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Maternal FGF2 Levels Associated with Child Anxiety and Depression Symptoms Through Child FGF2 Levels

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Abstract

Background: Recent research implicates fibroblast growth factor 2 (FGF2) in anxiety and depressive symptoms of childhood. This study is the first to examine an intergenerational pathway linking FGF2 levels in mothers to FGF2 levels in children, and to the children's anxiety and depressive symptoms.

Methods: We assayed serum FGF2 in 259 mothers and their children, with a range of anxiety and depressive symptoms: 194 were mothers of clinic-referred anxious and depressed children; 65 were mothers of non-referred children. We examined associations between FGF2 levels in mothers and children, and anxiety and depression symptoms. We used structural equation modeling (SEM) to examine associations between maternal and child FGF2 levels, and between maternal and child FGF2 levels and symptoms of anxiety and depression in and children.

Results: FGF2 levels in mothers and children were significantly positively correlated. Children's FGF2 levels were significantly negatively correlated with their ratings of anxiety and depression. Results of the SEM model showed that increases in maternal FGF2 levels were significantly

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All authors (Drs. Lebowitz, Marin, Orbach, Salmaso, Vaccarino, Silverman) participated in the design of the study and the writing and/or editing of the manuscript. Dr. Orbach performed the immunoassays measuring FGF2 levels.

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associated with increases in child FGF2, which in turn was associated with decreases in child anxiety and child depression, controlling for maternal anxiety and depression.

Limitations: We relied on self-reported ratings of anxiety and depression, and on a single measurement of FGF2 levels for each participant.

Conclusions: Our results point to a role for FGF2 in the intergenerational transmission of risk for, and resilience to, anxiety and depression in youth.

Keywords

Anxiety; Children; Depression; Fibroblast Growth Factor 2

Introduction

Anxiety and depressive disorders are highly prevalent among youth, with rates that have doubled since the COVID-19 pandemic, surpassing 20% for anxiety and 25% for depression (Racine et al., 2021). They frequently co-occur, suggesting shared underlying mechanisms and pathophysiology. Research implicates fibroblast growth factor 2 (FGF2), as one common biological substrate (Deng, Deng, Zhang, & Tang, 2019; Salmaso et al., 2016; Turner, Akil, Watson, & Evans, 2006)

Lebowitz and colleagues (2021) recently reported the first evidence linking serum FGF2 levels to indicators of anxiety and depression in youth. Children referred for anxiety and depression had significantly lower FGF2, compared with non-referred children. FGF2 levels were significantly negatively correlated with indicators of anxiety and depression, and positively correlated with reward responsiveness, which is impaired in depression.

In addition to these novel and significant group differences and correlations, confirmatory factor analysis (CFA) supported the contribution of FGF2 to a latent variable representing anxiety/depression. A well-fitted model emerged with FGF2 loading negatively on anxiety/depression, explaining approximately 5% of its variance.

These data further align with research suggesting alterations in growth factor systems can impact risk of psychopathology (Kiraly et al., 2017; Terwisscha van Scheltinga, Bakker, & Kahn, 2010) through subtle neurodevelopmental alterations to brain structure. The data highlight the potential role of FGF2 in intergenerational transmission of, or buffering against, vulnerability to anxiety and depression. Indeed, it is well-established that rearing environment and childhood events impact neurodevelopment with long-term effects (Fumagalli, Bedogni, Slotkin, Racagni, & Riva, 2005); FGF2 may play a role in such impact.

