Imaging-Genetic Strategies to assess Childhood Cognitive Development

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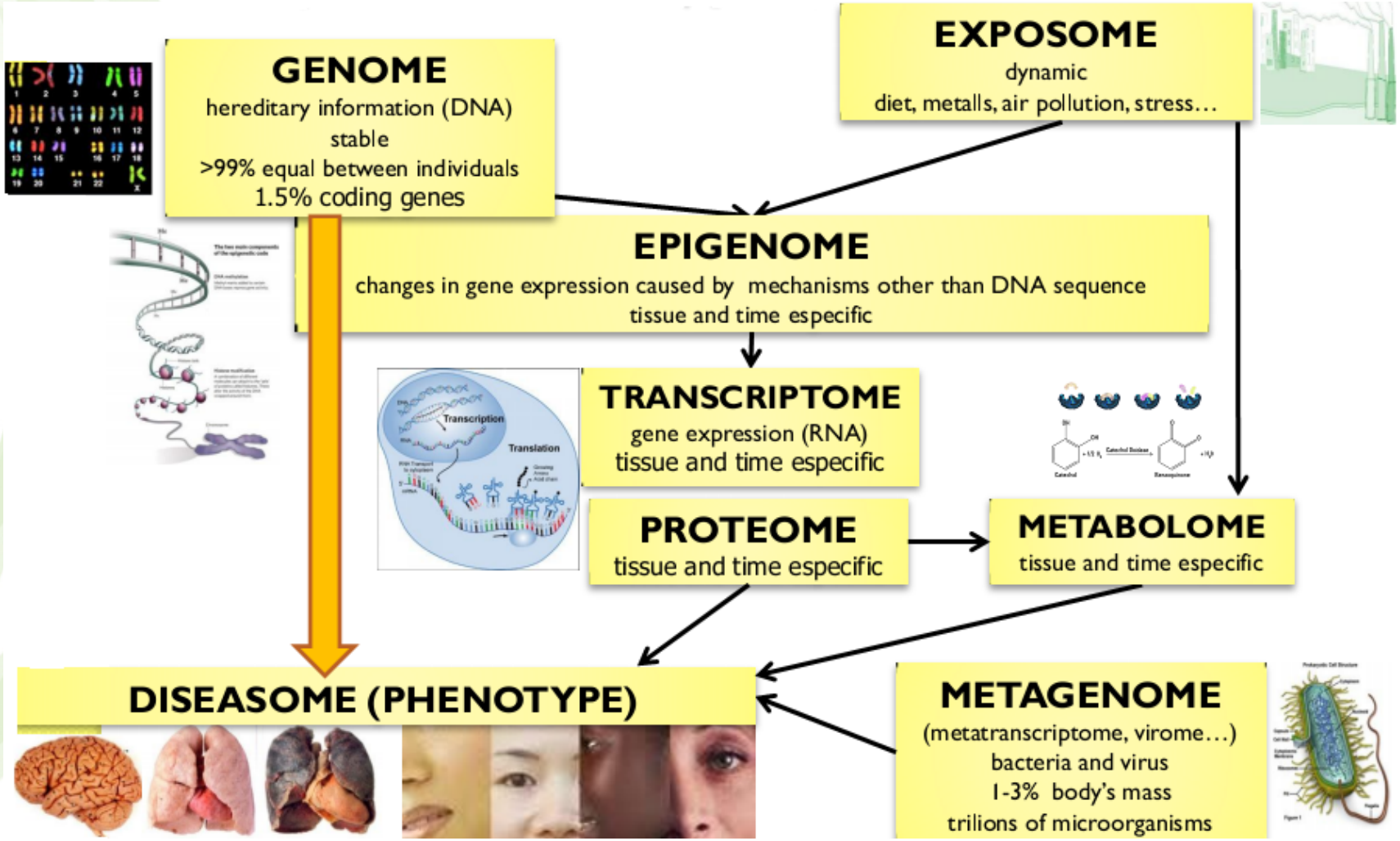
Objective

Research question

Integration of **Genomic** and **Neuroimaging** data
in **childhood cognitive development**.

