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Intergenerational transmission of brain structure and function in humans:

A narrative review of designs, methods, and findings

(Running title: Intergenerational neuroimaging)

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Graphical abstract

Intergenerational transmission of brain structure and function in humans

What are the neural underpinnings of the intergenerational transmission of cognitive and affective phenotypes?

METHODOLOGY OF THE PARENT-CHILD DESIGN

A diversity among studies in:



Measures (structural/functional)



Experimental designs



Statistical analyses (univariate/multivariate, voxel-wise/ROI, spatial/temporal)

METHODOLOGY OF THE MULTIGENERATIONAL DESIGN



Measures (structural/functional)



Healthy or affected extended pedigrees



Standardized statistical analysis (voxel-wise/ROI)

INTERGENERATIONAL TRANSMISSION: MAIN FINDINGS

Identification of cerebral markers that improve our general understanding of psychiatric and neurodevelopmental disorders



Factors influencing parent-child similarity:



Age or pubertal status of the child



Sex of the parent and the child



Parental education and behavior

FUTURE DIRECTIONS FOR THE PARENT-CHILD DESIGN



- Consensus on methodology (structural features, functional tasks)



- Longitudinal studies



- Whole-brain voxel-wise analysis
- Control for unrelated dyads

FUTURE DIRECTIONS FOR THE MULTIGENERATIONAL DESIGN



- Consensus on methodology (structural features, functional tasks)



- Comparing affected pedigrees to healthy pedigrees



- More control for shared environment

Abstract

Children often show cognitive and affective traits that are similar to their parents. Although this indicates a transmission of phenotypes from parents to children, little is known about the neural underpinnings of that transmission. Here, we provide a general overview of neuroimaging studies that explore the similarity between parents and children in terms of brain structure and function. We notably discuss the aims, designs, and methods of these so-called *intergenerational* neuroimaging studies, focusing on two main designs: the parent-child design and the multigenerational design. For each design, we also summarize the major findings, identify the sources of variability between studies, and highlight some limitations and future directions. We notably argue that the lack of consensus in defining the parent-child transmission of brain structure and function leads to measurement heterogeneity, which is a challenge for future studies. Additionally, multigenerational studies often use measures of family resemblance to estimate the proportion of variance attributed to genetic versus environmental factors, though this estimate is likely inflated given the frequent lack of control for shared environment. Nonetheless, intergenerational neuroimaging studies may still have both clinical and theoretical relevance, not because they currently inform about the etiology of neuromarkers, but rather because they may help identify neuromarkers and test hypotheses about neuromarkers coming from more standard neuroimaging designs.

Keywords

Intergenerational neuroimaging; Cerebral marker; Intergenerational transmission; Parent-child similarity; Multigenerational study; Heritability

Highlights

- We review neuroimaging studies investigating neural markers of traits transmission
- Studies have used both parent-child and multigenerational designs
- Studies provide insights but suffer from lack of methodological standardization
- Multigenerational studies should also account for shared environment

1. Introduction

Children often show traits, both cognitive and affective, that are similar to their parents. For example, parents and children tend to be similar in terms of general intelligence (Bjorklund et al. 2009; Black et al. 2009; Anger and Heineck 2010), executive control abilities (Goos et al. 2009; Pingault et al. 2021), and academic skills (Bernabini et al., 2021; Braham and Libertus, 2017; Navarro et al., 2018, Brown et al., 2011; van Bergen et al., 2015). Children's emotional lability and dysregulation are also positively correlated with parental emotional dysregulation (Buckholdt et al. 2014; Li et al. 2019), as are signs of depression (Gotlib and Hammen 2009). Therefore, it is largely undisputed that there is a significant phenotypic similarity between parents and children, which suggests an intergenerational transmission of traits within families.

Over the past two decades, a growing number of studies have attempted to explore the neural mechanisms underlying this intergenerational transmission of traits. Generally speaking, this literature follows at least three main goals. The first goal is to identify the specific measures of neural similarity that are associated with different types of phenotypic similarity between parents and children. Phenotypic similarity between parents and children certainly suggests that there is some neural similarity, both at the level of brain structure and brain function. However, because there is a large degree of modularity in aspects of brain organization (Bertolero et al. 2015), neural similarity over generations is likely to depend on both the trait and the brain regions investigated. For example, in task-based neuroimaging, the brain regions in which patterns of activity would be most similar between parents and children might be different in a language processing task compared to a visuo-spatial task. In other words, investigating intergenerational similarity of brain structure and function is often not so much a question of *whether* neural similarity exists between parents and children, but rather a question of *where* this similarity is the most consistently observed and how it may change with a given trait. In that sense, neuroimaging designs in which brain similarity is measured across generations are a specific instance of designs in which the focus is on assessing how specific brain regions similarly contribute to a given function across individuals (as compared to

traditional designs in which measures are typically averaged over a sample of participants) (Etzel et al. 2020).

A second goal of intergenerational neuroimaging studies is to determine whether neural similarity between parents and children predicts the transmission of traits from the former to the latter. Although phenotypic similarity is often observed between parents and children, there is substantial variability between families. For example, the risk of developing a cognitive or affective disorder in children is often increased when the disorder is present in parents (Merikangas et al. 1998; Chen et al. 2017). However, in many cases children may not develop the disorder expressed by their parents (Haft et al. 2016), which suggests a lesser neural similarity in those families than in families in which both children and parents express the disorder. Comparing neural similarity between families with different degrees of phenotypic similarity may thus provide a window into the brain mechanisms that support the intergenerational transmission of phenotypes. In some ways, this is a relatively stringent test of neuromarkers, as a neural mechanism that would characterize a trait should be absent (or reduced) when that trait is not transmitted from parents to children. Intergenerational neuroimaging studies may thus also provide complementary information to case-control studies, in which neuromarkers are typically identified by comparing groups of individuals with and without the disorder.

Finally, a third goal of some intergenerational neuroimaging studies is to estimate the *familiality* of brain structures or functions that are associated with a given trait, i.e., the extent to which the variation in structural or functional brain measures within a population can be attributed to familial differences among individuals; (Kendler and Neale 2009)). This becomes possible when studies no longer exclusively focus on two generations but collect brain measures of individuals across multiple generations, including siblings, cousins, grandparents, and more distant relatives (Roalf et al. 2015; Sudre et al. 2017; van der Lee et al. 2017; Bas-Hoogendam et al. 2018a). Familiality can then be estimated based on the varied degrees of relatedness within a family structure (Winkler et al. 2010; Tissier et al. 2017; Bas-Hoogendam et al. 2018b). Note that these studies typically do not

use the term *familiality* but rather *heritability*, which is typically defined as the extent to which the variation in a measure within a population can be attributed to genetic differences among individuals. However, because genetic and environmental variations remain correlated even in multigenerational designs (more related individuals tend to live in more similar environments), it is unclear whether multigenerational studies may disentangle between those influences. Therefore, we chose to use the more neutral term *familiality* in the present review. The relation between *familiality* and *heritability* will be discussed in section 5.3.

In sum, examining the brain mechanisms mediating the intergenerational transmission of behavioral phenotypes may have both clinical and theoretical relevance. As said above, this is not so much because these studies may inform about the etiology of neuromarkers (typically these studies cannot dissociate between genetic or environmental influences, see section 5.3). But intergenerational neuroimaging studies may be most useful because these could provide an interesting way to either identify neuromarkers or test hypotheses about neuromarkers coming from more standard neuroimaging designs and case-control studies. For example, intergenerational studies may investigate similarity in brain structure and function across two generations differently affected by a condition or explore the *familiality* of brain structure and function that are related to traits within expanded families.

