without a significant increase in cortical thickness[24].

**Functional Variability is Linked to Long-Range and Local Connectivity**

The human brain is organized with some areas specialized for local, modular processing and others acting as hubs for integrating information across long distances[25].

- **Finding: Functional variability was strongly and positively correlated with the degree of distant connectivity (r=0.32) but negatively correlated with the degree of local connectivity (r=-0.33)[26]. This suggests that brain regions primarily engaged in local processing (like sensory and motor areas) are highly consistent across individuals, whereas regions that serve as hubs for integrating information across the brain are highly variable.**

**High-Variability Regions Predict Individual Differences in Cognition**

**A PubMed-based meta-analysis was performed to see if the brain regions identified as highly variable in this study overlap with regions previously shown to predict individual differences in cognition and behavior[2727]. The analysis included 15 studies covering personality traits, memory, anxiety, intelligence, and more[28282828].**

- **Finding: The results revealed that approximately 73% of the brain locations previously linked to individual differences in cognitive and behavioral domains are located within the regions of high functional variability identified in this study[29].**

## DISCUSSION

**Potential Causes of High Variability in Association Cortex**

**The high variability in the association cortex is likely the result of several converging factors:**

- **Evolution and Development: These are phylogenetically late-developing regions that undergo a disproportionate enlargement during human evolution and have the most protracted maturation course, leaving them exposed to variable environmental experiences for a longer period during times of high neuroplasticity[30303030].**
- **Weaker Genetic Influence: The structure of these late-maturing areas appears to be less genetically influenced during development, allowing for a greater impact from postnatal environmental factors[31].**
- **Synaptic Plasticity: These regions show the highest rates of synaptic overproduction in early childhood, followed by extensive synaptic pruning, which may provide more "freedom" for experience to shape the final circuitry[32].**

**Clinical Relevance and Implications for Neuroimaging**

**The findings have significant clinical and research implications:**

- **Neuropsychiatric Disorders: While functional variability is crucial for higher cognition, it might also create an increased susceptibility to the formation of abnormal circuitry seen in neuropsychiatric disorders, many of which emerge** during adolescence when these highly variable, long-range connection hubs are finalizing their development[33333333].

- Individualized Therapy: Knowing the distribution of individual variability is critical for personalized medicine. For instance, if a target for surgical resection or therapeutic brain stimulation (like TMS) is in a highly variable area, relying on group averages would be inappropriate, and patient-specific connectivity mapping would be necessary[34343434].
- Interpretation of Group Maps: Neuroimaging results are typically presented as statistical maps averaged across a group of subjects[35]. This study shows that researchers are inherently less likely to get a statistically significant group result in highly variable regions (like the prefrontal cortex) and more likely to get one in low-variability regions (like the motor cortex)[36]. This means the risk of false-negatives is non-uniformly distributed across the brain, a critical consideration when interpreting fMRI studies[37].