# From mother to child: How intergenerational transfer is reflected in similarity of corticolimbic brain structure and mental health

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Plamina Dimanova [a,b,*], Réka Borbás [a], Nora Maria Raschle [a,b,*]

[a] *Jacobs Center for Productive Youth Development, University of Zurich, Zurich, Switzerland*
[b] *Neuroscience Center Zurich, University and ETH Zurich, Zurich, Switzerland*

ABSTRACT

*Background:* Intergenerational transfer effects include traits transmission from parent to child. While behaviorally well documented, studies on intergenerational transfer effects for brain structure or functioning are scarce, especially those examining relations of behavioral and neurobiological endophenotypes. This study aims to investigate behavioral and neural intergenerational transfer effects associated with the corticolimbic circuitry, relevant for socioemotional functioning and mental well-being.
*Methods:* T1-neuroimaging and behavioral data was obtained from 72 participants (39 mother-child dyads/ 39 children; 7–13 years; 16 girls/ 33 mothers; 26–52 years). Gray matter volume (GMV) was extracted from corticolimbic regions (subcortical: amygdala, hippocampus, nucleus accumbens; neocortical: anterior cingulate, medial orbitofrontal areas). Mother-child similarity was quantified by correlation coefficients and comparisons to random adult-child pairs.
*Results:* We identified significant corticolimbic mother-child similarity ($r = 0.663$) stronger for subcortical over neocortical regions. Mother-child similarity in mental well-being was significant ($r = 0.409$) and the degree of dyadic similarity in mental well-being was predicted by similarity in neocortical, but not subcortical GMV.
*Conclusion:* Intergenerational neuroimaging reveals significant mother-child transfer for corticolimbic GMV, most strongly for subcortical regions. However, variations in neocortical similarity predicted similarity in mother-child well-being. Ultimately, such techniques may enhance our knowledge of behavioral and neural familial transfer effects relevant for health and disease.

## 1. Introduction

Human brain development is a prolonged process starting in utero and continuing throughout life. Variables influencing human brain formation are, however, already accumulating across generations preceding the individual. Ultimately, brain development is a process shaped by various genetic and environmental factors and their interactions. Children's successful socioemotional development is linked to healthy neurodevelopment and these trajectories are influenced by the communities and individuals surrounding the child (e.g., parents, siblings, peers (Gee, 2020)). Intergenerational transfer effects thereby describe genetic and non-genetic traits' transmission from parents to their children (Ho et al., 2016; Minami et al., 2022; Yamagata et al., 2016). While such transfer effects are behaviorally well documented (e.g., for cognitive functions, physical and psychological well-being (Anger and Heineck, 2010; Fan et al., 2020; Hardie and Turney, 2017)), studies

investigating intergenerational transfer effects on brain structure or function are scarce (Colich et al., 2017; Fehlbaum et al., 2022; Minami et al., 2022; Takagi et al., 2020). Ultimately, intergenerational neuroimaging studies may help us understand complex skill transfer, but also highlight mechanisms linked to familial predisposition and individual's susceptibility for risk and resilience.

Longitudinal structural neuroimaging studies have advanced our knowledge about the development of neocortical and subcortical brain structures (Blakemore, 2012; Frick et al., 2003; Lenroot & Giedd, 2006). Activity-independent morphologic processes during early gestation lead to the formation of major brain structures in utero, while a more fine-grained specialization and maturation of the neurons and their embedding in associated circuitries follows. Some processes, including migration and synaptogenesis, continue for a protracted period during the postnatal phase (Stiles and Jernigan, 2010). While early processes including neurulation or synaptic proliferation are thus intrinsically

regulated, others such as the building and elimination of unused connections over time are more strongly influenced by environmental experiences and signal-dependent processes (Huttenlocher and Dabholkar, 1997). On a neuronal level, regional loss of gray matter decelerates and stabilizes particularly once the associated peak of brain maturation is reached around the second life decade (Lebel and Beaulieu, 2011; Mills et al., 2016; Mills and Tamnes, 2022). Overall, sex- and age-dependent interindividual variation in the developmental trajectories of the human brain exists (Aubert-Broche et al., 2013; Giedd, 2004; Mills et al., 2014). More specifically, neocortical and subcortical regions follow distinct, regionally-specific linear or non-linear trajectories as we age (Mills et al., 2014, 2021; Raznahan et al., 2011; Tamnes et al., 2017; Vijayakumar et al., 2016). Evidence reported by Østby et al. (2009) highlights the heterogeneity in specialization of subcortical regions (e. g., thalamus, caudate nucleus, putamen, amygdala, hippocampus). During the second and third life decades, gray matter volume in striatal structures has been demonstrated to decrease, while amygdala and hippocampus, are suggested to follow an inverted U-shaped developmental curve (Goddings et al., 2014; Herting et al., 2018; Wierenga et al., 2014; Wierenga et al., 2018). Neocortical maturation broadly follows a posterior-to-anterior trajectory with regions in the anterior frontal and temporal cortex reaching a maturational peak the latest, some only during early to mid-twenties (Giedd, 2004; Mills and Tamnes, 2022).