Converging lines of evidence support our hypothesis of an intergenerational pathway. FGFs are deeply implicated in neurodevelopment, regulating neurogenesis and neuronal repair, (Reuss & von Bohlen und Halbach, 2003) while genetic alterations in the FGF2 system lead to structural brain changes that impact risk of psychopathology (O'Donovan et al., 2009). In rodents, FGF2 gene-knockout likewise alters brain structure, including in cortical regions (Turner et al., 2006). Studies of environmental factors and manipulation also support FGF2's

role in vulnerability to anxiety and depression. FGF2 mediates rodent's neurobiological outcome following brain lesions, evidenced by heightened recovery in pups who received direct FGF2 administration, compared with lesioned pups who did not (Kolb & Gibb, 2007). Direct administration is not required however, for FGF2 to play a role in brain recovery. Repeated stroking, simulating parental rearing behavior, increased FGF2 release and improved recovery. Furthermore, stroking a pregnant mother rat attenuated the impact of future lesions on her offspring, as did direct administration of FGF2 to the pregnant rat (Kolb & Gibb, 2007). Additionally, prenatal stress in rat dams impacted offspring's FGF2 expression in multiple brain regions and altered FGF2 gene expression regulation in response to stress (Fumagalli et al., 2005). Exposure to glucocorticoid stress hormones during late pregnancy also led to persistent changes in the regulatory machinery of FGF2 in rats (Molteni et al., 2001).

These findings demonstrate FGF2's key roles influencing vulnerability to anxiety and depression through intergenerational processes. Here, we take an important next step toward elucidating these intergenerational pathways. Specifically, we examine pathways linking FGF2 levels in mothers to FGF2 levels in their children, *and* to their children's anxiety and depression symptoms.

Method

Participants

Participants were 259 mothers (26 to 64 years, $M = 42.64$ years, $SD = 6.39$) and their children with a broad range of anxiety and depressive symptoms: 194 were mothers of clinic-referred anxious and/or depressed children (47% female assigned at birth, 6 to 11 years, $M = 8.59$ years, $SD = 1.70$; mothers were 26 to 64 years, $M = 43.89$ years, $SD = 5.59$); 65 were mothers of non-referred children without psychiatric history (48% female assigned at birth, 6 to 12 years, $M = 8.65$ years, $SD = 1.95$; mothers were 27 to 55 years, $M = 39.00$ years, $SD = 7.19$). 149 (35%) of the children in this study participated in Lebowitz and colleagues (2021). Non-referred participants were recruited from the community and compensated $50 for their participation. Table S1 (see supplement) summarizes participant demographic characteristics.

Measures

Anxiety—Child Anxiety was assessed with the child-report Screen for Child Anxiety Related Disorders (SCARED; Birmaher et al.,1997). SCARED contains 41 items, rated on a 3-point scale. SCARED is widely used with established psychometric properties including internal consistency, test-retest reliability and validity (Monga et al., 2000). Internal consistency in the current sample was .91 for both Cronbach's α and McDonald's ω.

Maternal Anxiety was assessed using the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). BAI is a 21-item questionnaire rated on a four-point scale. Scores range from 0 to 63. BAI is widely used with well-established psychometric properties including internal consistency, test-retest reliability and validity (Fydrich, Dowdall, &

Chambless, 1992). Internal consistency in the current sample was .96 for both Cronbach's α and McDonald's ω.

Depression—Child Depression was assessed using the child-reported Children's Depression Inventory (CDI; Kovacs, 1980). CDI contains 27 items, each having three response options (e.g., *'I am sad once in a while, I am sad many times,* and *I am sad all the time*'). Total scores range from 0 to 54. CDI is widely used with established psychometric properties including internal consistency, test-retest reliability and validity (Logan & Goetsch, 1993). Internal consistency in the current sample was α = .88 and McDonald's ω = .86.

Maternal Depression was assessed using the Beck Depression Inventory (BDI; Beck, Epstein, Brown, & Steer, 1988). BDI is a 21-item self-report questionnaire rated on a four-point rating scale. Scores range from 0 to 63. BDI is widely used with well-established psychometric properties including internal consistency, test-retest reliability and validity. Internal consistency for in the current sample was .90 for both α and ω.