Introduction - Omics



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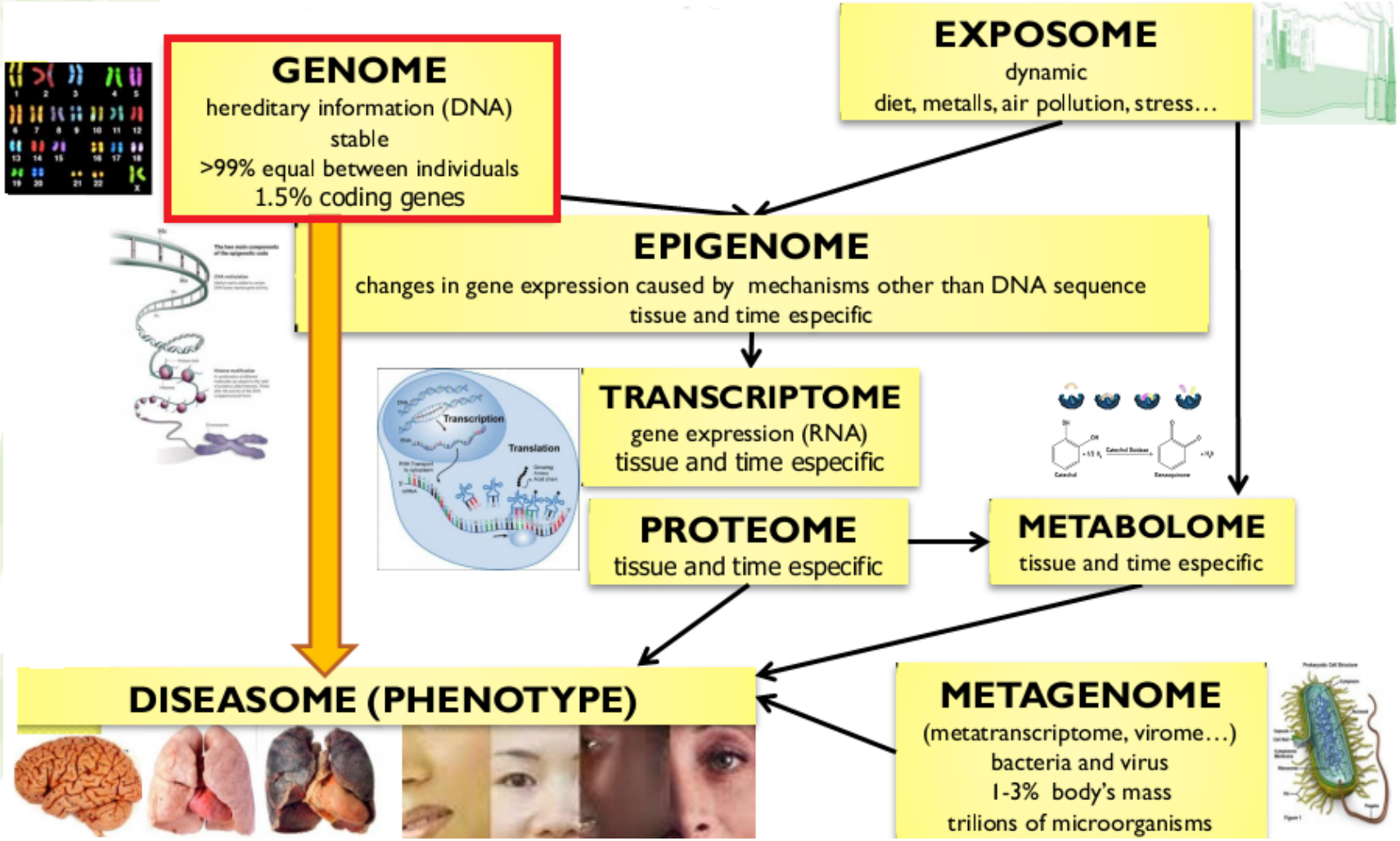
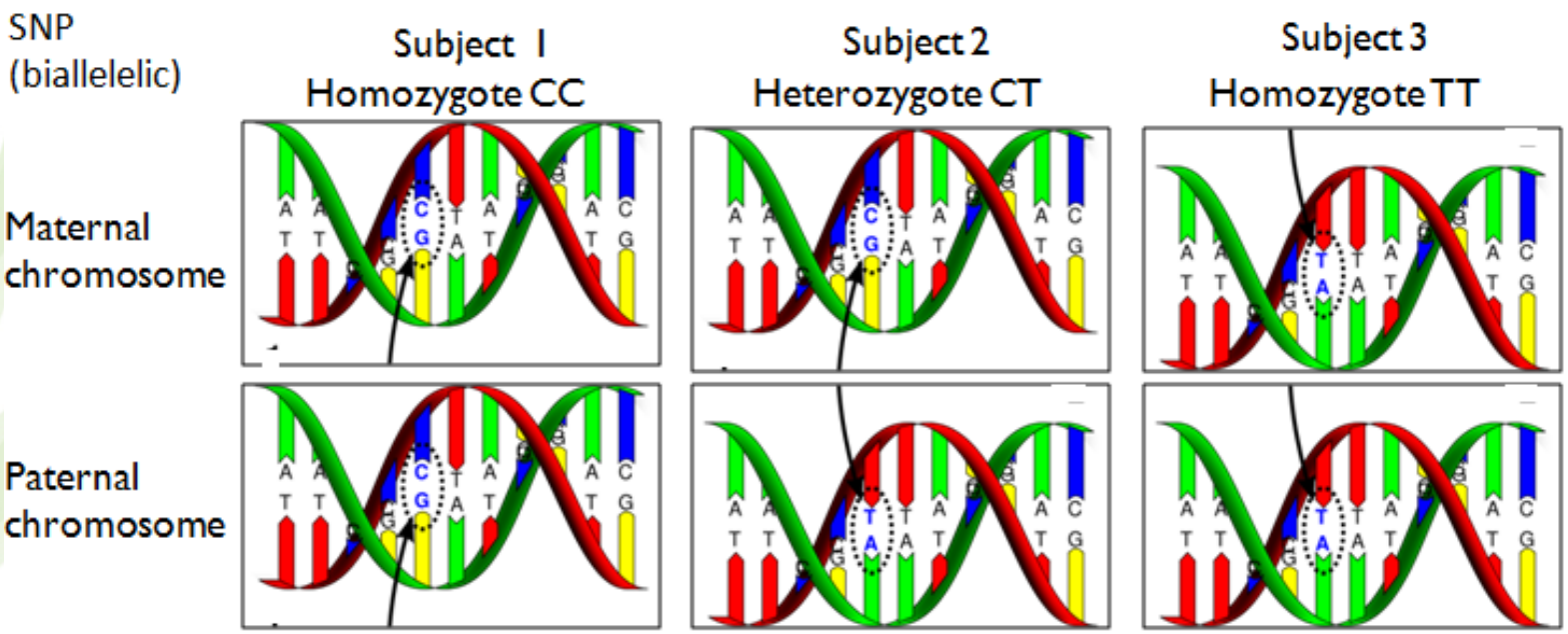


