Intergenerational Neuroimaging of Human Brain Circuitry

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Abstract

Neuroscientists are increasingly using advanced neuroimaging methods to elucidate the intergenerational transmission of human brain circuitry. This new line of work promises to shed insight into the ontogeny of complex behavioral traits, including psychiatric disorders, and possible mechanisms of transmission. Here, we highlight recent intergenerational neuroimaging studies and provide recommendations for future work.

Keywords

imaging genetics; neuroimaging; intergenerational transmission; mega-analysis; cross-fostering

Extensive work identifying risk genes indicates that complex behaviors (e.g., depression, anxiety) in humans are in part heritable \textsuperscript{[1]}. Evidence that parental behavior and experiences (e.g., trauma exposure) can lead to epigenetic changes in offspring nevertheless indicates that intergenerational transmission of traits and behaviors includes both genetic and non-genetic (epigenetic, environmental) influences \textsuperscript{[2–3]}. Genetic and epigenetic effects, however, occur at the molecular level and are distal from complex behavioral phenotypes \textsuperscript{[4]}. Intermediate phenotypes or endophenotypes at the level of brain circuitry lie in the lacuna between DNA sequences and clinical symptoms and presumably have a simpler molecular basis than disease states, thereby allowing researchers to focus on delineating the neurobiological architecture specific to the illness \textsuperscript{[4]}. Thus, understanding the intergenerational transmission of brain circuitry by examining similarity or concordance of endophenotypes in parent-offspring dyads may shed insight on inheritance mechanisms involved in complex behavioral traits, the pathophysiology of brain-based diseases, potential biomarkers of treatment success (e.g., increased myelination in corticolimbic tracts) and modifiable targets (e.g., prenatal nutrition) for interventions.

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Here, we highlight recent neuroimaging studies that advance our understanding of the intergenerational transmission of human brain circuitry, with a focus on endophenotypes for psychiatric disorders. We discuss strengths and limitations of each approach and offer recommendations for future research.

Consortia pooling genomic and neuroimaging data from multiple sites have been important in generating normative data across diverse populations and identifying potential endophenotypes of psychiatric disease [5]. The ENIGMA consortium, for example, has applied standardized preprocessing protocols to diffusion imaging data from five large twin/sibling studies and one extended pedigree study [6]. Researchers then computed heritability estimates of fractional anisotropy (FA), a quantitative index of white matter properties useful for understanding tract organization, using meta-analysis and mega-analysis approaches. In both approaches, the variance of the brain phenotype of interest, FA, was modeled by the sum of the variance due to additive genetic factors and the variance due to environmental effects (shared and individual). The additive genetic effects were estimated from correlations among family members, structured by a kinship matrix, and heritability was computed as the ratio of additive genetic variance to total phenotypic variance. Researchers found significant heritability effects in whole-brain and tract-specific FA across all cohorts (although cohort-specific effects were also found), with highest heritability in the corpus callosum and lowest heritability in the fornix. Importantly, these studies identified whole-brain and tract-specific FA as potential endophenotypes for future imaging genetics studies investigating psychiatric disorders. These studies, however, relied heavily on twin/sibling data, which do not provide parental information and therefore cannot directly assess intergenerational effects. Furthermore, different correlation structures depending on the family design (e.g., including grandparents or cousins) will yield different heritability estimates that may have an impact on meta-analytic approaches, which assumes that larger cohorts yield more precise heritability estimates [7]. Assuming equal sample sizes, twin designs provide more precise estimates of heritability, but a sufficiently large extended pedigree design has the advantage of better estimating the covariance structure in a kinship matrix and providing heritability estimates that are less likely to be inflated by effects of shared environment [7].

Some researchers have begun to estimate shared heritability of brain and behavior phenotypes using extended pedigree designs. For instance, in a multiplex-multigenerational study of people with schizophrenia, Roalf et al. used a standard measure of computing heritability and modeled each individual’s regional brain volume (or shape) as a function of additive genetic effects estimated from correlations among family members, individual-specific residual environmental factors, and covariates (age, sex, site); the authors found significant heritability effects in limbic volume and shape, suggesting these to be potential endophenotypes for schizophrenia [8]. Similarly, Fox et al. measured FDG-PET and behavioral responses during a well-standardized task of threat processing in a large familial sample of preadolescent rhesus monkeys [9]. The authors computed heritability of brain metabolism, heritability of a behavioral anxiety phenotype, and the bivariate heritability of both phenotypes, then conducted voxelwise bivariate genetic correlations, and found strong associations between metabolism in a prefrontal-limbic-midbrain circuit and anxious
behavior. Therefore, using neuroimaging data to conduct genetic correlations is a powerful way to identify brain regions that share genetic factors with behavioral traits (Fig 1A). Extended pedigree designs, however, are more susceptible to uncontrolled age-related influences (which we discuss further below when discussing general limitations and future directions) and are more logistically difficult to recruit (the sample studied by Fox et al., while representative of rhesus monkey families who interbreed, is also not typical of human families). Nevertheless, we expect that future intergenerational neuroimaging studies in humans utilizing extended pedigree designs will be poised to identify robust endophenotypes.

