



Neural markers of familial risk for depression – A systematic review

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ABSTRACT

Structural and functional brain alterations are found in adults with depression. It is not known whether these changes are a result of illness or exist prior to disorder onset. Asymptomatic offspring of parents with depression offer a unique opportunity to research neural markers of familial risk to depression and clarify the temporal sequence between brain changes and disorder onset. We conducted a systematic review to investigate whether asymptomatic offspring at high familial risk have structural and functional brain changes like those reported in adults with depression. Our literature search resulted in 44 studies on 18,645 offspring ranging from 4 weeks to 25 years old. Reduced cortical thickness and white matter integrity, and altered striatal reward processing were the most consistent findings in high-risk offspring across ages. These alterations are also present in adults with depression, suggesting the existence of neural markers of familial risk for depression. Additional studies reproducing current results, streamlining fMRI data analyses, and investigating underexplored topics (i.e. intracortical myelin, gyrification, subcortical shape) may be among the next steps required to improve our understanding of neural markers indexing the vulnerability to depression.

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide (Herrman et al., 2022). It is characterized by episodes of sadness and lack of interest, that can last weeks, months, and in some cases years. The highest risk for depression onset is during adolescence and early adulthood (Duan et al., 2019). Depression affects between 30 % and 40 % of the world's population during their lifetime (James et al., 2018). The contribution of genetic and environmental factors to depression can also be expressed at the level of brain development (Nabeshima and Kim, 2013). Structural and functional differences in the brain of depressed adults have been found in key areas associated with mood, thought regulation, and reward behavior (Dai et al., 2019). Whether these neural markers precede depression onset and increase vulnerability to the disorder or develop during the illness is an open question. Detecting neural markers that precede and predict MDD would allow for earlier implementation of interventions that could improve the quality of life, prevent, or delay MDD onset and decrease the economic burden on the healthcare system (de Oliveira et al., 2020).

High familial risk studies can provide some insight into whether neural markers predate or occur during depression. One of the strongest risk factors for MDD is having a parent with MDD, with both, shared genetic and environmental factors playing a role (Uher et al., 2014; van Dijk et al., 2021). One in three high familial risk offspring will go on to develop a mood or psychotic disorder by early adulthood (Rasic et al., 2013). Therefore, examining at-risk offspring allows us to identify possible early neural markers before disorder onset.

1.1. Neural markers of depression in adults

Magnetic Resonance Imaging (MRI) provides a non-invasive method of identifying disorder-related patterns of brain changes associated with MDD (Zhang et al., 2018). Structural scan sequences allow us to investigate brain morphology, such as cortical and subcortical gray matter volumes. Diffusion tensor imaging (DTI) helps examine white matter microstructure by imaging intricate connectivity networks within the brain (Soares et al., 2013). Functional magnetic resonance imaging (fMRI) depicts brain function, showing live activation patterns at rest

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and/or during tasks (Zhang et al., 2018). We briefly present the most consistent findings from large-scale neuroimaging studies of depression below.

1.1.1. Brain structure

Cortical volume is composed of cortical thickness and cortical surface area, which are genetically and phenotypically distinct (Panizzon et al., 2009; Winkler et al., 2010). Adults with MDD have thinner orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, and temporal lobes (Bora et al., 2012; Lai, 2013; Zhao et al., 2014). Reduced cortical thickness in these regions is associated with poorer clinical outcomes and may contribute to emotional and cognitive regulation deficits seen in depression (Schmaal et al., 2017). In contrast, the surface area was not significantly altered in MDD adults, suggesting a specific involvement of cortical thickness in depression (Schmaal et al., 2020).

Subcortical gray matter regions, that contribute to memory and emotion, have been extensively studied. The hippocampus, a region implicated in memory and reward, is smaller in adults with MDD with the CA-1 region particularly affected (Geerlings and Gerritsen, 2017; Grasby et al., 2020; Ho et al., 2022, Schmaal et al., 2016). The thalamus, a subcortical structure that helps control and integrate emotion, memory, and arousal, shows significant volume reductions in adults with depression (Lu et al., 2016; Zhang et al., 2016). Findings on the structure and volume of the amygdala, a critical contributor to emotional response, are inconsistent with some evidence suggesting a larger amygdala whilst others report volume reduction (Ho et al., 2018; Schmaal et al., 2016).

Fractional anisotropy (FA) is frequently used to measure white matter. Higher FA values are observed when the diffusion of water molecules is directionally constrained, suggesting a greater degree of white matter integrity and compactness of white matter tracts (Soares et al., 2013; van Velzen et al., 2020). Depression is associated with reduced FA in the corpus callosum, corona radiata, internal capsule, external capsule, uncinate fasciculi, and cingulate gyrus (van Velzen et al., 2020). The poorer structural integrity of these white matter tracts may contribute to deficits in mood regulation (Sanjuan et al., 2013; Schmaal et al., 2020).