Serum FGF2 Levels—Samples were collected using VACUETTE® serum clot activator tubes (456073P, GREINER BIO-ONE). Samples were collected between 12PM and 3PM, after participants had arrived at the lab and completed other study tasks. After allowing samples to clot for 30 minutes at room temperature they were centrifuged for 30 minutes at 4000 rpm, aliquoted and stored at −80°C. FGF2 levels were analyzed using a high-sensitivity enzyme linked immunosorbent assay kit (HSFB00D; R&D Systems). Measurements were performed in triplicates and concentrations calculated using Prism7 (Graph-Pad) according to relevant standard curves.

Procedures

The study was approved by the University's Institutional Review Board. Following initial telephone-screening, children and mothers were invited for in-person evaluations. After providing informed assent/consent, children and mothers completed a standardized questionnaire battery and blood samples were collected by trained phlebotomists.

Data Analysis

To account for the significant differences between the clinic-and non-referred participants, we controlled for maternal age ($t(248) = 5.59$, $p < .001$), maternal ($\chi^2(5) = 53.09$, $p < .001$) and child race ($\chi^2(5) = 58.26$, $p < .001$), marital status ($\chi^2(3) = 37.25$, $p < .001$), and family income ($\chi^2(2) = 47.17$, $p < .001$), in relevant subsequent analyses. We used multiple regression with dummy coded variables (Jaccard & Tursi, 2003) to examine mean differences on study variables between the clinic-referred and non-referred samples. The regression coefficient associated with the 'Clinic vs non-Referred' variable represents the mean difference between the group scored 1 (non-referred sample) and the group scored 0 (clinic -referred sample). We used structural equation modeling (SEM) to examine associations between maternal and child FGF2 levels, and between maternal and child FGF2 levels and symptoms of anxiety and depression in and children. We followed recommendations by Kline (2016) to evaluate model fit.

Results

Preliminary Analyses

Robust multivariate outlier analyses were conducted using the projection-type method (Wilcox, 2011). This method revealed 15 outliers. Analyses were conducted with and without outliers and the statistical significance of all paths of interest remained the same. Analyses are thus presented with the outliers. To accommodate missing data and non-normality, we used full information maximum likelihood and a maximum likelihood estimator with robust standard errors, respectively as implemented in MPlus 8.5 (Muthén & Muthén, 1998–2012).

Main Analyses

Descriptive Statistics and Bivariate Correlations.—Descriptive statistics and correlations are presented in Table 1. We examined associations between maternal anxiety, depression, and FGF2, and their respective associations with child FGF2, anxiety and depression. Maternal and child FGF2 levels were significantly positively correlated. Maternal FGF2 levels were not significantly correlated with the other study variables. Children's FGF2 levels were significantly negatively correlated with their self-rated anxiety and depression; children's FGF2 levels were not significantly correlated with mothers' anxiety or depression.

Multiple regression showed that controlling for maternal age, maternal and child race, marital status, and family income, maternal FGF2 levels were not significantly different between the clinic-referred and the non-referred samples (β = 0.86, SE = .79, $t = 1.09$, $p = .28$). There were also no significant differences between the clinic- and non-referred samples on children's FGF2 levels (β = 1.60, SE = 1.11, $t = 1.45$, $p = .15$), or maternal depression (β = −0.92, SE = 1.11, $t = -0.82$, $p = .41$). Clinic-referred mothers rated themselves significantly higher in anxiety than non-referred mothers (β = −3.65, SE = 1.52, $t = -2.41$, $p = .02$). Clinic referred children rated themselves significantly higher in anxiety (β= −13.69, SE = 2.30, $t = -5.94$, $p < .001$) and depression (β= −17.67, SE = −0.84, $t = -17.30$, $p < .001$) than non-referred children.