Overall, various factors including genetic and environmental effects, sex differences, and region-based specifics thus influence brain development. While genes are thought to most strongly determine when and how certain brain regions develop, environmental factors, including early experiences, are most influential for how well different networks are built and certain abilities are acquired (Hensch, 2005). Parental care lays the foundation for an individual's healthy development, and current and later physical and mental well-being (Aquilino and Supple, 2001). Parents influence children's brain development and psychological well-being through behaviors including caregiving, socialization of emotion, selection of social and educational environment, and neighborhood safety (Anger and Heineck, 2010; Hong et al., 2021; Schwartz et al., 2014; Whittle et al., 2014). Intergenerational transfer of behavioral traits is well documented through family studies, including the transmission of internalizing and externalizing behaviors (Hardie and Turney, 2017) or emotion regulation styles (Han et al., 2015). Beyond environmental effects, individuals' mental well-being is associated with neurobiological functioning. The structure and function of the corticolimbic circuitry, including amygdala, hippocampus, nucleus accumbens, and areas of the prefrontal cortex (Alcalá-López et al., 2018), have been commonly linked to variations in mental well-being. Moreover, reciprocal interaction and bidirectional connectivity between such regions are considered the core of healthy emotional processing, adaptive behavior, and overall psychological well-being (Comte et al., 2016).

Neuroimaging studies may inform about the resemblance of brain morphology and activation patterns within families (Colich et al., 2017; Fehlbaum et al., 2022; Poissant et al., 2014; Takagi et al., 2021). Past studies have aimed to inform about mechanisms of familial risk transmission and included clinical populations, such as social anxiety (Bas-Hoogendam et al., 2018), depression (Abraham et al., 2020; Colich et al., 2017; Foland-Ross et al., 2016; Minami et al., 2022), but also developmental disorders such as dyslexia (Vandermosten et al., 2020). Similarly, intergenerational neuroimaging studies including parent-child dyads have been conducted in healthy populations. Examination of corticolimbic gray matter volume similarity in parent-child dyads indicates a possible matrilineal transfer dominance, most specific for mother-daughter dyads (Yamagata et al., 2016). Takagi et al. (2021) provided evidence for parent-child similarity measured by resting state activation or gray matter volume. Similarly, Fehlbaum et al. (2022) demonstrate intergenerational transfer for regions of the human reading network in mother-child dyads. Furthermore, mother-child similarity varied in dependence on the structural correlate under investigation (e.

g., gray matter volume, surface area, and cortical thickness). Overall, studies highlight that parent-child similarity in brain structure and function is present and specific to relatives, with parent-child similarity being higher than similarity in non-related adult-child dyads (Fehlbaum et al., 2022; Takagi et al., 2021).

Such findings point towards the unique potential of intergenerational neuroimaging designs to advance our understanding of the precise neurobiological mechanisms underlying intergenerational traits transmission. Nevertheless, neuroimaging studies including parents and children remain rare. First evidence indicates possible beneficial effects of neural parent-child similarity on children's psychological well-being (Lee et al., 2018), however the precise circumstances when this is the case and what the underlying mechanisms are remain to be investigated. To bridge this gap, this manuscript focuses on the investigation of structural brain similarity in mother-child dyads for the corticolimbic circuitry and their associations to mental well-being.

The main aim of this study is the investigation of brain structure and behavioral similarity associated with the corticolimbic circuitry in mother-child dyads. To reach this aim, we first test **(1)** similarity in gray matter volume of the corticolimbic circuitry of mother-child dyads. Secondly, **(2)** mother-child similarity in behavioral reports of mental well-being is computed. Finally, **(3)** we test whether the degree of similarity in mother-child brain structure is linked to varying similarity in dyadic mental well-being. We expect **(H1)** a significant mother-child similarity in corticolimbic gray matter volume, which is higher in mother-child dyads as compared to randomly assigned adult-child pairings. In line with prior evidence of a possible mother-daughter rather than mother-son transfer dominance, in the corticolimbic tract (Yamagata et al., 2016), we further expect **(H1.1)** a higher mother-daughter similarity as compared to mother-son similarity. Due to an earlier maturation of subcortical compared to neocortical regions (Mills et al., 2021), we predict **(H1.2)** mother-child similarity in subcortical structures to be higher compared to similarity in neocortical structures. Due to the strong association between parental and child well-being (Carlsson et al., 2014; Fan et al., 2020), **(H2)** similarity in scores of well-being in mother-child dyads is expected. Previous studies have reported that higher brain similarity is linked to higher similarity in behavioral correlates that are associated with psychosocial functioning, impacting individuals' mental well-being (Baek et al., 2022; Finn et al., 2018; Lee et al., 2017; Nummenmaa et al., 2012; Parkinson et al., 2018). Based on the crucial role of the corticolimbic circuitry in emotion processing and regulation associated with mental well-being and psychopathologies (Comte et al., 2018; Gee, 2016; Kim et al., 2019; Raschle et al., 2019), we hypothesize that **(H3)** the degree of dyadic similarity in the corticolimbic circuitry is linked to the degree of dyadic similarity in well-being.

## 2. Methods

### 2.1. Participants

Forty-one mother-child dyads, including 35 mothers and 41 children (six mothers participating with two children) participated in our neuroimaging study, which included the acquisition of anatomical brain data and behavioral assessments. Two dyads were excluded from the analyses due to missing scores and the note of a significant developmental delay of one child, respectively. This resulted in a final sample of 39 mother-child dyads, including 39 children (16 ♀; age range: 7–13 years, mean age = 9.41 ± 2.09 years) and 33 mothers (age range: 26–52 years, mean age = 40.97 ± 5.95 years). All children had average or above-average IQ scores (mean verbal IQ = 111.54 ± 17.17, mean nonverbal IQ = 109.23 ± 13.79). Mothers' education was measured through the International Standard Classification of Education (ISCED; (Organisation for Economic Co-operation and Development, 1999)). Mothers had a mean ISCED score of 5.48 ± 2.18, corresponding to short-cycle tertiary education and ranging from high school graduation

level to doctoral degree. The study was approved by the local ethics committee (Ethinkkomission Nordwest- und Zentralschweiz); children gave their assent and mothers signed an informed consent form for their children and themselves.