2. The present review

The present paper is not the first review of the literature on intergenerational neuroimaging. Ho et al. (2016) were the first to focus on these studies and to conceptualize some critical aspects of the designs, methods, and key questions. However, as this narrative review will make clear, the field has expanded since that seminal review and a still-limited but growing number of studies have begun to examine the intergenerational transmission of a variety of traits, including those involved in cognitive and academic abilities (i.e., 22 studies reviewed here were not published at the time of Ho

et al.'s review, see Table 1 and Table 2). Since Ho et al. (2016), studies have notably also used a greater variety of techniques, such as diffusion tensor imaging (DTI), electroencephalography (EEG), as well as functional and structural magnetic resonance imaging (respectively, fMRI and sMRI).

The goal of the present review is twofold. The primary aim is to discuss the experimental designs and measures that are used to assess neural similarity in intergenerational studies, as well as those that are not used yet but could be directions for future studies. In doing so, we will build on the early conceptualization put forward by Ho et al. (2016) and extend it to other dimensions, for example covering how neural similarity can be envisioned in terms of spatial and temporal measures and in terms of univariate and multivariate measures. A secondary aim is to provide an update of Ho et al. (2016) and critically evaluate the main findings obtained by intergenerational neuroimaging studies to date, especially as they relate to the three goals of intergenerational studies detailed above. Although the present study is not a systematic meta-analysis of the literature, we also aim to provide detailed information regarding each study discussed here so that readers may evaluate the findings. As mentioned above, intergenerational neuroimaging studies have focused on investigating similarity over two generations of individuals (i.e., parent-child design) or over multiple generations (i.e., multigenerational design). Therefore, the methods, measures, and findings from both types of studies are reviewed in two separate parts.

3. Selection of studies reviewed

The PRISMA flow diagram showing the selection of studies discussed in this review is shown in **Fig. 1**. All studies discussed in this review were identified from PubMed in May 2023 using the following search terms, which had to be in either the title or abstract of the results: “((mother daughter[Title/Abstract]) OR (parent child[Title/Abstract]) OR (multigenerational[Title/Abstract]) OR (family study[Title/Abstract]) OR (family-based study[Title/Abstract]) OR (intergenerational[Title/Abstract])) AND ((neuroimaging[Title/Abstract]) OR (mri[Title/Abstract]) OR

(EEG[Title/Abstract]) OR (fMRI[Title/Abstract]) OR (Voxel-Based Morphometry[Title/Abstract]) OR (MEG[Title/Abstract]) OR (DTI[Title/Abstract]) OR (brain similarity[Title/Abstract]) OR (brain concordance[Title/Abstract]))". We only considered articles published between the years 2000 and 2023. These were supplemented by 3 more papers found with additional searches on Google scholar, using similar search terms. Moreover, we also examined all references from the review by Ho et al. (2016). Finally, the study by Fehlbaum et al. (2022) is one of the most recent papers published on intergenerational neuroimaging, so we also examined references cited in this paper.

All of these papers were screened with the following inclusion criteria:

- (1) Participants scanned had to be humans
- (2) Both related parents and their children (at least) had to be brain-scanned
- (3) Brain similarity between the related dyads had to be assessed OR heritability (i.e., familiarity in the context of the present review) of brain measures from parent to child had to be assessed

Exclusion criteria were:

- (1) Hyperscanning studies or studies looking at the brains during interaction between a parent and their child. We were interested in the downward transmission from parent to child, and not the bidirectional effects of parent-child interaction.
- (2) Studies considering children and parents as two different groups (e.g., one group of affected children compared to a group of first-degree relatives). In such cases, the focus of the study is not intergenerational transmission per se but rather dyad status (i.e., proband versus first-degree).

Following these criteria, we considered 31 studies: 16 studies on exclusively parent-child dyads (see **Table 1**) and 15 studies using a multigenerational design (see **Table 2**). We begin by discussing parent-child studies before turning to multigenerational studies.

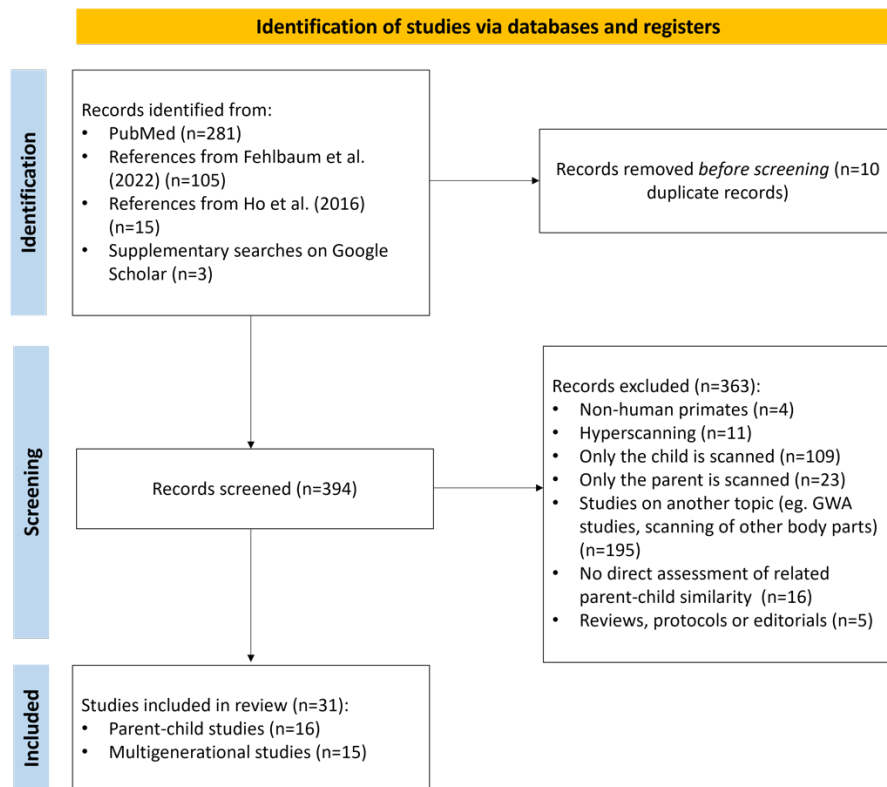


Figure 1. PRISMA flow diagram showing the selection of studies discussed in this review.

4. Parent-child studies

The overarching goal of parent-child studies is to measure brain similarity between a given sample of parents and their children, i.e., across two generations. Measures of brain similarity may be further associated with the transmission of a phenotype of interest. Below we detail the variety of measures, designs, and analyses that have been employed to assess brain similarity between parents and children. **Table 1** lists the parent-child studies identified in this review, with their main topics of interest, measures, dependent variables, and findings, as well as a number of indicators that can be used to assess the confidence in their results (e.g., sample size, presence of preregistration, correction for multiple comparisons).

Table 1: Parent-child neuroimaging studies referred to in this review.

Reference	Topic of interest	Population	N of dyads; control (if applicable)	Country	Sex ratio (m/f) parents; controls (if applicable)	Sex ratio (m/f) children; controls (if applicable)	Age range parents; control (if applicable)	Age range children; controls (if applicable)	Measure	Main findings	Preregistration (y/n)	Dependent variable	Analysis (whole-brain or ROIs)	Similarity corrected for multiple comparisons (y/n)	Size of the largest effect reported for parent-child similarity, Pearson coefficient (if ROI analysis)	A priori power analysis (y/n)
Abraham et al., 2020	Depression	Depressed parents and at-risk children, healthy control dyads	24; 20	USA	12/12; 9/11	10/14; 11/9	46-51; 46-50** (total range: 38-59)	18-22; 19-24** (total range: 10-31)	DTI	Lower similarity in WM connections between basal ganglia and temporal cortical areas in dyads with a depressed parent. Better parental care predicted greater similarity in WM connections.	n	WM connectivity	ROIs (n=48 connections)	y (FDR)	r=0.57	n
Ahtam et al., 2021	Cortical sulcal patterns	Healthy mother-child	16	USA	0/15	8/8	30-46	4-6	sMRI	Stronger sulcal pattern similarity for child-mother pairs than child-unrelated pairs. Higher mother-child similarity in the right hemisphere.	n	Cortical sulcal patterns (position, depth, area)	ROIs (n=10 sulci)	y (FDR)	0.91*	n
Bilgi et al., 2015	Personality traits	Healthy mother-daughter	22	Turkey	0/22	0/22	41-52**	19-24**	sMRI	Mother-daughter positive correlations in GM density related to	n	VBM	Whole-brain	n	N.A.	n