Structural Model

Fit statistics for the SEM model (see Figure 1) indicated excellent model fit (i.e., chi square = 1.05, $p = .90$; RMSEA = .000; CFI = 1.0; SRMR = .02). Results showed that increases in maternal FGF2 (path coefficient = 0.43, 95% CI 0.16, 0.69, $p = .002$) were significantly associated with increases in child FGF2, which in turn was associated with decreases in child anxiety (path coefficient = −0.53, 95% CI −0.89, −0.18, $p = .003$) and depression (path coefficient = −0.38, 95% CI −0.72, −0.04, $p = .03$), controlling for maternal anxiety and depression. Pathways linking maternal symptoms (anxiety, depression) to child FGF2 and child symptoms were not significant. Findings indicate an indirect linkage between maternal FGF2 and child anxiety and depression via child FGF2 levels.

Discussion

We found maternal and child FGF2 levels are significantly positively correlated and increased maternal FGF2 is predictive of increased child FGF2, which in turn predicts lower levels of both anxiety and depressive symptoms in the child. This is the first study, though preliminary, to test an intergenerational pathway linking FGF2 and psychiatric symptoms in mothers to anxiety and depression in youth, through youth FGF2 levels. Our findings provide important and novel insight into the cross-generational transmission of anxiety and depression and the possible role for FGF2 in this complex process.

These findings align with the growing body of research surrounding the role of FGFs in the risk for psychiatric problems. Together, they indicate that higher maternal FGF2 may serve as a protective factor, buffering children against such risk and increasing resilience in the face of other risk factors, such as maternal anxiety and/or depression.

One potentially fruitful direction for future research relates to the genetic heritability of variations in FGFs, in particular FGF2. Research has begun to identify specific genetic markers implicated in the risk for anxiety disorders (Olfson et al., 2022). The current study cannot say whether, and to what extent, the correlation between maternal and child FGF2 levels results from genetic heritability or other, non-genetic, factors.

The intergenerational pathway also has potential translational implications. For example, given findings from animal research showing that environmental factors can continue to impact FGF2 postnatally, early life interventions in humans that increase FGF2 may reduce risk of anxiety and depression, with long-term benefits even across the life span.

It is notable that no significant correlation emerged between maternal symptoms of anxiety and depression and maternal FGF2 levels. More research, including with larger samples, is required to determine whether such a correlation does exist or whether the association is specific to youth. If the association is specific to youth, it will be important to determine why this is, as well to clarify the age at which this link tapers off.

Limitations include reliance on child-reported symptoms of anxiety and depression. Multi-informant data and direct behavioral observations provide a more comprehensive picture of youth's clinical presentation. FGF2 levels were assessed once, where repeated measurement may yield better indications of FGF2 functioning. This is mitigated by Lebowitz et al's (2021) findings indicating strong significant correlations between FGF2 measurements taken six months apart. Also of note, FGF2 levels were collected after participants had spent some time in the lab, completing other study tasks such as responding to questionnaires. Given evidence suggesting that FGF2 levels may increase in response to stress (Bland et al., 2007; Bryant, Richardson, & Graham, 2022; Turner, Eren-Koçak, Inui, Watson, & Akil, 2016), it is possible that the association between mother and child FGF2 was increased due to the shared experience of completing the other tasks before collection. This could represent either a genetic or non-genetic pathway as the FGF2 response to stress may itself be genetically heritable. This study along with that of Lebowitz and colleagues' (2021) underscore the need to conduct further research into FGF2's role in the cross-generation transmission of risk for, and resilience to, anxiety and depression in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Maternal FGF2 levels are positively correlated with youth FGF2 levels
- Maternal FGF2 levels are associated with youth anxiety symptoms through youth FGF2 levels
- Maternal FGF2 levels are associated with youth depressive symptoms through youth FGF2 levels
- Results demonstrate a novel cross-generational pathway for the role of FGF2 in the risk for, and resilience to, youth anxiety and depression