## 2.2. Behavioral assessments

Children's mental well-being was assessed through the Strengths and Difficulties Questionnaire (SDQ; (Goodman, 1997)). The SDQ is a brief behavioral screening questionnaire filled out by parents to assess psychological adjustment of children and adolescents between 4 and 17 years. Twenty-five items build five subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationships problem, and prosocial behavior. The scores of emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationships problem are summed into a total score, reflecting children's behavioral and emotional problems. Children's cognitive abilities were assessed through the fourth version of the Hamburg-Wechsler-Intelligenztest für Kinder (HAWIK-IV; (Petermann and Petermann, 2011)). The subtests matrix reasoning and vocabulary were applied to acquire children's verbal and non-verbal IQ.

Mothers' mental well-being was acquired through a self-report of the Brief Symptom Inventory (BSI; (Derogatis, 1993)) used for assessing subjective physical and psychological symptoms in adults. The questionnaire includes 53 items distributed in nine subscales: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. A global severity index was calculated as an average score across all 53 items. The ISCED scores (Organisation for Economic Co-operation and Development, 1999) and questions contained in the McArthur scale (Euteneuer et al., 2014) were used as a proxy for mothers' intelligence and socioeconomic status.

## 2.3. Neuroimaging

All participants completed a neuroimaging session conducted at the University Hospital in Basel, Switzerland. Whole-brain structural T1-weighted magnetization-prepared rapid gradient-echo data was acquired on a Siemens 3 T Prisma scanner with a 20-channel head coil. A simultaneous multislice acquisition procedure with the following specifics was applied: voxel size: $1.0 \times 1.0 \times 1.0$ mm; TR= 1900 ms; TE= 3.42 ms; TA= 4.26; flip angle= 9 degrees; field of view= $256 \times 256$ mm, 192 slices with a slice thickness of 1.00 mm. Dummy scans preceded image acquisition and were directly discarded, allowing accounting for T1 equilibration effects.

### 2.3.1. Data preprocessing

Structural neuroimaging data was preprocessed in FreeSurfer v7.1.0 (https://surfer.nmr.mgh.harvard.edu/) using the standard "recon-all" pipeline. The quality of the segmented and reconstructed images was visually inspected and in case of insufficient quality, i.e., inaccurate delineation of the pial surface, separating the cerebrospinal fluid and gray matter, and the white surface, separating the gray and white matter, manual corrections were implemented, and the preprocessing steps after the segmentation were repeated. The process of visual inspection, manual correction, and preprocessing for each participant was reiterated until no further edits of the delineation of the pial and white surfaces were needed.

### 2.3.2. Region of Interest (ROI) analyses

Gray matter volume (GMV) sum scores were built for corticolimbic network and relevant components of interest, including (**i**) the full corticolimbic circuitry (GMV$_{CLC}$) defined according to prior meta-analytic work by Alcalá-López et al. (2018) comprising one mask for subcortical (GMV$_{sc}$) and another for neocortical regions (GMV$_{nc}$). (**ii**) GMV$_{sc}$ included bilateral amygdala, hippocampus, and nucleus accumbens volumes. (**iii**) GMV$_{nc}$ included bilateral rostral anterior cingulate cortex and ventromedial prefrontal cortex. Subcortical ROIs were defined through FreeSurfer's automatic segmentation procedure (Fischl et al., 2002), whereas neocortical ROIs were based on the Desikan/Killiany atlas ((Desikan et al., 2006); individual GMV sum scores are provided in the Supplementary Table 1).

## 2.4. Data analysis

MATLAB-based scripts and R were used for behavioral and neuroimaging analyses, following pre-processing in Freesurfer.

### 2.4.1. Mother-child similarity in corticolimbic volume

First, a lasso-regression was conducted to identify the most relevant covariates when using mothers' corticolimbic gray matter to predict children's corticolimbic gray matter scores, employing the 'glmnet'-package in R. To this end, mothers' corticolimbic GMV, as a predictor of interest, was entered together with possible relevant covariates including children's age, age squared, sex, familial socioeconomic status, and mother-child age gap in a regression predicting children's corticolimbic GMV scores. Based on the lasso-regression output, children's sex was the only variable explaining relevant variation in outcome. Thus, all conducted analyses included children's sex as a covariate (except when testing for sex-difference between mother-daughter and mother-son similarity).

Mother-child similarity in corticolimbic GMV (**H1**) was examined by use of group-wise Pearson correlation. To test whether the obtained mother-child similarity is stronger in related pairings (i.e., higher similarity score for the group including mother-child dyads compared to groups where female adult-child pairs are randomly assigned) we implemented a permutation approach in Matlab (https://www.mathworks.com/products/matlab.html) in line with Fehlbaum et al. (2022). Group scores of unrelated female adult-child parings were calculated using thousand iterations resulting in the normal distribution of similarity scores between non-related adult-child pairings. The reiterations of all correlational scores were z-transformed, averaged, and back-transformed to a correlation coefficient reflecting the average group similarity of random adult-child pairs. The comparison between mother-child and average random adult-child group similarity was conducted in cocor through test for independent groups (Diedenhofen and Musch, 2015) and reported as a z-score, reflecting familial specificity.

Sex-specific mother-child transfer effects (**H1.1**) were tested by comparing mother-daughter and mother-son group similarity separately through the same procedure (e.g., correlation, permutation, average groups similarity assessment). Mother-daughter GMV similarity was compared to mother-son GMV similarity in cocor through a test for independent groups (Diedenhofen and Musch, 2015).