										personality traits in multiple brain regions						
Casey et al., 2007	ADHD	ADHD parent-child, healthy control dyads	20; 10	USA	5/15; 2/8	16/4; 8/2	34-61; 38-52	15-19; 15-18	DTI	Significant correlation between ADHD parent-child prefrontal fiber-tract FA, but not in control parent-child dyads	n	FA	ROI (n=1)	y (Bonferroni)	r=0.61	n
Colich et al., 2017	Depression	Depressed mothers and at-risk daughters, healthy control dyads	15; 23	USA	0/15; 0/23	0/15; 0/23	37-51; 43-51**	11-14; 11-14**	fMRI (task)	Within ROIs involved in the anticipation of reward and loss, only the bilateral putamen response to the anticipation of loss showed similarity between mothers and daughters, regardless of mother's depression history	n	BOLD	ROIs (n=11)	n	r=0.54	n
Fehlbaum et al., 2022	Reading network	Healthy mother-child	69	Switzerland, Canada	0/69	41/28	26-55	7-14	sMRI	Significant similarity for mother-child dyads in reading network for IG, SA and GMV, but not CT or sulcal morphology. Similarity in IG, SA and GMV is specific to mother-child pairs	y	CT, SA, GMV, ROI (n=1) IG, sulcal morphology	y (Bonferroni)	r=0.54	n	

Foland-Ross et al., 2016†	Depression	Remitted mothers and at-risk daughters, healthy control dyads	14; 23	USA	0/14; 0/23	0/14; 0/23	40-51; 43-51	11-16; 10-15	sMRI	Thinner CT in bilateral fusiform and inferior temporal and lateral occipital gyri for remitted mothers and at-risk daughters than healthy control dyads Significant correlation of mother-daughter CT in these regions only for remitted mothers	n	CT	ROIs (n=2)	n	r=0.63	n
Hill et al., 2020	Frontal EEG asymmetry	Healthy mother-infant	31	USA	0/32	18/15	26-36**	11-13 months	EEG	Mother-infant FAA moderately correlated (when alpha ranges were optimized) Mother-infant FAA convergence was strongest in the high alpha range for mothers and broad alpha range for infants	n	FAA	ROI (n=1)	n	r=0.41	n
Kim et al., 2021	Earliness of similarity	Healthy mother-newborn	30	USA	0/30	16/14	19-42	37.14–41.57 weeks	fMRI (rs)	Significant mother-child FC similarity within the first few months after birth, and increases with age of the infant Higher FC similarity in brain networks that mature earlier	n	FC	Whole-brain, ROIs (n=8 seeds)	y (FDR)	N.A.	n

Minami et al., 2022	Depression	Remitted parents and at-risk children	44	Japan	15/19	22/22	49-66**	19-35**	sMRI	Significant similarity for remitted mothers and their daughters' GM structure in the default mode and central executive networks, not identified in any other parent-offspring dyad	n	GM density, Whole-brain, GMV, SA, CT ROIs (n=68)	y (Bonferroni)	r=0.89	n	
Ozalay et al., 2016	Depression	Depressed mothers and at-risk daughters, healthy control dyads	24; 24	Turkey	0/24; 0/24	0/24; 0/24	42-50; 41-52	18-26; 18-25	sMRI	Significant GM difference between depressed mothers and controls in right temporoparietal region and dmPFC. Similar significant GM differences between at-risk daughters and control daughters	n	GMV, CT	Whole-brain, ROIs (n=32)	n	N.A.	n
Su et al., 2022	Emotional response	Healthy parent-child	41	China	10/31	19/22	29-49	7-12	fMRI (movie)	Higher correlation in activity of the dmPFC and vmPFC and in parent-child than random dyads adult-child dyads. Higher correlation in connectivity of the dmPFC with social and emotional systems in parent-child dyads	n	BOLD, FC	Whole-brain, ROIs (n=2 seeds)	y (FDR)	N.A.	n

Takagi et al., 2021	Identifying dyads	Healthy parent-child	84	Japan	3/81	45/39	39-47**	11 and 13 (longitudinal)	fMRI (rs + sMRI)	Parent-child brains are sufficiently similar structurally and functionally to identify dyads. Structure and function provide complementary information.	n	BOLD (FC), GMV	Whole-brain, ROIs (n=10 networks)	n (permutation testing)	75.55%* n**
Vandermos ten et al., 2020	Reading network	Healthy parent-child	44	USA	21/23	21/12	38-50**	7-8**	DTI	Parent-child correlation for FA in right FA in bilateral IFOF but not in AF	n	FA	ROIs (n=4)	n (but combined with Bayesian approach)	r=0.67 n
Wang et al., 2018	Frontal EEG asymmetry	Healthy parent-child	39	China	9/30	20/19	36-43**	7-11**	EEG	Parent-child resting FAA not significantly correlated. Relationship moderated by parental psychological control.	n	FAA	ROI (n=1)	n	r=-0.11 n
Yamagata et al., 2016†	Depression	Healthy parent-child	67	USA	29/30	20/19	33-48	5-13	sMRI	Positive correlation in maternal corticolimbic GMV with daughters significantly greater than other parent-offspring dyads.	n	GMV	Voxelwise in ROI (n=1)	n	N.A. n

Notes. ADHD, attention deficit hyperactivity disorder; AF, arcuate fasciculus; BOLD, blood-oxygen-level dependent; CT, cortical thickness; dmPFC, dorsal medial prefrontal cortex; DTI, diffusion tensor imaging; EEG, electroencephalography; FA, fractional anisotropy; FAA, frontal alpha asymmetry; FC, functional connectivity; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; GM(V), grey matter (volume); IFOF, inferior fronto-occipital fasciculus; IG, local gyrification; ROI, region of interest; rs, resting-state; SA, surface area; sMRI, structural magnetic resonance imaging; VBM, voxel-based morphometry; vmPFC, ventral medial prefrontal cortex; WM, white matter.

N.A.: not applicable

*not a correlation but graph-based sulcal pattern similarity calculated using an exponential function

**approximated range based on mean +/- SD

*** classification accuracy

†studies included in the review of Ho et al. (2016)

4.1. Measures

Broadly speaking, similarity between two brains can be characterized at the structural and functional levels. These two levels provide complementary information with regard to the question of whether two brains are similar or different (Takagi et al. 2021). Structural similarity concerns similarity in the anatomical properties of the brain, which is necessarily measured in the three-dimensional space. A number of measures can be considered to investigate structural similarity, including grey matter density and volume, cortical thickness, cortical surface area, local gyrification, sulcal morphology, and organization of white matter tracts. The relation between these measures is not always clear (Winkler et al. 2010) and each may be differently affected by development (Fehlbaum et al. 2022). Thus, different structural measures may provide complementary information (Ozalay et al. 2016). To date, however, only three neuroimaging studies have combined two or more structural features to investigate structural similarity (Ozalay et al. 2016; Fehlbaum et al. 2022; Minami et al. 2022).

In contrast to structural similarity, functional similarity concerns similarity in brain activity. These functional properties can be evaluated in the spatial as well as the temporal domains, and functional similarity may therefore concern both of these domains. For instance, while Colich et al. (2017) focused on similarity of spatial patterns of activity, Kim et al. (2021) and Su et al. (2022) studied voxel-wise similarity of brain activity across time. Finally, using electroencephalography (EEG), Hill et al. (2020) and Wang et al. (2018) calculated frontal alpha asymmetry score, which is the difference between frontal right and left alpha activity averaged across time (the focus being on a difference between hemispheres).