Introduction - Omics

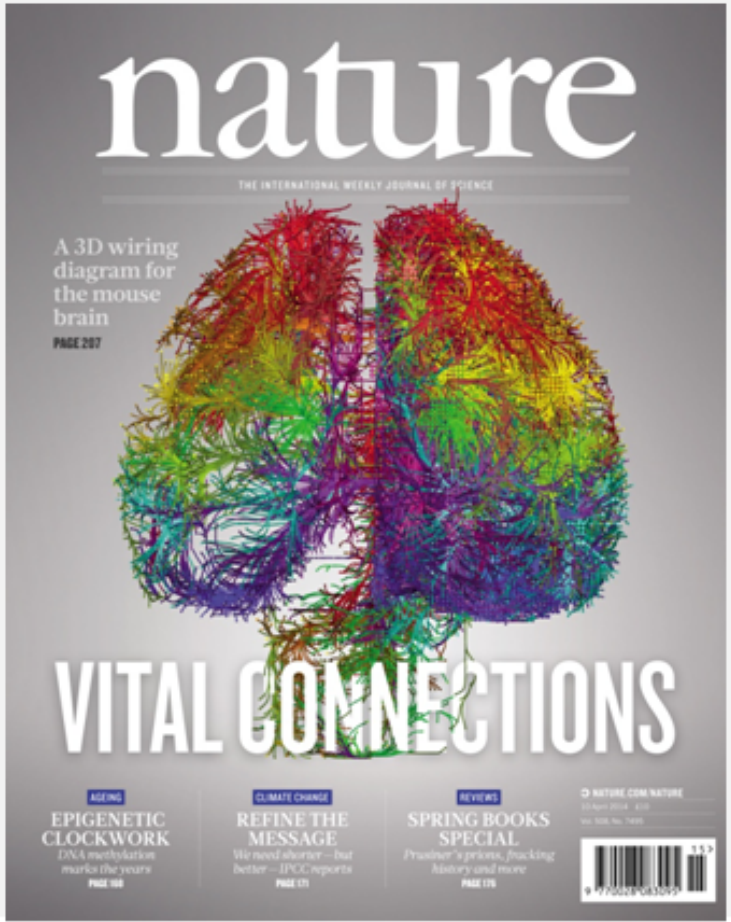
Single Nucleotide Polymorphisms (SNPs) are:

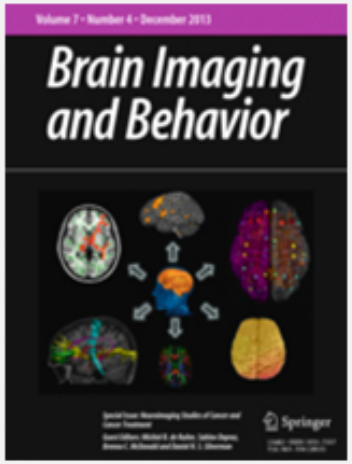
DNA sequence variations that occur when a **single nucleotide** in the genome sequence is **altered**, and it occurs in at least 1% of the population.