To test differences in neocortical and subcortical similarity (**H1.2**), the above procedure was repeated for each network. GMV$_{sc}$ similarity and GMV$_{nc}$ similarity were compared through analysis of dependent non-overlapping data in cocor (Diedenhofen and Musch, 2015).

Furthermore, regression analyses were conducted to estimate the predictive effect of maternal GMV on children's GMV. Children's sex was added as covariate of no interest to the regressions.

### 2.4.2. Mother-child similarity in well-being

To test (**H2**) mother-child similarity in psychological well-being, group-wise Pearson correlation deriving from children's SDQ total score and mothers' BSI global severity index were conducted. Next, a regression analysis was conducted introducing mothers' mental well-being (BSI global severity index) as a predictor and children's mental well-being (SDQ total score) as dependent variable.

### 2.4.3. Dyadic association between corticolimbic structure and mental well-being

Structural brain correlates and well-being scores of mothers and children were z-standardized. Degree of dyadic similarity was obtained by calculating the difference between child's and mother's z-standardized values for corticolimbic GMV and well-being for each mother-child dyad. Negative values reflect higher z-standardized scores in the mother compared to her child, while positive values indicate higher z-standardized scores in the child compared to its mother. The distribution of the dyadic mother-child scores was examined through Shapiro-Wilk test of normality. To test the predictive effect of dyadic similarity in corticolimbic GMV on dyadic similarity in well-being **(H3)**, a stepwise linear regression was calculated. The degree of dyadic similarity in well-being was entered as a dependent variable, while the degree of dyadic similarity in corticolimbic GMV was introduced as a predictor.

### 2.4.4. Post-hoc investigation in a control region

A post-hoc control investigation was conducted to test mother-child neural similarity in a control region of no interest (i.e., the primary visual cortex which is not part of the corticolimbic circuitry). Procedures followed the same approach as for all analyses reported for the corticolimbic tract: 1) extracted GMV values for the left and right primary visual cortex were combined for children's and mothers' scores separately; 2) mother-child similarity and familial specificity of the similarity scores was tested by comparing the mother-child similarity to unrelated female adult-child similarity; 3) mothers' and children's GMV scores were z-standardized and the degree of dyadic similarity was calculated as the difference between children's and mothers' z-standardized scores. A prediction model was calculated using the degree of dyadic similarity in well-being as an outcome and degree of dyadic similarity in the visual cortex's volume and children's sex as predictors.
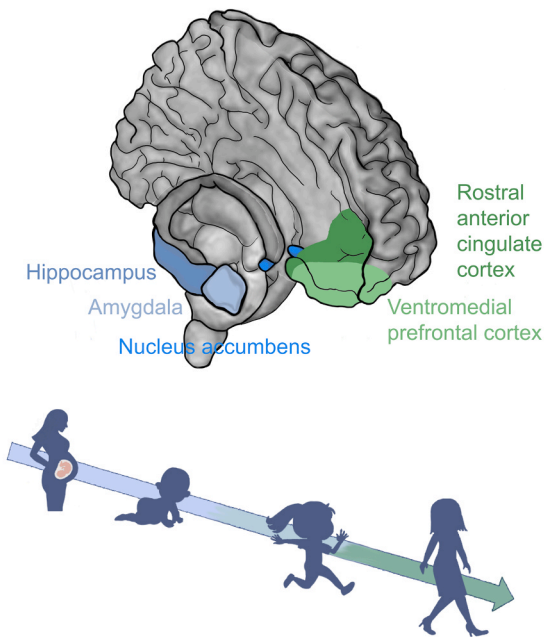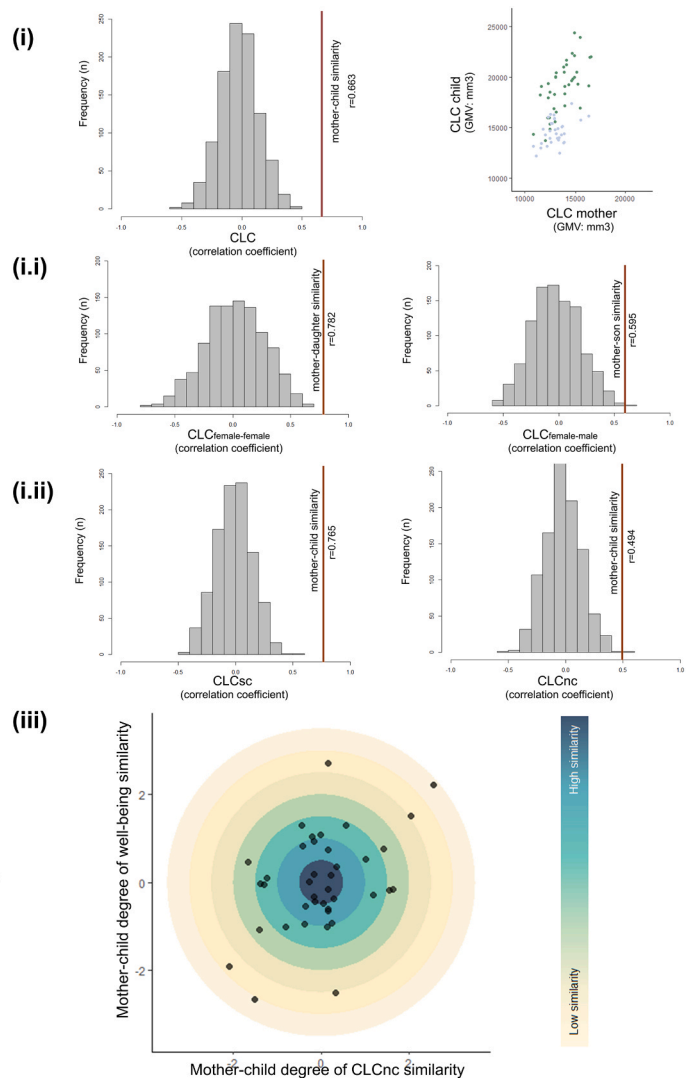