Functional similarity may be measured at rest or during a task. As already pointed out by Ho et al. (2016) in their seminal review, an advantage of task-related measures is that they allow for the assessment of brain activity (or connectivity) that is associated with a behavior of interest. For instance, Colich et al. (2017) used a monetary incentive delay task to evaluate how neural similarity

relates to depression, while Su et al. (2022) asked participants to watch an emotionally negative movie in the scanner to study how neural similarity mediates the link between family environment and child psychological wellbeing. A drawback of task-related measures, however, is that the use of different tasks between studies may make it difficult to compare results associated with a phenotype of interest. Comparability between studies is an advantage of resting-state studies (Wang et al. 2018; Hill et al. 2020; Takagi et al. 2021; Kim et al. 2021), which measure brain activity of participants in the absence of a task (van Diessen et al. 2015; Lv et al. 2018). Resting-state studies may also be more adapted to pediatric neuroimaging, as task-based neuroimaging may be challenging with young children (Raschle et al. 2012). However, resting-state studies do not allow for the study of similarity in brain networks associated to a phenotype of interest. They also make it difficult to control for the behavior of subjects (van Diessen et al. 2015). That is, each subject may experience different mental states, which might influence activity of default mode networks (and thus intergenerational similarity).

4.2. Experimental designs

By definition, all parent-child neuroimaging studies share a common interest in measuring the neural similarity between a parent and their child (i.e., a related dyad). However, depending on their objectives, studies may vary with respect to the baseline against which that similarity is compared to (see **Table 1**). For example, a number of studies have explored whether differences in similarity between related dyads are linked to some phenotype of interest. Such studies have typically measured similarity in regions associated with a variety of traits (Bilgi et al. 2015; Wang et al. 2018; Hill et al. 2020; Vandermosten et al. 2020). Others have followed dyads longitudinally (Kim et al. 2021) or compared similarity between different combinations of related dyads (e.g., father-child versus mother-child) (Yamagata et al. 2016; Minami et al. 2022). As stated earlier, a frequent goal of parent-child studies is to test whether neural similarity between parents and children is

associated with the transmission of a disorder. Several studies have therefore compared related dyads in which the parent is (or was) affected by a disorder to related dyads in which the parent is (or was) not affected (Casey et al. 2007; Foland-Ross et al. 2016; Ozalay et al. 2016; Colich et al. 2017; Abraham et al. 2020). Finally, studies may also investigate what is unique to the similarity between parents and children from related dyads. These studies have typically compared related dyads to dyads of parents and children that were unrelated (Ahtam et al. 2021; Takagi et al. 2021; Fehlbaum et al. 2022; Su et al. 2022). Overall, these different choices introduce some degree of variability between studies that need to be considered when examining the literature. For example, studies exclusively assessing brain similarity among related dyads do not provide any information regarding how specific that similarity is to related (versus unrelated) individuals. This specificity can only be assessed by using unrelated dyads as baseline. As another example, studies that examine the similarity of dyads over time or between different types of parent-child dyads are uniquely positioned to inform about factors moderating similarity, such as age, sex, or presence of a disorder. We discuss in greater detail the limitations of different types of design in a later section (see Section 4.6).

4.3. Statistical analyses

Although brain similarity can be conceptualized at both the spatial and the temporal level (see above), a majority of studies have focused on spatial analyses. The most frequently encountered index of brain similarity across these studies is a correlation between a given brain measure in parents and in children (Casey et al. 2007; Foland-Ross et al. 2016; Yamagata et al. 2016; Ozalay et al. 2016; Wang et al. 2018; Hill et al. 2020; Vandermosten et al. 2020; Takagi et al. 2021; Fehlbaum et al. 2022; Minami et al. 2022). Brain measures often come from the average activity or structural index of several voxels within given regions of interest (ROIs) (Casey et al. 2007; Foland-Ross et al. 2016; Ozalay et al. 2016; Wang et al. 2018; Hill et al. 2020; Vandermosten et al. 2020; Takagi et al. 2021;

Fehlbaum et al. 2022; Minami et al. 2022), but they may also be computed voxel-by-voxel across ROIs (Yamagata et al. 2016) or across the whole brain (Bilgi et al. 2015). Each method has its advantages and disadvantages (Poldrack 2007; Kriegeskorte et al. 2009). While ROI analyses may limit the number of multiple comparisons, they are subject to biases depending on the way the ROIs were selected. In contrast, while whole-brain analyses allow researchers to explore relations across the entire brain without a priori constraints, they raise issues about multiple comparisons which need to be adequately controlled.

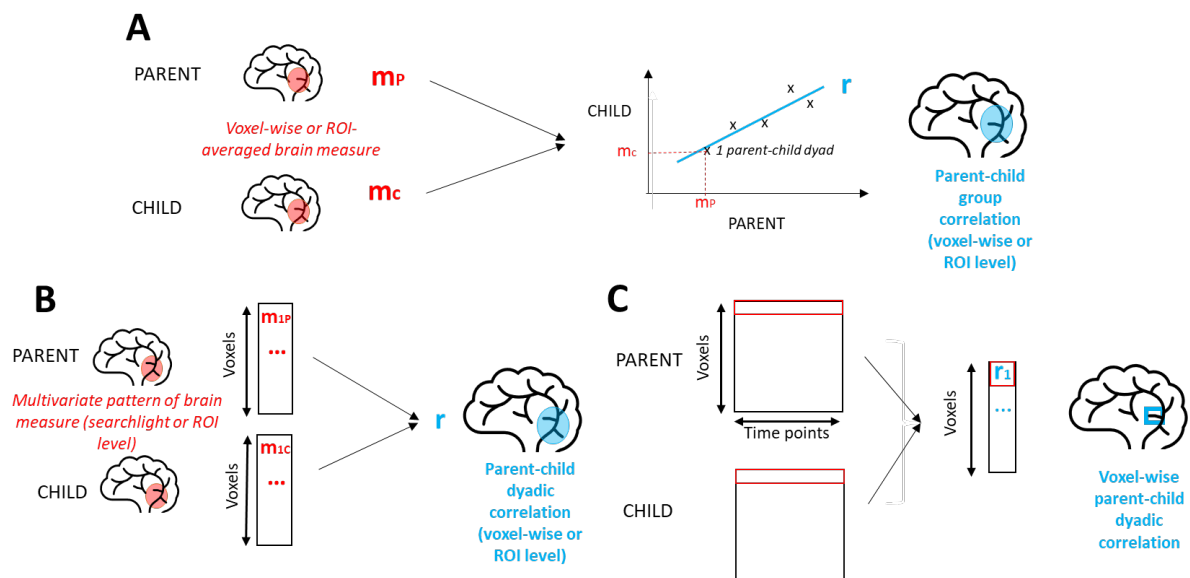


Fig. 2. Statistical analyses in parent-child neuroimaging studies. (A) Univariate data analysis. The brain measure (m_P for the parent, m_C for the child) is considered at the voxel level or averaged at the ROI level. A correlation is calculated between measures of parents and children, either in the ROI or at the voxel-wise level. (B) Multivariate data analysis. For each parent-child dyad, a correlation is calculated between multivariate patterns of brain measures at the ROI or searchlight level, resulting in a correlation for the ROI or the voxel. The searchlight is a radius sphere that runs through the whole parent and child brains and centers on each voxel of the brain. (C) Temporal approach on functional data. For each voxel, a correlation is calculated between time series of the parent and the child. As an output, for each dyad, a map of voxel per voxel correlations is obtained. Abbreviations: ROI; region of interest.