Introduction - Neuroimaging

In **recent years** there has been **explosive interest** in using imaging techniques to **explore the human brain**.





Introduction - Neuroimaging

What is Neuroimaging?

Branch of medical imaging which focuses on **take images** of the inside of the **brain** which are used to analyze **how the brain works, and how various activities impact the brain**.

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Why Neuroimaging?

By using **Neuroimaging**, scientist can **address complex issues** that may be beyond the scope of other neurological techniques.

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- Structural Magnetic Resonance Imaging (MRI)
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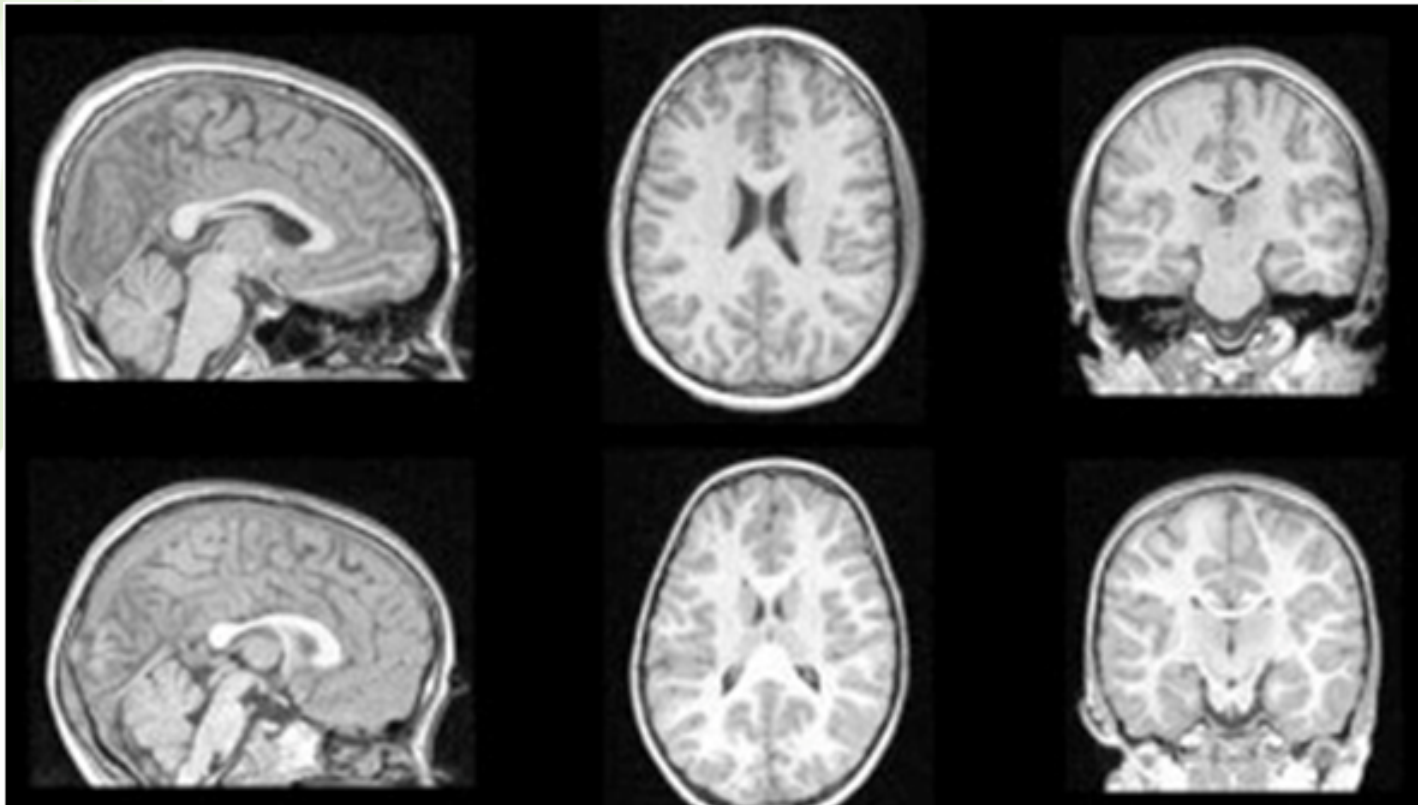