**Fig. 1.** Mother-child similarity in corticolimbic brain structure and mental well-being. Regions of interest for the corticolimbic circuitry (CLC) including subcortical structures (blue): amygdala, hippocampus, and nucleus accumbens and neocortical areas (green): rostral anterior cingulate and ventromedial prefrontal cortex are displayed on the left side along with the main aims and hypotheses investigated. Histograms and graphical displays of our main findings are illustrated on the right side and include: Histograms of the distribution of the group-wise similarity coefficients of 1000 iterations (gray bars) and group-wise similarity (vertical red line) for (i) mother-child dyads and similarity for the entire CLC; (i.i) individually, for mother-daughter (left) and mother-son (right) similarity for the entire CLC; (i.ii) for the subcortical (left; $CLC_{sc}$) and neocortical (right; $CLC_{nc}$) regions of the corticolimbic circuitry, respectively; and (iii) a scatterplot depicting the association between degree of dyadic similarity in neocortical gray matter volume and degree of dyadic similarity in well-being (darker colors indicate higher similarity). The scatterplot in the right upper corner includes mothers' and children's gray matter volume scores for subcortical (blue) and neocortical (green) regions of interest.

## 3. Results

### 3.1. Mother-child similarity in corticolimbic volume

Mother-child group-wise similarity in GMV within the corticolimbic circuitry **(H1)** was significant ($r(37) = 0.663$, $p < 0.001$, *95% CI [0.439, 0.809]*) and higher as compared to groups of random adult-child pairings ($r(37) = -0.025$, $p = 0.516$; $z = 3.492$, $p = 0.001$, *95% CI [0.299, 1.033]*; Fig. 1, right panel (i)).

Both, mother-daughter and mother-son groups demonstrated significant GMV similarity ($r_{mother-daughter}(14) = 0.782$, $p < 0.001$, *95% CI [0.468, 0.921]*; $r_{mother-son}(21) = 0.595$, $p = 0.003$, *95% CI [0.242, 0.809]*), which was higher as compared to groups with random adult-child pairings for both mother-daughter ($r(14) = 0.019$, $p = 0.505$; $z = 2.633$, $p = 0.009$, *95% CI [0.181 1.283]*) and mother-son dyads ($r(21) = -0.027$, $p = 0.489$; $z = 2.253$, $p = 0.024$, *95% CI [0.076, 1.082]*; Fig. 1, right panel (i.i)). The comparison between the group-wise similarity of mother-daughter and mother-son dyads **(H1.1)** did not reveal a significant difference ($z = 1.025$, $p = 0.305$, *95% CI [−0.193, 0.566]*). In order to follow-up on this finding and based on prior evidence of sex-specific transfer effects (Minami et al., 2022; Yamagata et al., 2016), a post-hoc analysis was conducted in GPower 3.1 (https://gpower.software.informer.com/3.1/) to assess whether the present group size and power for the identification of sex-differences may have impacted our results. The examination revealed an effect size of 0.365 and power of 0.176, indicating that a larger sample than the one examined here would be required for detecting a significant difference between mother-daughter and mother-son similarity. Thus, the lack of difference between mother-daughter and mother-son similarity should be interpreted with caution.

Mother-child dyads demonstrated similarity for both, subcortical and neocortical regions ($r_{sc}(37) = 0.765$, $p < 0.001$, *95% CI [0.593, 0.871]*; $r_{nc}(37) = 0.494$, $p = 0.002$, *95% CI [0.211, 0.700]*). Random adult-child group similarity was non-significant at $r(37) = -0.016$, $p = 0.508$ for subcortical and at $r(37) = -0.024$, $p = 0.514$ for neocortical regions and overall differed significantly from mother-child similarity ($z_{sc} = 4.347$, $p < 0.001$, *95% CI [0.420, 1.112]*; $z_{nc} = 2.399$, $p = 0.016$, *95% CI [0.093, 0.893]*; Fig. 1, right panel (i.ii)). The comparison between mother-child similarity in subcortical and neocortical regions of the corticolimbic circuitry **(H1.2)** revealed a significantly higher similarity index for subcortical regions ($z = 2.173$, $p = 0.030$, *95% CI [0.026, 0.556]*).

Linear regression analyses further revealed that mothers' corticolimbic GMV significantly predicted children's corticolimbic GMV ($\beta = 0.610$, $t(36) = 5.314$, $p < 0.001$; $F(3,36) = 20.150$, $p < 0.001$, adjusted $R^2 = 0.502$). Since our results indicated significantly stronger mother-child similarity scores for subcortical compared to neocortical areas, regression analyses were conducted with subcortical and neocortical regions separately (individual scores depicted in Fig. 1, right upper corner). Maternal subcortical GMV scores significantly predicted children's subcortical GMV ($\beta = 0.725$, $t(36) = 7.136$, $p < 0.001$; $F(3,36) = 35.050$, $p < 0.001$, $R^2 = 0.628$). Mother's neocortical GMV was a significant predictor for children's neocortical GMV ($\beta = 0.463$, $t(36) = 3.407$, $p = 0.002$; $F(3,36) = 9.181$, $p = 0.001$, adjusted $R^2 = 0.301$).

