Understanding the Developing Behavioral Phenotype: Focus on Imaging Correlates

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Understanding Individuality
Individuality

• Relatively persistent behavioral attributes distinguishing otherwise demographically similar individuals,
  – such as emotional or cognitive biases, accumulated domain-specific knowledge, or level of fluency of mental skills.
• Meaningful only within a developmental context.
  – For example, a given proficiency level for a specific skill may be high among age peers in the culture but low among older peers.
• Thus a behavioral phenotype emerges through the cumulative effects of factors influencing it over the life of the individual.
Individuality

- A domain-specific behavioral phenotype of a developing child can be modeled as a function of the effects of:
  - 1) the hypothetical domain-relevant neural genotype,
  - 2) environmental effects on the neural apparatus relevant to the skill or domain (e.g., early brain damage or toxicity),
  - 3) cumulative experiences encountering and manipulating material in the domain, and
  - 4) interactions between these factors.
Preview

- Imaging studies of the developing neural architecture (results from PING).
- Behavioral correlates in children
- Interpretation of the associations
- Effects of genetic variation
- A conceptual framework for integrating the evidence
Imaging Studies of Postnatal Brain Development

The neural architecture undergoes continuous remodeling, not just during the preschool years, but throughout childhood and adolescence.

Specific Aim:
Create a public pediatric imaging-genomics database

Participants:
Ages 3-20
Screened and initially consented
> 1700
Key deliverables QC’ed acceptable
> 1200

Key Deliverables:
- Demographic, Neuromedical History & Family History Data
- Neuropsychological Assessment using NIH Cognition Toolbox
- Social-emotional phenotypes in a subset (PhenX Rising project)
- Multimodal Imaging (T1, T2, HARDI, resting state fMRI)
- Genome-wide genotyping
Annualized rate of change in cortical anatomy

Thickness

Volume

Age in years

n = 637
308 females
329 males

Tim Brown, Josh Kuperman, Terry Jernigan, and Anders Dale for the PING Study
White Matter Growth Associated with Post-natal Proliferation of Oligodendrocytes and Myelin Deposition
Maturation-dependent microstructure length scale in the corpus callosum of fixed rat brains by magnetic resonance diffusion–diffraction (Weng et al., 2007)

Increase in size and myelination in corpus callosum axons of rats 84 (left) and 21 (right) days old.
N = 1042, Sex effect: Fs > 25, ps < .0001
N = 1019, Age effect: $p < .0001$
Prediction of Individual Brain Maturity Using fMRI
(Dosenbach et al., Science, 2010)

• “Functional maturation is driven both by the segregation of nearby functional areas,
  – through the weakening of short-range functional connections,
• and the integration of distant regions into functional networks,
  – by strengthening of long range functional connections.”

N = 238
R² = .55
Neuroanatomical Assessment of Biological Maturity
(Brown et al., Current Biology, 2012)

231 brain phenotypes: T1 = 45, Diffusion = 124, T2 = 62
Neuroanatomical Assessment of Biological Maturity
(Brown et al., Current Biology, 2012)

- N = 885
- Mean prediction error of 1.03 yrs.
- Employed a multivariate distance measure and “leave-one-out” cross-validation
- Determined the age that provides the best fit for each subject by comparing measures for that subject to smooth, nonlinear age trajectories (of the mean and covariance) derived from all other individuals.
- Stringently controlled overfitting.

- Multimodal solution (R²=.92)
- T1 = 45 (R²=.82), Diffusion = 124 (R²=81), T2 = 62 (R²=.83)
How do you summarize your main findings?

Multimodal model

Rho = 0.96, R² = 0.92
Mean error = 1.03 years
Neuroanatomical Assessment of Biological Maturity
(Brown et al., Current Biology, 2012)
Behavioral Correlates of Imaging Measures

Individual differences in these neural architectural parameters are mirrored, to some extent, by behavioral individual differences.
Study of Behavioral Individual Differences in Danish Children
Madsen et al. 2009; Vestergaard et al. 2010; Madsen et al. 2011

- 95 school children, 7-13 years old
- sMRI, DTI, cognitive testing
- Inhibitory function measured with CANTAB Stop Signal Task (SSRT)
- Spatial working memory measured with CANTAB self-ordered search task
- Choice reaction time measured with CANTAB reaction time task
Stop Signal Task

SST design

Go trial (75%)

Stop trial (25%)

Response

central sulcus
Precentral sulcus
Inferior frontal sulcus

preSMA
IFC
STN

• Individual differences in children’s inhibitory function is related to FA differences within the neural circuit previously implicated in SST performance.
Spatial Working Memory Task
Spatial Working Memory Performance Related to FA in Superior Longitudinal Fasciculus
Brain microstructural correlates of visuospatial choice reaction time in children
KS Madsen, WFC Baaré, A Skimminge, M Vestergaard, HR Siebner and TL Jernigan (2011)
Individual Differences in Children’s Performances on Cognitive Tasks Mirror Differences in Fiber Tract Structure