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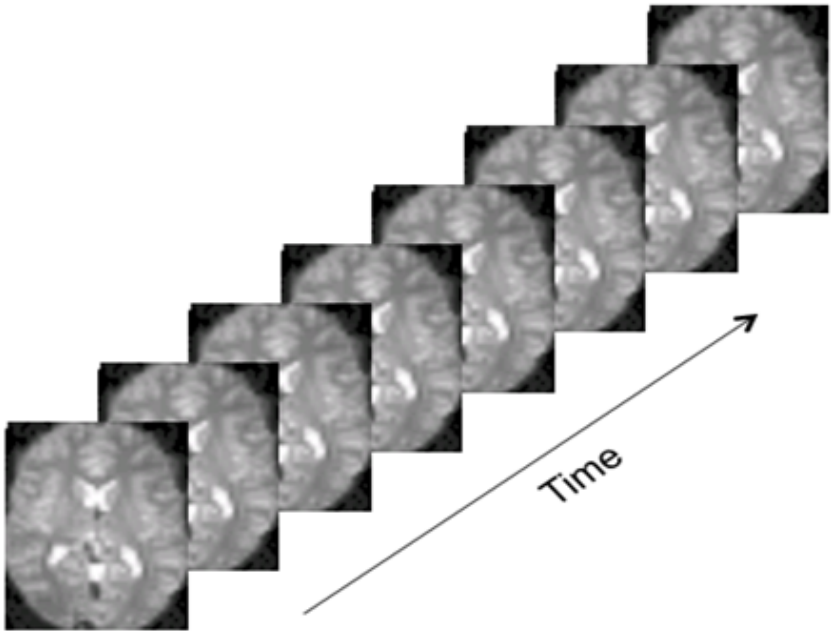

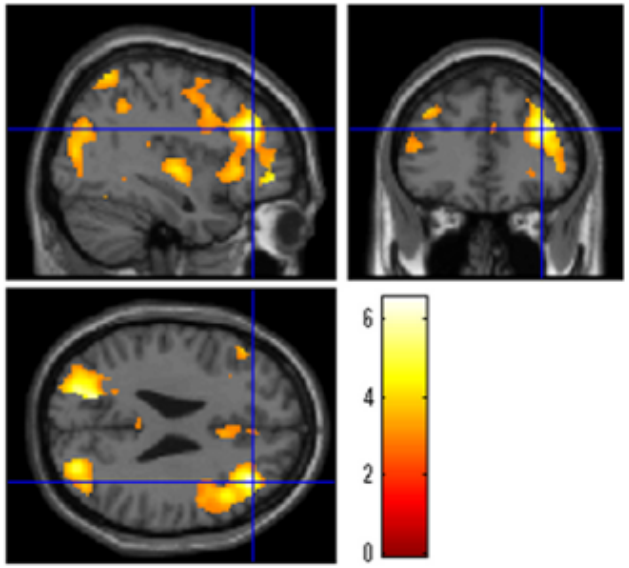

Imaging Genetics

Objective

Combine genetic information and neuroimaging data in the same subjects to **discover neuromechanisms** linked to psychiatric disorders.