### 3.2. Mother-child similarity in well-being

Well-being scores of children and mothers **(H2)** were significantly positively associated ($r(37) = 0.409$, $p = 0.011$, 95% CI [0.108, 0.642]). A linear regression analysis revealed that mothers' mental well-being (BSI global severity index) was a significant predictor for children's well-being (SDQ behavioral problems score; $\beta = 0.401$, $t(36) = 2.288$, $p = 0.011$; $F(3,36) = 4.772$, $p = 0.015$, adjusted $R^2 = 0.166$).

### 3.3. Dyadic association between corticolimbic structure and mental well-being

Since our analyses investigating mother-child similarity in neocortical and subcortical corticolimbic GMV revealed a stronger similarity for sub- as compared to neocortical regions (possibly due to a prolonged maturation of neocortical region), we examined the predictive effect of degree of dyadic similarity in neocortical and subcortical regions individually. The scores reflecting the degree of dyadic similarity were normally distributed for well-being (W=0.978, $p = 0.646$), subcortical GMV (W=0.988, $p = 0.945$), and neocortical GMV (W=0.957, $p = 0.147$). In our third hypothesis **(H3)**, we tested whether the degree of dyadic similarity in well-being was significantly predicted by the degree of dyadic $GMV_{sc}$ and/or $GMV_{nc}$ similarity, while controlling for children's sex. Based on the Bayesian information criterion, the model including the degree of dyadic $GMV_{nc}$ similarity was preferred. The degree of dyadic similarity in well-being is significantly predicted by the degree of dyadic similarity in $GMV_{nc}$ ($\beta = 0.372$, $t(36) = 2.417$, $p = 0.021$; $F(3,35) = 4.838$, $p = 0.014$, adjusted $R^2 = 0.168$). The degree of dyadic similarity in $GMV_{nc}$ and well-being is plotted in Fig. 1, right panel (iii).

### 3.4. Post-hoc investigation in a control region

A complementary post-hoc investigation, conducted for the primary visual cortex as a control region outside of the corticolimbic circuitry revealed significant mother-child similarity ($r(37) = 0.612$, $p = 0.001$, 95% CI [0.368, 0.777]) that was significantly higher than the average random female adult-child similarity ($r(37) = -0.019$, $p = 0.503$; $z = 3.103$, $p = 0.002$, 95% CI [0.231, 0.986]) for the visual cortex. Next, the regression model testing the predictive effect of degree of dyadic similarity in the visual cortex on the degree of dyadic similarity in well-being revealed no significant association between degree of dyadic similarity in visual cortex volume and well-being ($\beta = 0.092$, $t(36) = 0.556$, $p = 0.582$; $F(3,36) = 1.818$, $p = 0.177$, adjusted $R^2 = 0.041$).

## 4. Discussion

In a group of 39 mother-child dyads we demonstrate mother-child similarity in brain structure of the corticolimbic circuitry which is furthermore associated with dyadic similarity in mental well-being. Specifically, mother-child similarity in corticolimbic gray matter volume was significant and unique for mothers and their children. This means that mother-child group similarity was significant and stronger compared to random female adult-child pairs without a biological or personal relationship. Corticolimbic gray matter volume in mothers predicted corticolimbic gray matter volume in children. Further examinations revealed that mother-child similarity in subcortical regions, which tend to reach an earlier maturational peak, was higher compared to mother-child similarity in neocortical regions. However, the expected matrilineal transfer dominance with a stronger mother-daughter as compared to mother-son similarity for corticolimbic gray matter volume was not found, a result possibly impacted by the low power to examine such subgroups. Finally, the association between the degree of dyadic similarity in corticolimbic regions and mental well-being was tested. Variations in the degree of dyadic similarity in neocortical regions predicted the degree of dyadic similarity in mental well-being. Notably, distinct familial mother-child gray matter volume similarity was also observed for a control region outside of the corticolimbic tract (i.e., visual cortex), indicating that mother-child similarity in brain structures may be observed to various degrees for different regions of interest. The relevance of such similarities may thus mostly derive from relations to further behavioral variables (e.g., skill acquisition or mental well-being as demonstrated here for the corticolimbic tract).

## 4.1. Mother-child similarity in mental well-being

Past research has highlighted the important role intergenerational transfer mechanisms play for cognitive and behavioral skills development and mental well-being. For example, children's cognitive abilities such as coding speed and word fluency, are strongly associated with their parents' performance on the same tests (Anger and Heineck, 2010). Parental traits associated with mental well-being are similarly linked to their children's well-being (e.g., (Borbás et al., 2021)). Exemplary, impulsiveness in parents, which has been linked to internalizing disorders, has been associated with adolescents' depression symptoms (Wolff et al., 2020). Pointing into a similar direction, a study conducted in mothers and their kindergarten children revealed significant correlation between mothers' state anxiety and children's behavioral problems (Künster et al., 2012). In line with such findings, our analysis revealed similarity in scores of mental well-being between mothers and their children. Thereby, mothers' well-being significantly and positively predicted children's well-being scores. Notably, beyond the direct association tested here, bidirectional effects between mothers' and children's psychological well-being have to be expected and are suggested in ecological models (Paschall and Mastergeorge, 2016), thus warranting a closer investigation in future studies.