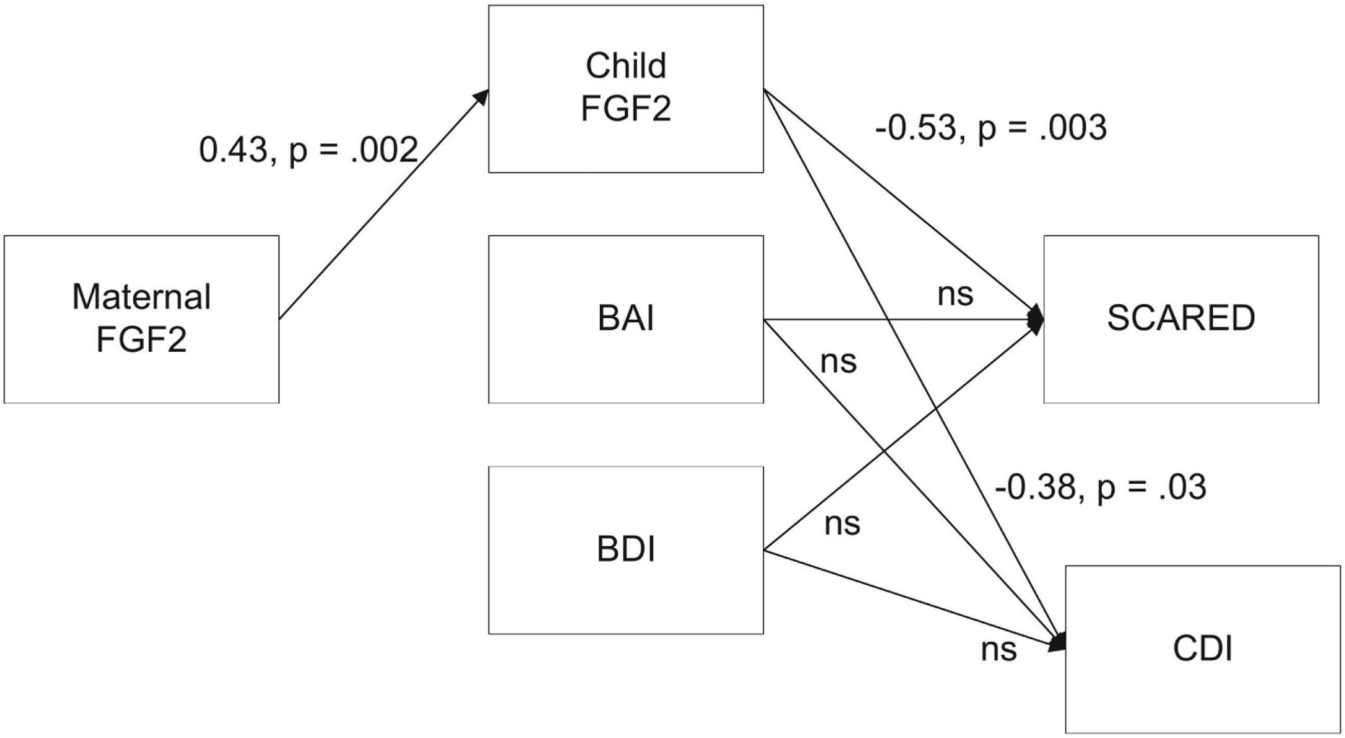

Fig. 1.

Note: SCARED: Screen for Child Anxiety Related Emotional Disorders; CDI: Child Depression Inventory; FGF2: Fibroblast Growth Factor 2; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory.

Table 1

Descriptive Statistics and Correlations for Study Variables

	M	*SD*	1	2	3	4	5	6
1. FGF2 mother	4.81	4.43	-					
2. FGF2 child	5.33	5.32	.37***	-				
3. BAI	7.65	9.36	.03	−.13	-			
4. BDI	6.66	6.95	.07	−.09	.59***	-		
5. SCARED	27.36	14.08	−.05	−.24***	.08	.11	-	
6. CDI	20.62	9.34	−.09	−.28***	.15*	.08	.39***	-

Note. BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; SCARED = Screen for Child Anxiety and Related Emotional Disorders; CDI = Children's Depression Inventory.

* $p < .05$;

** $p < .01$;

*** $p < .001$