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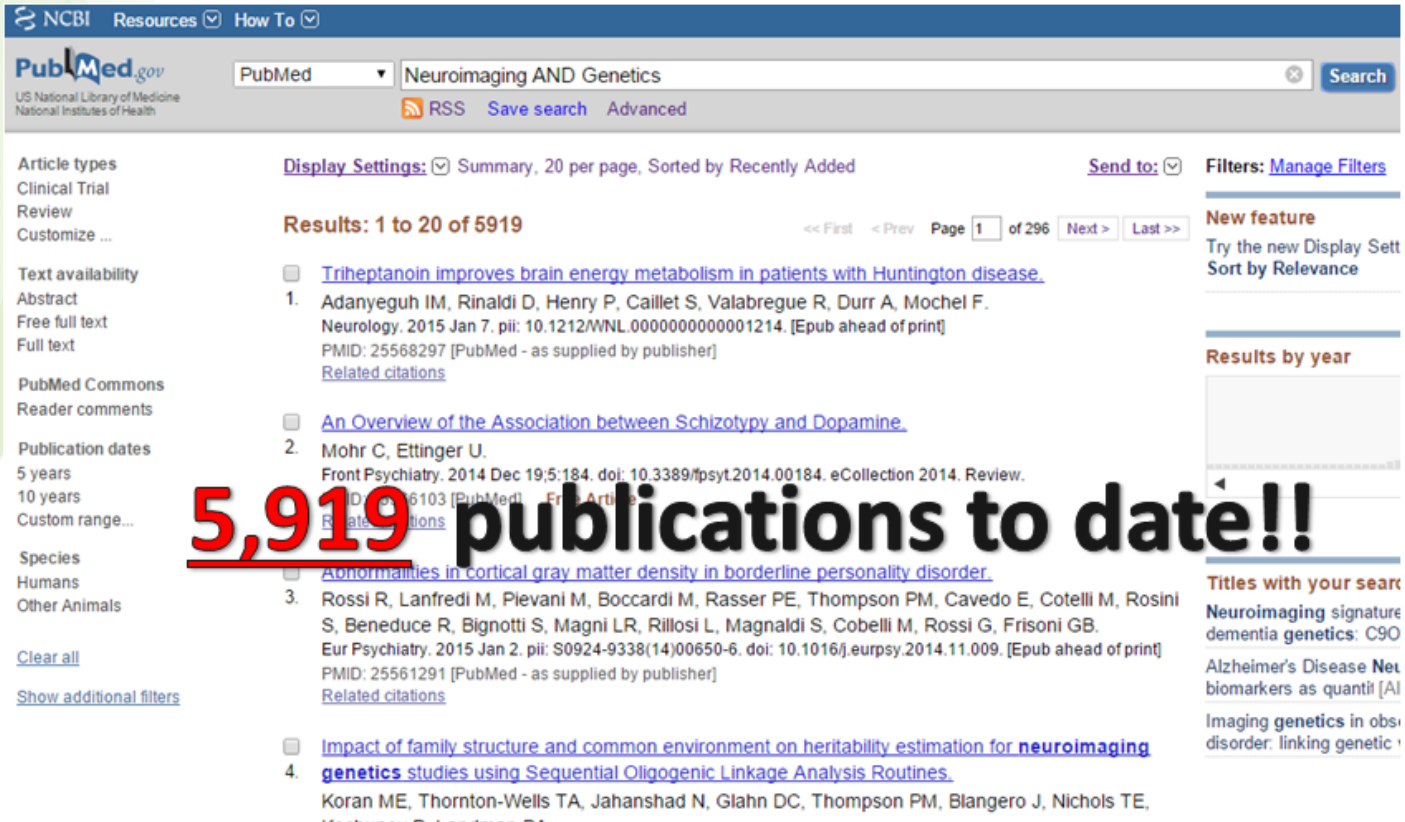
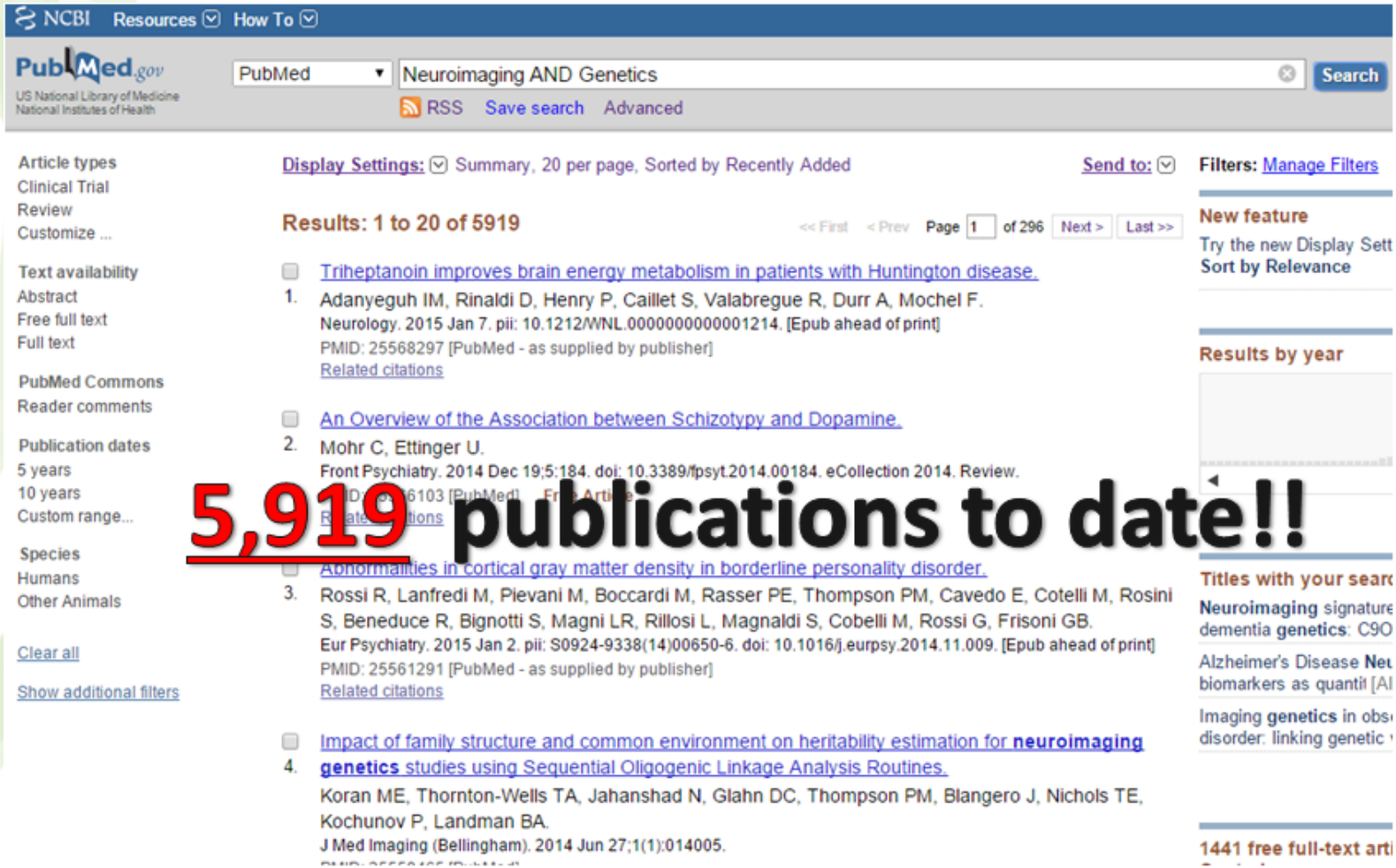