Spatial working memory

Psychomotor speed

Response Inhibition
Reduced Surface Area of VMPF Cortex is Associated with Childhood Anxiety (Newman et al., SfN 2012)

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$N = 234$
High Anxiety in Children Associated with a Developmental Neural Phenotype
Behavioral Variability is Related to Individual Differences in Brain Architecture

- Performance on behavioral tasks across multiple domains correlates modestly with gray matter and fiber tract structural characteristics.
- The associations remain after controlling for age and global parameters.
- It appears that profiles of behavioral attributes are reflected in neural architectural patterns.
- Recent evidence suggests that some behavioral phenotypes may be associated with developmental endophenotypes.
How should we interpret these associations?

• To what extent might they reflect early patterning in the nervous system due to genetic variability?

• To what extent might they reflect cumulative neuroplastic effects on the neural architecture associated with experience and learning?
What role does development itself play?

The associations could reflect intrinsically or extrinsically driven differences in phase of biological maturation.
Do genetic factors mediate the variability in neural architectures associated with behavioral differences in children?
Genes Exert Strong Effects on Brain Morphology

• Twin studies have revealed high heritability of brain morphology.

• Panizzon et al. (2009) recently reported that 2 attributes of the neural architecture, cortical surface area and cortical thickness are both highly heritable, but exhibit no genetic association.

• Genetic effects on developmental trajectories have now also been observed.
Area Patterning of the Mammalian Cortex

O’Leary et al., Neuron, 2007
Genetic Architecture of Human Cortical Arealization (VETSA project)

Fuzzy Clustering Based on Genetic Correlation Matrix: 4 Cluster Solution

Chi-Hua Chen et al, Neuron, 2010
Genetically Informed Hierarchical Cortical Parcellation

- Parcellation of the cortex based on clustered genetic correlations among vertex measures of cortical expansion (Chen et al., Science, 2012).
- Data from the Vietnam Era Twin Study of Aging (Kremen et al., Twin Res Hum Gen, 2006).
GWAS of Relative Occipital Areal Expansion

SNP rs6116869 in Gene GPCPD1

Bakken et al., PNAS, in press
Developmental Neural Phenotype Associated with DAT1 polymorphism (Madsen et al., HBM, 2012)
Developmental Behavioral Phenotypes Associated with DAT1 polymorphism (Schork et al. SfN, 2012)

SSRT Results

Multiple regression analysis on 154 subjects (79 Females) testing for a main effect of genotype and a genotype x age interaction on SSRT, adjusting for site, age, age\(^2\).
Experience-Dependent Plasticity

Neural architectural parameters that exhibit high heritability appear to be modified by intensive interventions likely to engage specific neural circuitry.
Conceptual Model

• Variations in early genetic patterning in brain, e.g., of cortex and connecting fiber tracts (and many other neural parameters not strictly architectural), may introduce very subtle biases in the infant’s sensorimotor processing.

• In addition, other developmental phenotypes may continue to emerge throughout childhood, reflecting the effects of genetic variants on ongoing maturational processes.

• In part because of these effects, as development proceeds, some types of information may garner more or less salience to the individual.
Conceptual Model (cont’d)

• In some individuals, this may lead to relative inattention to – and languishing skills in - some domains relative to others (e.g., reading, mathematics, social interaction, etc.)

• These differences may be accompanied by emotional outcomes that have effects on reward system dynamics (engagement – avoidance).

• Such effects on reward processing may further enhance or reduce active processing of specific types of material.

• Conceptual and reward effects are likely to influence both the behavioral phenotype and the associated neural circuitry.
Some Implications

- If subtle neural effects present early in life cascade into individual differences through the development of perceptual-motor and motivational biases, it may be more useful to think of these experiential mediators as the proximal causes, rather than the neural origins, *per se*.
- Domain bias and reward dynamics that constrain learning, or limit functional adaptation, are likely to be preventable and reversible with intelligent intervention.
- Such intelligence depends upon a better understanding of the ways that genetic variation and experience interact to make us unique individuals.
Acknowledgements

• PING Investigators
• UCSD Center for Human Development
• Tim Brown (MMIL), Erik Newman (CHD)
• DRCMR, Copenhagen University
• Kathrine Skak Madsen and William Baare, HUBU
• National Institute of Drug Abuse & National Institute of Child Health and Human Development
• Danish Medical Research Council & Lundbeck Foundation

Anders Dale