Although we anticipate that large studies with extended pedigree designs will aid in identifying robust intergenerationally transmitted endophenotypes, other researchers have directly measured concordance of an endophenotype of interest between parent-offspring dyads using smaller cohorts that are more logistically feasible. Foland-Ross et al. compared cortical thickness measurements in two groups of mothers (depressed, nondepressed) and their nondepressed daughters (categorized accordingly as high- or low-risk) [10]. Cortical thickness in regions-of-interest (ROIs) that showed significant differences between depressed and nondepressed mothers were computed for each daughter; hierarchical linear regression with mother’s cortical thickness and risk status were then used as predictors of regional cortical thickness. The authors found that cortical thinning in depressed but not nondepressed mothers significantly predicted cortical thinning of the same regions in their daughters. While these results suggest that cortical thinning is a matrilineal endophenotype of depressive risk, no other dyads (e.g., father-daughter) were assessed.

In the first study to test sex-specific intergenerational effects of human brain structure, Yamagata et al. examined gray matter volumes (GMVs) in a voxelwise manner in biologically related parent-offspring dyads: mother-daughter, mother-son, father-daughter, and father-son [11]. Voxelwise statistical maps within the corticolimbic ROI comparing GMV of mother-daughter dyads to other dyads showed stronger positive correlations between mother-daughter dyads in the amygdala, hippocampus, and prefrontal cortex, suggesting female-specific transmission of this circuitry, and consistent with other work strongly implicating corticolimbic circuits in mood and anxiety disorders [1]. While this approach differs from a sex-specific kinship matrix in that the proportion of shared genetic information among individuals is not modeled, this approach by Yamagata et al. represents an important next step in this area of research by assessing sex-specific transmission patterns (and possibly parent-of-origin effects) and is ideal for investigators with specific hypotheses regarding mechanisms of intergenerational transmission of brain circuitry (e.g., matrilineal versus patrilineal transmission; Fig 1B).

Nevertheless, the relative contribution of genetic, epigenetic, and environmental factors in the intergenerational transmission of brain circuitry is unclear. Moreover, the developmental stage (prenatal, postnatal) at which these different influences are instantiated is not known. In animal work, cross-fostering designs are used to disentangle inherited factors from pre- and postnatal influences [12]. Although human studies cannot randomly assign offspring to prenatal conditions, the rapidly increasing number of children born via in vitro fertilization (IVF) (1% of ~4 million newborns in 2010 in the US) with surrogate parents now makes it
possible to conduct natural cross-fostering studies in humans. For example, Rice et al. examined the records of 779 first-grade children born through IVF either by a related or unrelated mother [13]. While the authors found that smoking during pregnancy predicted offspring birth weight as well as offspring antisocial behavior in both genetically related and unrelated pregnancies, only related dyads showed a significant association between maternal smoking and offspring antisocial behavior. These results rule out prenatal factors as a mechanism between maternal smoking behavior and offspring antisocial behavior and demonstrated the feasibility of human cross-fostering studies in disentangling origins of complex behavioral traits during early life. Using similar methods, Gaysina et al. assessed children from biological, adopted, and IVF families and found significant associations between maternal smoking during pregnancy and conduct problems in children reared by genetically related and unrelated mothers [14], suggesting that, unlike for antisocial behavior, maternal smoking is a prenatal risk factor for conduct disorder. While this design is not without confounds (e.g., age differences between donor and recipient parents, potential medical issues in recipients, possibility of IVF inducing epigenetic effects in offspring), natural cross-fostering neuroimaging studies using IVF designs will allow for the first time dissociation between prenatal influence from other intergenerational mechanisms of brain circuitry.