Imaging Genetics

151,902 publications to date!!

Imaging Genetics

Imaging Genetics



Imaging Genetics

Objective

Aim to **identify and characterize genetic variants** that **influence measures derived from brain** images **to better understant human brain structure and function**.

Statistical Strategies

- Univariate-Neuroimaging / Univariate-Genetics
- Multivariate-Neuroimaging / Multivariate Genetics
- Joint multivariate association

Univariate-Neuroimaging / Univariate-Genetics

Univariate-Neuroimaging / Univariate-Genetics

- Consist on a **massive univariate approach**.
- Independent association tests are performed for **whole-brain and whole genome**.
- Around **90**% of published studies are based on this kind of analysis strategy.

Application Example

Integrating **Genome-wide Association** results and **Structural Magnetic Resonance** data for childhood **Attention-deficit hyperactivity disorder (ADHD) symptoms.**

Imaging genetics in ADHD

The aims of this study are:

1. **Identify novel genetic variants** associated with childhood ADHD symptoms in general population.
2. **Extend findings using MRI** to examine potential intermediate neural phenotypes of significant polymorphisms.

Imaging genetics in Attention-Deficit/Hyperactivity Disorder

Stage 1:

Identify novel genetic variants associated with childhood ADHD symptoms in general population.

- **1,592 children** from the BREATHE project.
- **240,103 SNPs** were analyzed using linear regressions.
- **12 SNPs** showed **suggestive evidence** of association with ADHD symptoms ($p < 10E\text{-}05$).
- **6 intragenic SNPs** were **taken forward for neuroimaging analysis**.