## 4.2. Mother-child similarity in the corticolimbic circuitry

We report significant mother-child similarity in corticolimbic gray matter volume, which is specific for mother-child pairs. Our findings are in line with previous research providing evidence for intergenerational transfer of morphological brain features (Bas-Hoogendam et al., 2018; Fehlbaum et al., 2022; Minami et al., 2022; Takagi et al., 2021; Yamagata et al., 2016). Contrary to the findings by Yamagata et al. (2016) and Minami et al. (2022) we did, however, not find a stronger mother-daughter similarity over mother-son similarity for corticolimbic gray matter volume, but the observed mother-child similarity effect was equally present for both sexes. Even though research highlights the importance to consider sex when studying brain structure (Aubert-Broche et al., 2013; Giedd, 2004; Mills et al., 2014, 2016, 2021; Raznahan et al., 2011), such differences may be less pronounced in the age-range of the participants studied here. Beyond that sex-specific effects may be less detectable within a similarity index resulting from mother and son/daughter dyads (Shafee et al., 2023). Additionally, a post-hoc power analysis indicated low power at the current group size, warranting caution when interpreting our results. Differences in findings might further be due to analytical strategies and sample choices between studies (e.g., distribution of age and sex across children).

When testing differences in mother-child similarity of neo- and subcortical regions, we observed stronger mother-child structural brain similarity in subcortical regions, including bilateral amygdala, hippocampus, and nucleus accumbens, as compared to neocortical regions of interest. Moreover, regression analyses revealed that for the present age group of 7–13-year-old children tested, maternal corticolimbic gray matter volume explained 50.2% of the variance in corticolimbic volume of their children. Moreover, subcortical gray matter volume explained 62.8% of the variance in subcortical GMV of children's corticolimbic circuitry, while maternal neocortical GMV explained a comparably lower, though still significant amount of children's GMV around 30.1%. This is in line with evidence reporting greater variance in the heritability of cortical thickness, ranging around 0–75% across the neocortex, compared to heritability of subcortical gray matter volume at 48–85% (Kremen et al., 2010). The authors suggested a larger effect of environmental factors contributing to the measure of cortical thickness in neocortical regions. However, the reported difference between neo- and subcortical areas is based on two different morphological features, cortical thickness and gray matter volume. Such may be interpreted with caution, since evidence suggests that similarity obtained by different morphometric measures may differ significantly even within the same

region (Fehlbaum et al., 2022).

Our findings of a higher similarity and predictiveness for subcortical compared to neocortical regions may partly be explained by differences in maturational peaks, with subcortical regions reaching an overall earlier peak in development. During late childhood and early adolescence, subcortical structures demonstrate moderate to no more changes in gray matter volume, while volumetric changes in prefrontal areas are still ongoing (e.g., continuing decreases in gray matter volume (Herting et al., 2018; Mills et al., 2014; Østby et al., 2009; Tamnes et al., 2013; Westlye et al., 2010)). Takagi et al. (2021) have reported increase in parent-child gray matter volume similarity during early adolescence. Since subcortical areas mature earlier and during a developmental period when parent-child relations hold great influence, alterations or disruptions in such systems may be supported best in the first few years of life through systemic family approaches. In contrast, alterations in neocortical morphology and function may be open to change for a longer time, and receptive to treatment and intervention approaches that can further leverage beyond the primary relations of the adolescent and employ strategies involving counterparts from other social environments. Nevertheless, the here reported differences in neo- and subcortical areas of interest may have to be considered with caution from a methodological perspective. While we performed visual inspections and extensive quality control prior to analyzing the structural data from all participants, we cannot exclude the possibility that the higher reliability of measuring volumes in subcortical over neocortical regions (Hedges et al., 2022) could have affected our findings.

## 4.3. Relating dyadic corticolimbic scores to well-being

Our analysis revealed that degree of dyadic similarity in neocortical but not subcortical gray matter volume of the corticolimbic circuitry in mothers and their children predicted the degree of similarity in their scores of well-being. More precisely, those mother-child dyads, whose neocortical GMV indices were less similar, also differed more in well-being, while dyads with more similar neocortical GMV were also more similar in their mental well-being scores. Ultimately, our study points toward the possibility that diverging from one's parents' scores in neurobiological markers and/or well-being outcomes may be a marker of resilience (advantage) or reflects the potential for lower functioning despite the absence of known risk factors. In situations with an adverse upbringing or environment, divergence in well-being could be a sign of resilience. On the other hand, examining parent-child similarity in dyads where children, despite growing up in an expected environment, have poorer mental health, might provide important insights into the disruption of developmental trajectories associated with childhood psychopathologies.

The corticolimbic tract has been associated with emotion processing and regulation and alterations in these regions are commonly reported in psychopathologies (Comte et al., 2018; Goodkind et al., 2015; Kim et al., 2019; Raschle et al., 2019; Silvers et al., 2021). While emotion processing and emotional reactivity are linked to subcortical limbic structures, neocortical regions and particularly prefrontal areas are most strongly associated with emotion regulation and cognitive control (Gee et al., 2013). Hierarchical changes in the neural coupling between sub- and neocortical corticolimbic regions across age (Casey et al., 2019) are linked to the increasing importance of emotion regulation (John and Gross, 2004) required for independent and healthy social functioning. It could be hypothesized that a strong subcortical parent-child similarity may be mostly linked to individual emotional reactivity traits, which might not directly determine mental well-being. For example, studies show that the development of anxiety and depression following maltreatment is mediated by children's emotion regulation skills (Maughan and Cicchetti, 2002), which is similarly true for the relationship between later substance abuse and traumatic symptoms (Berking and Wupperman, 2012). Individuals' actions following the mere processing of emotions, include cognitive interpretation of the

given situation and require cognitive control associated with prefrontal neocortical regions. What sets children or individuals apart, may not be the emotions they encounter and process, but the ability how they deal with them. Our data may highlight the possibility that deviations from or similarity to parents in prefrontal cognitive control regions could be particularly relevant for understanding mental health determinants. Such may set individuals apart who succeed in breaking maladaptive intergenerational patterns.