The studies described above all employ univariate methods. That is, they only consider a given voxel or a given ROI at a time when investigating the correlation between the parental

measure and the child measure (see **Fig. 2A**). Yet, the past two decades have seen the emergence of multivariate methods in the neuroimaging field, which may enhance power and reliability (Kragel et al. 2021). To our knowledge, only one study has taken advantage of such methods. Colich et al. (2017) evaluated similarity between parents and children by calculating the correlation between voxel-wise patterns of task-related activity in parents and children in given ROIs, thus obtaining a correlation for each dyad as an index of similarity (see **Fig. 2B**). In theory, this method could be extended to whole-brain analyses using a searchlight approach, i.e., by defining a local neighborhood of voxels centered around each voxel in the brain volume and running a correlation of multivariate pattern of activity between parents and children within each neighborhood.

A few studies have investigated parent-child similarity in brain function by focusing on similarity in the temporal rather than the spatial domain (see **Fig. 2C**). This notably allows one to use temporal data from resting-state (Kim et al. 2021) or task-related design without the need to compare different conditions (Su et al. 2022). These studies typically measure the correlation between the time course of activity in parents and children for each voxel in the brain. This leads to a map of voxel-wise correlations for each dyad, which can be statistically compared between groups. Note that this approach can also be combined with a ROI approach to limit the multiple comparison problem (Kim et al., 2021, see below).

Finally, some studies have examined parent-child similarity in brain connectivity rather than localized activity or structure. Often, connectivity analyses consist in building a connectivity matrix between several ROIs (Abraham et al. 2020; Takagi et al. 2021), or between ROIs and voxels across the whole brain (Kim et al. 2021). Such connectivity can be structural, for example involving white matter fiber connections (Abraham et al. 2020), or functional, for example involving functional coupling of activity between regions (Takagi et al. 2021; Kim et al. 2021; Su et al. 2022). Parent-child similarity is then typically assessed by calculating correlations between the whole matrices of parents and children (Takagi et al. 2021; Kim et al. 2021) or for each single fiber connection (Abraham et al. 2020). Su et al. (2022) used another strategy and directly calculated the correlation between the time

series of a seed from one participant and the time series of voxels across the whole brain from another participant. Matrices of correlations were then averaged across participants. Finally, in their temporal voxel-wise analysis (see above), Kim et al. (2021) synchronized the time series within parent and child dyads for each voxel, such that time series should be similar when connectivity patterns are similar. Voxel-wise correlation of time series was then used as an estimate of parent-child similarity in functional connectivity.

Thus, parent-child neuroimaging studies have employed diverse methods and statistical analyses, which have an impact on the very definition of brain similarity across studies. Studies have also focused on brain similarity in the context of a variety of traits, which we review below.

4.4. Main findings

As can be seen from **Table 1**, most studies have investigated the transmission of traits such as mood and depression while a smaller number of studies have focused on reading and attention. **Table 1** lists the main conclusions from each study, along with a number of indicators that can be used to assess the confidence in the results, such as sample size, presence of preregistration, or correction for multiple comparisons. Clearly, studies have employed a variety of techniques and analytic strategies, which make it relatively difficult to compare their findings with each other. It is nonetheless interesting to examine how the body of literature relates to the main objectives that are spelled out at the outset of this review.

We argued that a first goal of intergenerational studies is to identify the measures of neural similarity that are associated with different types of phenotypic similarity between parents and children, with the idea that neural similarity may depend on both the trait and the brain regions investigated. Overall, studies have indeed found structural and functional similarity between parents and children in a number of brain regions that they have associated with specific traits. For example, Yamagata et al. (2016) linked parent-daughter similarity within the corticolimbic circuitry to

intergenerational effects on mood regulation, Fehlbauer et al. (2022) and Vandermosten et al. (2020) associated parent-child similarity in left-hemispheric regions and pathways to the transmission of reading skills, and Hill et al. (2020) argued that similarity in EEG frontal alpha asymmetry may reflect similarity in emotion regulation. Yet, it is difficult to assess the specificity of these measures of similarity for the given trait, as most studies have focused on specific ROIs and often rely on reverse inferences to speculate on what the similarity might mean. Investigating trait-specific neural similarity would require either functional studies comparing how similarity differ in different tasks or studies more generally linking similarity to individual differences in behavioral measures of traits, though those studies would undoubtedly require a significant increase in sample size compared to current studies (Marek et al. 2022).

We also argued that a second goal of parent-child studies is to determine whether neural similarity between parents and children predicts the transmission of traits from parents to children. As shown in **Table 1**, a few studies have started to explore this question, mainly by comparing dyads in which a condition is transmitted from parents to children (or has a greater risk of being transmitted) to healthy dyads. For example, several studies have compared dyads in which mothers have a history of depression to dyads with no such history (Foland-Ross et al. 2016; Ozalay et al. 2016; Colich et al. 2017; Abraham et al. 2020), showing differences in brain similarity between those cases (with the exception of Colich et al. 2017). Casey et al. (2007) also used a design in which parents and children both affected by ADHD were compared to healthy controls, also suggesting differences in prefrontal similarity as a function of the dyad status. Though these studies are interesting proofs of concept for the use of parent-child designs to explore neuromarkers, studies remain scarce and likely underpowered given that most of them rely on univariate correlations between parents and children (see section 4.3) in relatively small sample sizes. Studies also currently lack designs comparing dyads in which a condition is transmitted versus is not transmitted from parents to children, which is a more stringent test of neuromarkers than comparing affected versus unaffected dyads.

Finally, parent-child designs allow researchers to examine whether neural similarity is moderated by other variables. For instance, Abraham et al. (2020) found that parent-child neural similarity in WM tracts increased with a measure of parental care. Although this might suggest an effect of caregiving on parent-child similarity (as the authors suggest), it is important to keep in mind that such designs are not genetically-sensitive. Therefore, it is unclear whether such moderating effects result from an environmental influence (e.g., caregiving itself) or from a genetic influence (e.g., parents who report more parental care might differ genetically from parents who report less parental care). This issue is also present in studies that investigate whether similarity is related to parental education (Kim et al. 2021) or other parental characteristics (Wang et al. 2018). More generally, the issue of whether intergenerational designs might be able to dissociate genetic from environmental effects is discussed later (see section 5.3).

4.5. Factors influencing parent-child brain similarity

Parent-child studies have suggested that several factors may influence neural transmission from parents to children. First, parent-child neural similarity may depend on the age of children (Takagi et al. 2021; Kim et al. 2021) or their pubertal status (Colich et al. 2017). Specifically, studies suggest that similarity tends to increase as children get older, which is likely to reflect neurodevelopmental changes. Indeed, human brain development is protracted, changing in structure during adolescence and into early adulthood (Paus 2005; Stiles and Jernigan 2010; Houston et al. 2014). To some extent, it is not surprising that as children's brain slowly matures, it becomes more alike the parental brain, which has already reached maturity. It is also likely that genetic effects on brain function may increase over development (Lenroot and Giedd 2008). Indeed, as children get older, they have more opportunities to seek an environment and experiences in line with their genetic predispositions. Environmental feedback might in turn reinforce this tendency, thereby contributing to an increase in intergenerational similarity with age. In any case, more developmental

studies are needed to investigate how the intergenerational transmission of brain structure and function is affected by developmental trajectories. Not only would longitudinal studies allow for following at-risk participants as they develop or not the disorder, but these studies could also help determine whether neural phenotypes of transmission are vulnerability factors and not simply epiphenomena. As highlighted by Ho et al. (2016), such studies might also investigate whether developmental trajectories of cerebral markers of interest are linear or nonlinear.