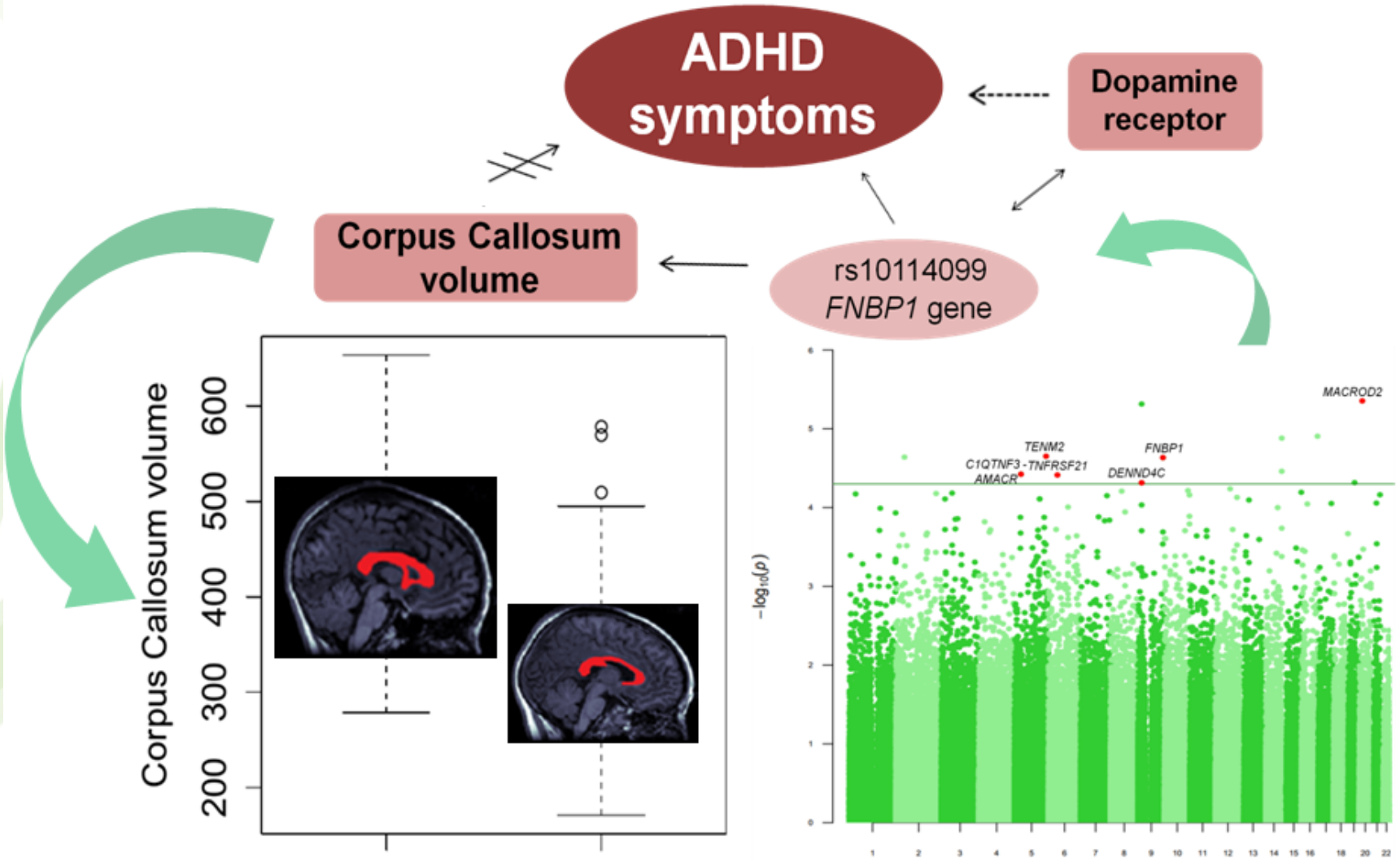
Imaging genetics in ADHD

Stage 2:

Extend findings using MRI to examine potential intermediate neural phenotypes of significant polymorphisms.

- **135 children** who underwent MRI-scanning.
- **66 brain regions** were analyzed using linear regressions
- **3 SNPs** were **significantly associated** with several brain regions
- The **rs10114099** SNP (*FNBP1*) remained **significantly associated** with volume changes in **Corpus Callosum** region after multiple testing correction.

Imaging genetics in ADHD



Statistical Strategies

Limitations in Univariate approaches

- Each **SNP individually**, is **not well suited for detecting subtle effects** of complex traits.
- **Spatial correlation** in imaging data is **ignored** producing a poor reproducibility and low statistical power.
- **Multiple comparison correction** often leaves no significant associations.

Multivariate methods are needed **to improve the statistical power** and the **biomedical knowledge** in Imaging and Genetic studies.

- Multivariate models.
- Joint Multivariate models.

Statistical Strategies

Multivariate methods

Can be used to **model the interaction** between SNPs or the **join effect** of multiple SNPs on imaging traits.

Common multivariate genetic strategies:

- Gene set analysis
- Sparse Regression analysis

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- Sparse Regression analysis

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Statistical Strategies

Join multivariate methods

To better capture the multivariate nature of the data and significantly **reduce the number of statistical tests**.

Common strategies:

- Canonical Correlation Analysis (CCA)
- Independent Component Analysis (ICA)
- sparse Reduced-Rank Regression (sRRR)

Future perspectives

- **Integrate various types of data** relevant to imaging genetics, beyond just two modalities.
- **Further developing current methods** and **integrating more information** will continue to be an important research frontier.
- These approaches will provide a **more unified understanding of neural mechanisms involved in human behavior** and its disruption in psychopathologies

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