Future studies are needed to address current limitations and gaps in this emerging field. Neurodevelopmental factors especially must be considered; children and adolescents, for instance, exhibit different structural and functional characteristics in most brain regions than do older adults [15]. While the studies reviewed here often included age as a covariate, age was typically modeled as a linear effect (although see the studies by ENIGMA [6] and Fox et al. [9]), despite evidence that nonlinear trajectories exist, depending on brain structure (e.g., hippocampus has a different trajectory than prefrontal cortex) and characteristic (e.g., cortical thickness has a different trajectory than surface area) [15]. Future studies comparing parent-offspring dyads or that include individuals spanning a wide age range will need to account for developmental effects specific to the trajectory of the endophenotype of interest, perhaps by computing individual deviance from normative data. Finally, no studies to date have examined the concordance of brain phenotypes between all genetic combinations (related and unrelated) of parent-offspring dyads, or examined pre-versus postnatal effects. Future cross-fostering IVF neuroimaging studies will be able to compare different types of IVF families such as homologous surrogacy, donor egg pregnancy, and heterologous surrogacy in order to dissociate genetic, prenatal, and postnatal environmental influences on parental and offspring endophenotypes (Fig 1C). And while it is likely that mega-analyses across multiple sites will ultimately be needed to robustly detect intergenerational patterns of neural circuitry, such methods are more amenable to task-independent data (e.g., structure, resting-state) that are less heterogeneous in experimental design and pre- and post-processing methods. Indeed, no human studies to date have examined intergenerational neural patterns using task-based neuroimaging. Circuits derived from well-validated tasks have the advantage of directly measuring brain function associated with a behavioral or psychological construct of interest rather than assuming function based on reverse inference. Genetic correlations computed from bivariate estimates of heritability from task-based brain and behavioral phenotypes are therefore capable of identifying robust endophenotypes.
underlying key disease-related constructs [9]. To promote mega-analyses, future studies may consider adopting standardized tasks, such as tasks recommended by NIMH RDoC.

In summary, intergenerational neuroimaging in humans holds significant implications for basic, developmental, and clinical neurosciences. We have highlighted recent approaches, including genetic correlations from large multiplex cohorts, direct estimates of concordance in parent-offspring dyads, and the exciting possibility of natural cross-fostering designs using IVF. We anticipate that these approaches will initially be used by individual research groups and should therefore adopt standardized neuroimaging tasks and preprocessing protocols, with the aim that consortia conducting mega-analyses of pooled data will identify the most reproducible and robust intergenerational patterns of human brain circuitry.

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GLOSSARY

Heritability
Amount of variation in a phenotypic trait attributable to genetics and is therefore not specific to intergenerational (i.e., parent to offspring) effects, which may include non-genetic effects.

Epigenetic
Regarding changes in the microstructure or expression of genes (e.g., DNA methylation, histone modification) without altering the actual DNA sequence. While parental experience and environmental effects (pre-and postnatal) can lead to epigenetic changes in offspring, whether acquired epigenetic changes can propagate through the germline and cause behavioral change in subsequent generations in humans still remains controversial [3].

Intergenerational transmission
The transfer of traits between parent to offspring, which includes genetic and non-genetic influences. For example, the impact of prenatal effects (e.g., parent nutrition, in utero environment), as well as postnatal rearing effects and other environmental factors could lead to epigenetic or behavioral changes in the offspring and are thereby intergenerationally transmitted.

Endophenotype
A stable phenotype that is heritable, co-segregates with the illness of interest, is not state-dependent, is present at a higher rate within affected families, can be reliably measured, and is specific to the illness of interest [4].

Meta-analysis
A statistical technique for combining results from independent studies without requiring raw data. The weights for effect sizes are based on the precision of the effect size estimates per study. Generally, the precision of the effect size is directly related to the study’s sample size, thus sample-size weighted estimates are often used in meta-analyses [7].

**Mega-analysis**

Because meta-analyses are limited in detecting effects since summary statistics are computed from each cohort separately, this technique for combining post-processed data from independent studies into a single analysis is more powerful and allows for more complex analyses.

**Kinship matrix**

Matrix that represents the probability that a random gene between pairs of related individuals is identical by descent (e.g., identical twins have approximately a 100% probability parent-offspring have approximately 50% probability).

**Genetic correlation**

Proportion of variance that two traits share due to genetic causes.

**Parent-of-origin effects**

When the phenotypic effect of an allele depends on whether it is inherited from the mother or father and is typically characterized through epigenetic mechanisms of genomic imprinting. Parent-of-origin effects are implicated in complex trait variation.

**References**


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FIGURE 1. Schematic of intergenerational imaging designs and methods (all images are only illustrative)

(A) As in Fox et al. [10], heritability of behavioral and brain phenotypes can be used to compute genetic correlations in neuroimaging data to identify regions where there is shared genetic influence is common to both phenotypes. (B) As in Yamagata et al. [12], neural concordance among all parent-offspring dyads as measured by correlations can be compared and sex-specific tests can be performed. (C) Future directions: natural cross-fostering using IVF permits assessment of genetic, prenatal, and postnatal effects on parent-offspring brain phenotypes.
is egg donor and birth mother), donor egg pregnancy (mother is not egg donor but is birth mother), or heterologous surrogacy (mother is egg donor but not birth mother).