Second, similarity may depend on the sex of both parent and child, with several studies showing female-specific similarity in brain regions associated with emotion regulation (Yamagata et al. 2016; Minami et al. 2022). It has been argued that this female-specific transmission of neuromarkers may parallel the female-specific transmission of depressive phenotypes, maternal depressive symptoms being correlated with symptoms in daughters but not in sons (Yamagata et al. 2016). Note that this might come from the influence of both environmental and genetic factors. For example, a mother might be more similar to her child than a father because she provides the prenatal environment to their child (Minami et al., 2022). Moreover, a mother might be more similar to her daughter because parents spend more time with same-sex children (Endendijk et al. 2018), which could ultimately lead to same-sex modeling and higher same-sex similarity between parents and children (Lewis et al. 2011). It is also possible that this sex-specific transmission may have a genetic origin, known as the parent-of-origin effect. Specifically, the impact of an allele on phenotype depends on whether the allele is inherited from the mother or the father (Ho et al. 2016). This parent-of origin effect can be sex-specific, with a differential gene expression depending on the sex of the child (Gregg et al. 2010), suggesting that for daughters but not sons, genes linked to depression may have more impact on the child phenotype when inherited from the mother than the father. Clearly, intergenerational studies cannot disentangle between these possibilities. Nonetheless, the influence of sex on the intergenerational transmission of brain circuits suggests that studies should systematically control for the sex of the parent and the child in the analyses (as well as the age, see above).

Finally, some other factors may influence parent-child similarity, such as parental education (Kim et al., 2021), parental care (Abraham et al., 2020), and parental psychological dispositions (Wang et al., 2018). As stated earlier, however, it remains unclear to what extent these factors explain neural similarity over and above genetic measures (which are not collected in the parent-child studies reviewed here).

4.6. Limitations

We highlight here a few limitations of current studies that investigate the parent-child transmission of brain structure and function. First, parent-child neuroimaging studies are characterized by a wide diversity of techniques, measures, and ways to assess neural similarity. Such a heterogeneity raises concerns regarding the replicability of findings. It might be beneficial to find some consensus regarding methodological practices. The use of standardized pre-processing protocols and standardized tasks in fMRI studies is necessary for mega-analyses (Ho et al. 2016). In sMRI studies, the same structural features should systematically be used from one study to the next to enhance comparability. For instance, Winkler et al. (2010) suggested that for genetic neuroimaging studies, cortical thickness and surface area should be preferred over grey matter volume. Indeed, the authors showed that surface area and cortical thickness are independent from one another and have distinct genetic origins, and thus provide complementary information. In contrast, grey matter volume is genetically and environmentally correlated to surface area and cortical thickness, which makes this measure relatively unspecific compared to others. Another issue with many studies is that the hypotheses, design, and analysis strategy are often not preregistered (see **Table 1**). Neuroimaging studies are often characterized by a large number of researcher degrees of freedom and preregistration would be beneficial to limit analytic flexibility and increase confidence in the results (Poldrack et al. 2017). Finally, sample sizes of parent-child studies tend to be relatively small, ranging from 16 to 84 participants in the studies included in **Table 1**. Though the

power of a given study to detect similarity will depend on a number of factors, including experimental design and how similarity is defined, there is a growing awareness that neuroimaging studies focusing on univariate brain-behavior associations are often underpowered and require much larger sample sizes (Marek et al. 2022). Although parent-child studies do not necessarily involve univariate brain-behavior associations, they often define similarity using univariate correlations of brain structure and function between parents and children (see **Fig. 1A**). It is therefore likely that these studies are underpowered, which question the replicability of their findings. Future studies might either need to significantly increase sample sizes when relying on parent-child correlations, or turn to other measures of similarity that might be more sensitive, such as multivariate pattern similarity (see **Fig. 1B**) (Spisak et al. 2023).

Second, parent-child studies have largely focused on intergenerational transmission based on a small number of hypothesis-driven ROIs. Although ROI-based analyses might enhance power by limiting the number of multiple comparisons (Saxe et al. 2006), a drawback of this approach is that it limits the discovery of similarity in other regions of the brain. For example, it is possible that brain similarity might be observed in regions that are not necessarily part of the canonical brain circuit involved in a given function. Studies using whole-brain voxel-wise analyses allow for such exploration, which has already been used successfully in some structural studies (Bilgi et al. 2015; Yamagata et al. 2016), but also in functional studies using voxel-wise correlation of time series (Kim et al. 2021; Su et al. 2022). Another possibility for a voxel-wise analysis of functional data is the use of a whole-brain multivariate analysis using a searchlight approach (Etzel et al. 2013). Such multivariate analyses have the advantage of being sensitive to multidimensional processes (Davis et al. 2014) as well as to subtle changes in multivariate patterns (Yang et al. 2012), therefore capturing more information than univariate analyses. In other words, whole-brain multivariate analyses might be informative in parent-child neuroimaging studies.

Third, an important limitation of several studies (Bilgi et al. 2015; Yamagata et al. 2016; Wang et al. 2018; Hill et al. 2020; Vandermosten et al. 2020; Kim et al. 2021) is that sometimes parent-child

similarity is only investigated in related dyads and not compared to unrelated dyads. However, even two unrelated brains may show some degree of similarity in either structure or function. For example, typical reading development is associated with functional and structural changes in a left-hemispheric network of regions, including the occipitotemporal, temporoparietal and inferior frontal areas (Schlaggar and McCandliss 2007). Thus, similarity in this network is expected in the population and only a comparison between related and unrelated pairs would allow one to conclude on intergenerational transmission. This is particularly true if similarity is measured from task-related activity, as even unrelated participants may show similar activity in a number of brain regions associated with the task. In other words, measuring parent-child similarity by only focusing on related dyads may raise the risk of overestimating what is transmitted from parents to children.

5. Multigenerational studies

Parent-child studies only focus on two generations of individuals, rather than on a broader family system. However, this broader family system is also known to influence child development (Rogers et al. 2022). Another type of intergenerational studies—multigenerational studies—specifically focuses on expanded families and investigates several generations of related individuals at the same time (Almasy and Blangero 1998). **Table 2** lists the multigenerational studies identified in this review, with their main topics of interest, measures, dependent variables, and findings, as well as a number of indicators that can be used to assess the confidence in their results (e.g., sample size, presence of preregistration, correction for multiple comparisons).

5.1. Measures, designs, and analyses

Multigenerational studies (see **Table 2**) recruit individuals from multiple generations within either healthy or multiplex families (i.e., families with several members affected by a disorder of interest). Although the composition of the sample may vary between studies, participants typically

include parents and offsprings as well as siblings and extended family members (e.g., grandparents, aunts, uncles, cousins). A critical feature of multigenerational neuroimaging studies is that neural measures are collected for each participant in addition to behavioral phenotype. Much like parent-child studies, several neural measures may be considered (see section 4.1.). Although most studies have focused on structural measures (Winkler et al. 2010; Fears et al. 2014; McKay et al. 2014; Roalf et al. 2015; Sudre et al. 2017; van der Lee et al. 2017; Bas-Hoogendam et al. 2018b; Prasad et al. 2022; Hofer et al. 2022), others have investigated functional measures, either at rest (Sudre et al. 2017; Bas-Hoogendam et al. 2021) or during a task (Harrewijn et al. 2018a, b; Bas - Hoogendam et al. 2019; Bas-Hoogendam et al. 2020b, a). The typical analysis strategy involves three main steps. First, the degree of relatedness between family members is represented using a kinship matrix, which includes the theoretical coefficients of familial relatedness between all pairs of individuals (e.g., 1 for the similarity with oneself, $\frac{1}{2}$ for parents and full siblings; $\frac{1}{4}$ for grandparents or half-siblings; $\frac{1}{8}$ for cousins; and 0 for unrelated individuals). Second, brain measures (collected either at the voxel or ROI level) are considered dependent variables in linear mixed models that often include as fixed effects covariates such as sex and age and as random effects the familial relatedness between individuals, represented by the kinship matrix (see **Fig. 3**) (Almasy and Blangero 1998; Tissier et al. 2017). Third, in this design, familiarity can be estimated for each voxel or for each ROI as the ratio of the additive familial variance (estimated from the kinship matrix) to the total phenotypic variance. It should be noted that most studies discussed here do not refer to familiarity but rather to heritability (the proportion of phenotypic variance that is due to genetic factors versus environmental factors). However, as we will see later, whether an estimate of familiarity can be interpreted as an estimate of heritability depends on a number of factors that are not always well controlled in studies. For that reason, we chose to use the more neutral term familiarity when reporting the results of these studies.