Notably, the community sample tested in the present study does only reflect on a normative well-being range and does not include distinct clinical subpopulations. Similar investigations have been conducted previously (Fehlbaum et al., 2022; Lee et al., 2017; Yamagata et al., 2016), but particularly studies in clinical populations with an increased risk from a biological and possibly environmental level are missing. Such studies may add to our understanding of complex trait transfers in parents with psychopathologies or children at risk for developing these (Abraham et al., 2020; Minami et al., 2022).

Previous studies looking into the association between familial brain similarity and mental well-being, include results such as by Foland-Ross et al. (2016). Studying cortical thickness in a group of mothers with recurrent depression and their at-risk daughters revealed thinner cortical layer in the left fusiform area of both compared to a control group of mothers and daughters with no previous history of depression, where this association and similarity was not present. Furthermore, for mothers with a history of depression cortical thickness scores in left fusiform gyrus predicted cortical thickness in their never depressed daughters, which was again not evident in the control group. Even though not linked to current markers of mental health, the findings signal intergenerational transmission of neurobiological correlates, associated with depression, prior to any behavioral indications in the at-risk daughters' population. Another study examining parents with a history of depression and their children reported similarity in the default mode and central executive networks' gray matter volume in mother-daughter dyads, but not mother-son, father-daughter nor father-son dyads (Minami et al., 2022). Moreover, maternal gray matter volume in the right caudal medial frontal gyrus was negatively correlated with anxiety traits in their daughters. These findings suggest that morphological brain features associated with a history of depression are most likely transferred from mothers to their daughters pointing towards increased risk for disorder manifestation. Taken together, both studies highlight the importance of intergenerational designs for identifying vulnerable populations and developing appropriate prevention programs.

### 4.4. Limitations & outlook

The presented results should be cautiously interpreted in the light of several limitations. First, dyadic research requires large participant groups. To achieve higher power, data sharing initiatives bear the potential to overcome limitations of single site, smaller neuroimaging studies (Klapwijk et al., 2021). Second, the children's group included more male participants. While effects of age, age squared, and sex were tested, we cannot fully exclude the possible influence of non-linear age-effects. Further, the sample size does not allow for studying potential direct impact of the sex imbalance on some of our analyses. Replication in a larger group of mothers and children might allow in-depth investigation of potential linear and non-linear region-specific age effects that might influence the neural dyadic similarity outcomes within individual regions of interest. Third, no neuroimaging data had been obtained from the fathers of the participating children. Parent-child research has predominantly featured mothers, missing the opportunity to study the role of fathers. Another mentionable limitation is that children's well-being scores were based on maternal report. Potential reporting biases need consideration as mothers' well-being might impact the perception of their child's problem behavior. Last, the cross-sectional design of the study does not allow examination of

reciprocal effects, which can be expected in dyadic relations (Stone et al., 2016).

Overall, intergenerational neuroimaging designs promise to aid to our understanding of basic, developmental, and clinical neuroscience through the illustration of intergenerational transfer of complex traits, behaviors, and well-being (Ho et al., 2016). However, many points of investigations remain. Future studies may first of all target full families, including fathers, mothers, and their children. Next to sex- and age-specific considerations, maturity scores in children (Cantlon and Li, 2013) or neural deviation scores in parents (e.g., regionally-specific brain age) may be considered (Fandakova et al., 2015). Importantly, longitudinal investigations would provide an opportunity for tapping into bidirectional influences between environment and individual (Paschall and Mastergeorge, 2016). Additional collection of genomic data from the participating families and alternative family designs (e.g., studying the role of foster families and adoption) would provide further knowledge about the mechanisms underlying intergenerational transfer, including genetic and environmental considerations (Hart et al., 2021). Future studies should further test parent-child similarity in different morphological brain features and inform about metric-specific variations or developmental timing. Gray matter volume, cortical surface area, and cortical thickness have different ontogenesis and are influenced by distinct genetic and environmental factors unravelling during different time points of development. Therefore, the use of different correlates may provide complementary information beyond an individual correlate on its own (Kremen et al., 2013; Mills and Tamnes, 2022). Furthermore, examination of similarity scores in functional activation patterns and connectivity measures along with those in morphological brain features in the same regions, may advance our understanding about the underlying mechanisms of complex skill transmission on neurobiological level and the potential driving factors. Studies of intergenerational transmission of brain circuitries or behaviors linked to mental well-being, risk for developmental disorders, and resilience may consider further variables, for example dyadic similarity in cognitive functioning or socioeconomic status. Intelligence and socioeconomic status have both been associated with mental well-being (Deary et al., 2010; Zettergren and Bergman, 2014) and have been suggested to serve as a protective variable in children at risk for mental health struggles (Herrmann et al., 2018; Johnston and Iarocci, 2017). Ultimately, intergenerational neuroimaging may contribute to the identification of risk and protective factors (e.g., biological or environmental risk factors), intervention targets on a behavioral (e.g., family, peer or individual systems) or neural level and may thus support healthy development.

### 5. Conclusion

The current study reports familially specific mother-child similarity in the gray matter volume of the corticolimbic circuitry. Mother-child similarity was higher for subcortical, compared to neocortical regions. Furthermore, mother-child dyads with more similar neocorticolimbic indices show higher similarity in their mental well-being. An increase in knowledge on the mechanisms underlying intergenerational transfer effects reflected in biology and behavior of mother-child dyads may improve our understanding of complex skill transmission and trajectories leading to health and disease, thus possibly informing diagnosis, treatment or support programs.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101324.

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