Table 2: Multigenerational neuroimaging studies referred to in this review

Reference	Topic of interest	Population	N of family members scanned	N of families	N of cases	Country	Sex ratio m/f	Age range	Imaging technique	Main findings (related to familiarity)	Environmental covariates calculated on family	Study preregistration (y/n)	Dependent variable(s)	Analysis (whole-brain or ROI)	Corrections for multiple comparisons for family (y/n)	Size of the largest effect reported (if analysis)	A priori power analysis (y/n)
Bas-Hoogendam et al., 2018b	Social anxiety disorder	LFLSAD	110	8	39	Netherlands	56/54	9-61	sMRI	Subcortical volume as well as CT and SA in temporal, frontal, occipital and parietal cortex showed moderate to high familiarity	n	y	Subcortical ROIs (n=46), CT, SA	n	y (FDR)	0.92	y
Bas-Hoogendam et al., 2019	Social anxiety disorder	LFLSAD	105	8	37**	Netherlands	49/49**	9-61	fMRI (task)	Moderate to moderately high familiarity within right hippocampus for neural habituation response No familiarity for other ROIs	n	y	BOLD	Voxelwise within ROIs (n=16)	n	/	y
Bas-Hoogendam et al., 2020a	Social anxiety disorder	LFLSAD	99	8	33**	Netherlands	45/46**	9-61	fMRI (task)	Moderate to moderately high familiarity of brain activation levels within mPFC, MTG, STS and STG, which are associated with social anxiety	n	y	BOLD	Voxelwise within ROIs (n=2)	n	/	y
Bas-Hoogendam et al., 2020b	Social anxiety disorder	LFLSAD	105	8	38**	Netherlands	49/49**	9-61	fMRI (task)	In 2 clusters of the amygdala of which activity was associated with social anxiety, voxels of moderate to moderately high familiarity (ranging from 0.20 to 0.63; 1 voxel in left cluster and 22 voxels in right cluster)	n	y	BOLD	Voxelwise within ROIs (n=2)	n	/	y
Bas-Hoogendam et al., 2021	Social anxiety disorder	LFLSAD	109	8	39**	Netherlands	56/53	9-61	fMRI (rs)	Familiarity > 0.20 for iFC of multiple voxels within SA-related clusters (dorsal attention and frontoparietal network)	n	y	FC	Networks (n=6)	n	/	y

Fears et al., 2014	Bipolar disorder	Multigenerational families enriched for bipolar disorder	527	26	N/A	Costa Rica, Colombia	230/297	18-87	sMRI, DTI	Significant familiarity for most measures (88%)	Country, n years of education	CT, SA, volumes, FA, axial/radial diffusivity	ROIs (n=39)	y (Bonferroni)	0.91	n	
Harrewijn et al., 2018a	Social anxiety disorder	LFLSAD	115	9	18	Netherlands	56/59	8-61	EEG (task)	No significant familiarity of EEG measures N1, FRN, P3 and theta power in response to social judgment	n	n	Feedback-related EEG brain potentials N1, FRN, P3 and theta power	ERP y (Bonferroni)	0.48	y	
Harrewijn et al., 2018b	Social anxiety disorder	LFLSAD	113	9	18	Netherlands	56/57	8-61	EEG (task)	Familiarity of delta-low beta and delta-high beta correlations during anticipation of giving a speech, but not significant when correcting for multiple comparisons	n	n	Correlation ROIs (n=3) between electrodes) delta and total/low/high beta	y (Bonferroni)	0.37	n	
Hofer et al., 2022	R2* iron	Families of first-degree relatives	130	59	/	Austria	59/71	38-85	sMRI	Familiarity of R2* iron in basal ganglia and cortex was moderate to high, with estimates ranging from 0.46 to 0.82	n	n	R2* iron	ROIs (n=9) y (FDR)	0.82	n	
McKay et al., 2014	Structural features	Multigenerational healthy families	1,010	49	/	USA	384/626	19-85	sMRI, DTI	Familiarity of SA and CT was position and metric dependent SA familiarity was higher than CT familiarity Significant familiarity of WM FA Significant effects of age and sex	n	n	CT, SA, FA	Whole-brain, ROI (n=62)	n	0.82	n
Prasad et al., 2022	Schizophrenia	Multigenerational multiplex families enriched for	198	23	23	USA	107/91	12-84	DTI	FA of 33/48 WM tracts examined with significant familiarity	Mothers' n highest education	FA	ROIs (n=48)	y (FDR)	0.70	n	

schizophrenia																
Roalf et al., 2015†	Schizophrenia	Multigenerational multiplex families enriched with schizophrenia	188	32	33	USA	97/89	25-63*	sMRI	Significant familiarity of subcortical and limbic volumes and shape No significant familiarity of amygdala based on volumes, but familiarity of focal subfields based on shape analysis	n	n	Subcortical ROIs (n=14) and limbic brain volume and shape	y (FDR)	0.81	n
Sudre et al., 2017	ADHD	Multigenerational multiplex families enriched for ADHD	213	24	N/A	USA	N/A	4-85	DTI, fMRI (rs)	Significant familiarity of microstructural features of association and commissural WM tracts but not projection tracts Significant familiarity of FC in default mode, cognitive control and ventral attention networks	n	n	FA, radial/axial diffusivity, FC	ROIs (n=11) y (Bonferroni or cluster-corrected alpha)	0.69	n
van der Lee et al., 2017	Structural features	Multigenerational healthy families	491	177	/	Austria, Netherlands	204/287	38-86	sMRI	Voxels with significant familiarity are predominantly located in subcortical regions and language areas of left hemisphere	n	n	GM density	Whole-brain y (FDR)	/	n
Winkler et al., 2010	Structural features	Multigenerational healthy families	486	N/A	/	USA	184/302	26-85	sMRI	GMV, CT and SA all show significant familiarity CT and SA are genetically and phenotypically independent GMV more closely related to SA than CT	n	n	GMV, CT, SA	ROIs (n=34) n	0.83	n

Notes. ADHD, attention deficit hyperactivity disorder; BOLD, blood-oxygen-level dependent; CT, cortical thickness; DTI, diffusion tensor imaging; EEG, electroencephalography; ERP, event-related potentials; FA, fractional anisotropy; FC, functional connectivity; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; GM(V), grey matter (volume); LFLSAD; Leiden Family Lab study on Social Anxiety Disorder (Bas-Hoogendam et al. 2018a); mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; ROI, region of interest; rs, resting-state; SA, surface area; STG, superior temporal gyrus; STS, superior temporal sulcus; sMRI, structural magnetic resonance imaging; WM, white matter.

*approximated range based on mean +/- SD

**missing data for part of the participants

†studies included in the review of Ho et al. (2016)

N/A: no information available

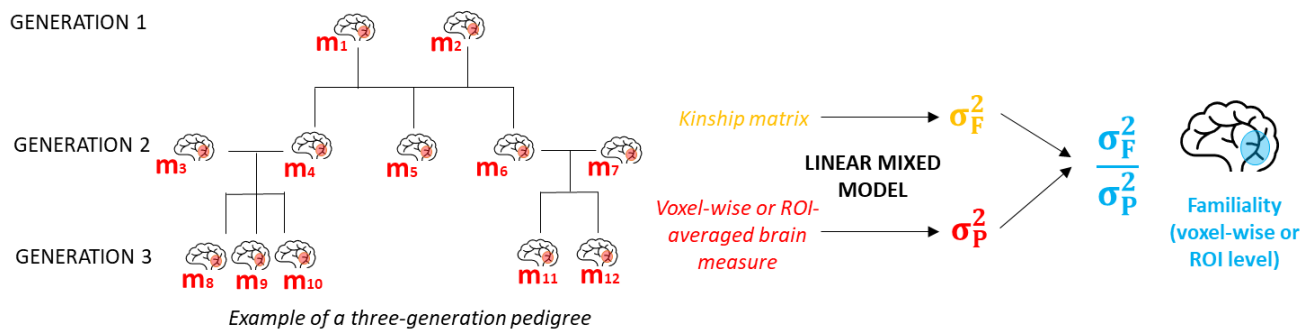


Fig. 3. Statistical analysis in multigenerational neuroimaging studies. Example for a three-generation pedigree. The degree of relatedness between the family members is summarized in a kinship matrix. The brain measure (m_i) for each family member is considered at the voxel level or averaged at the ROI level. The brain measure is considered a dependent variable in a linear mixed model, with degree of familial relatedness as a random effect. A maximum likelihood estimation of the phenotypic (σ_P^2) and familial (σ_F^2) variances is implemented, and familiarity is calculated as the ratio of the familial variance to the total phenotypic variance. As an output, a measure of familiarity (often termed heritability in studies, see section 5.3) is calculated either based on a voxel-wise map or ROI. Abbreviations: ROI; region of interest.

5.2. Main findings

The main findings from multigenerational studies are shown in **Table 2**. The size and familial structure of samples in these studies allow researchers to typically focus on two dimensions. First, they may investigate associations between the occurrence of a trait and a specific neuromarker among family members. For example, studies have found that grey matter characteristics and/or functional activity in various regions are associated with social anxiety (SA) (Harrewijn et al. 2018a, b; Bas-Hoogendam et al. 2018b, 2020b, a, 2021; Bas-Hoogendam et al. 2019) or ADHD (Sudre et al. 2017). Second, these studies may estimate the familiarity of neuromarkers, i.e., the extent to which variation in structural or functional brain measures can be attributed to familial differences among individuals. For instance, among studies focusing on the transmission of psychiatric and anxiety-related disorders, several have estimated familiarity within the Leiden Family Lab Study on Social Anxiety Disorder (LFLSAD) sample (Bas-Hoogendam et al. 2018a). This has been done for grey matter (Bas-Hoogendam et al., 2018b), activity associated with social processing in the fronto-temporal

system (Bas-Hoogendam et al. 2020a), hippocampus and amygdala (Bas-Hoogendam et al. 2019; Bas-Hoogendam et al. 2020b), as well as functional connectivity within attentional processing networks showing association with social anxiety (Bas-Hoogendam et al. 2021). Note that this contrasts with EEG studies of social anxiety, which have failed to find evidence for a familiarity of brain potentials (Harrewijn et al. 2018b) or brain synchronization (Harrewijn et al. 2018a).

Aside from anxiety disorders, multigenerational studies have also investigated neural markers of the transmission of schizophrenia and bipolar disorders, showing familiarity in several subcortical and limbic regions (Roalf et al., 2015; Fears et al., 2014) and white matter tracts (Prasad et al., 2022; Fears et al., 2014). Finally, other studies have investigated the transmission of structural brain characteristics in healthy families, showing familiarity in total brain volume, surface area, average cortical thickness, voxel-based morphometry and grey matter volume (Winkler et al. 2010; McKay et al. 2014; van der Lee et al. 2017) as well as global fractional anisotropy (McKay et al. 2014) and R2* iron (i.e., a relaxation rate indicator of the concentration of iron) (Hofer et al., 2022). Overall, multigenerational studies suggest that brain structure and function appear to be under relatively strong familial influence.

5.3. Advantages and limitations of multigenerational studies

A multigenerational design has a number of advantages compared to a parent-child design. For instance, their relatively large sample size (i.e., ranging from about 100 to 1,000 participants in **Table 2**) typically allows for better estimates of associations between traits and neuromarkers than what is possible from parent-child studies (which tend to have much smaller sample sizes, see **Table 1**). In theory, measuring neural similarity between parents and children as is typically done in parent-child designs (see **Fig. 2**) is also possible in multigenerational studies. However, such analyses are rarely conducted with multigenerational designs, researchers focusing instead on brain-behavior associations and estimation of familiarity across the entire sample. Note that such designs, which

typically include males and females, may also allow studying the parent-of-origin effect as the respective contribution of maternal and paternal familial effects may be partitioned (Wu et al. 2021).

Multigenerational family studies, however, also have a number of limitations. First, as discussed above, multigenerational studies usually rely on larger samples than parent-child designs, and data collection is both cost- and time-intensive (Bas-Hoogendam et al. 2016). This is why studies to date have largely relied on already-existing datasets of unrelated individuals (Hofer et al., 2022; Paus et al. 2015) or have focused on nonhuman primates (Fears et al. 2009; Fox et al. 2015, 2018; Tromp et al. 2019), which allows researchers to collect many phenotypic measures over many generations of large pedigrees with distant familial relationships (Fears et al. 2009). However, studying non-human primates makes it difficult to investigate human disorders, and markers found in non-human primates might not be applicable to humans and specific disorders. Second, multigenerational studies have mostly focused on a few extended pedigrees, which might limit the generalizability of the results (van der Lee et al. 2017). Third, most multigenerational studies have also focused on pedigrees of individuals affected by a given disorder, without comparing the results to pedigrees of healthy comparison subjects (Roalf et al. 2015). This may raise concerns regarding the specificity of the markers for the disorder as compared to the general population (Bas-Hoogendam et al. 2019).

Finally, a major issue with multigenerational studies lies in the interpretation of familiarity. To our knowledge, all studies reviewed here equate this notion with that of heritability, which describes the proportion of variance that is due to genetic factors versus environmental factors. For familiarity to be equivalent to heritability, however, environmental effects would need to be exclusively individual and unshared among family members, which is an assumption that is clearly wrong. Indeed, genetic similarity between family members is almost systematically confounded by environmental similarity (i.e., family members who are the closest genetically tend to live in more similar environments than family members who are more distant genetically). Thus, not taking into account shared environment among family members may lead to inflated estimates of heritability

(Almasy and Blangero 2010). Note that it is possible to get more accurate estimates of heritability from multigenerational designs, for example by adding environmental covariates when calculating familiarity to estimate shared environmental influences. However, this is seldom done in neuroimaging studies, as only two studies within the body of literature reviewed here have added environmental covariates when estimating heritability, such as mothers highest education (Prasad et al. 2022) and country and years of education (Fears et al. 2014) (see **Table 2**). More generally, it would be advisable for future studies interested in estimating heritability (and not only familiarity) of neuromarkers to include in their model as much environmental covariates as possible, for example information regarding socioeconomic status, lifestyle factors, as well as which individuals in the study share the same household or were reared together (Almasy and Blangero 2010). Even more accurate estimates of heritability could be gathered by including in the sample different individuals who are known to have varying degrees of genetic and environmental similarity (e.g., biological siblings reared together versus apart, monozygotic versus dizygotic twins).

6. Conclusion

There is little doubt that identifying the cerebral markers underlying the intergenerational transmission of cognitive and affective traits is of both theoretical and clinical significance. Both parent-child and multigenerational studies may help with this objective, each design providing complementary information. On a theoretical level, intergenerational studies may help testing hypotheses about neuromarkers coming from case-control studies. On a more practical level, the composite markers identified in parent-child studies, which may not be causal but correlated with aspects of the disorder (Lenzenweger 2013), might in the future serve as useful indicators of the disorder for diagnosis, prevention and tracking of illness state (Malcolm and Phillipou 2021). Multigenerational studies can also identify familial markers which, combined with improved designs allowing for parsing out genetic from environmental variance (which is currently lacking), may inform

in the future about the etiology of psychiatric and neurodevelopmental disorders (Flint et al. 2014; Fehlbauer et al. 2022).

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