1.1.2. Brain function

fMRI is the most common method of measuring brain function by detecting changes in magnetic properties of blood volume associated with brain activation (Chow et al., 2017). Brain function may be measured at rest, referred to as resting state, or while performing a task, such as reacting to emotional stimuli or participating in a reward/loss game. The fMRI method has larger heterogeneity of preprocessing and analytical methods than structural MRI, leading to greater variability of findings (Zhuo et al., 2019). The default-mode network (DMN) is most active when a person is in a state of wakeful rest and plays an important role in executive functioning (Sormaz et al., 2018). Meta-analyses have been inconsistent, with stronger (hyperconnectivity) and weaker (hypoconnectivity) DMN connections observed (Kaiser et al., 2015; Yan et al., 2019). Meanwhile, the cognitive control network (CCN) which is responsible for goal-directed thought processes, appears to be hypo-connected in adults with depression (Kaiser et al., 2015). Reduced activity in the reward network, specifically between the striatum-PFC and striatum-ACC, is found in MDD and related to increased depression severity (Satterthwaite et al., 2015; Segarra et al., 2016; Zhang et al., 2018). There is little agreement among task-based fMRI studies that investigate emotion regulation due to the larger heterogeneity of network region interest, making it difficult to draw conclusions across findings (Schmaal et al., 2020).

1.2. Current review

In this review, we will synthesize evidence from high familial risk

studies to investigate whether neural markers found in adults with depression exist in asymptomatic youth. We focus on four distinct periods of development to detect when brain differences may first emerge, including infancy (> 2), childhood (2 – 10), adolescence (11 – 18), and early adulthood (19 – 25). These age groups were selected to reflect stages of common cognitive, behavioral and neural development (Hardin et al., 2017). We expected familial high risk (FHR) youth to show similar trends to adults with depression, including reduced cortical thickness, reduced hippocampal volumes, and aberrant resting-state and reward network activation. We conclude by comparing our findings across ages and to adults with MDD followed by discussing limitations and future directions in this research field.

2. Methods

We conducted this review using Ovid MEDLINE and EMBASE databases for peer-reviewed studies published up to January 7th, 2022. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were adhered to (Liberati et al., 2009). We created a search strategy with the following search terms: (infan* OR bab* OR child OR youth OR adolescen* OR teen* OR young adult OR offspring* OR son* OR daughter* OR develop*) AND (paren* OR mother* OR maternal OR father* OR paternal OR famil* OR risk) AND (depress* OR MDD OR major depressive disorder OR major mood disorder) AND (neuro* OR brain*) AND (chang* OR alter* OR diff* OR function* OR structur* OR MRI* OR fMRI* OR connect* OR network*).

Search results were screened in two stages. First, authors AN and RU screened search results for relevance based on title and abstract, followed by a full-text review to confirm eligibility (Fig. 1). Disagreements at each stage were discussed and final decisions were made by consensus. References of eligible studies were examined to detect articles that might have been missed by the initial search. Studies were included if their primary aim was to investigate structural and/or functional brain differences between FHR and familial low risk (FLR) offspring. The FHR group was defined as having at least one parent with either a lifetime (past or present) major depressive disorder or elevated depressive symptoms throughout the majority of the offspring's lifetime (i.e. maternal prenatal and/or postnatal depression). The latter group was included because depressive symptomology is the common paradigm present in literature that assesses younger (i.e. infants, pre-school) FHR offspring. FLR group included offspring of parents with no history of major mood and/or psychotic disorders. We excluded studies where the offspring had a current or lifetime history of major mood or psychotic disorder themselves at the time of brain scanning. To map brain differences across the developmental brain period, we included studies with offspring between the ages of 1 week to 25 years.

Table 1 presents a summary of the 44 eligible articles, included in this review. All results from eligible studies presented in this review made cross-sectional comparisons between neural markers in FHR and FLR youth.

3. Results

3.1. Infancy

This literature review identified 5 studies on the brain of 246 infants aged 5–40 weeks (Table 1. A). This includes 3 studies assessing brain structure, 1 study assessing brain function, and 1 study assessing both.

3.1.1. Brain structure

Maternal depression may have significant implications on offspring brain development from an early age (Duan et al., 2019). Literature on FHR infants and young children largely focuses on the effects of maternal depression during pregnancy and the postnatal period. FHR infants as young as 4 weeks show structural brain differences compared to FLR. Three out of three studies on white matter identified reduced

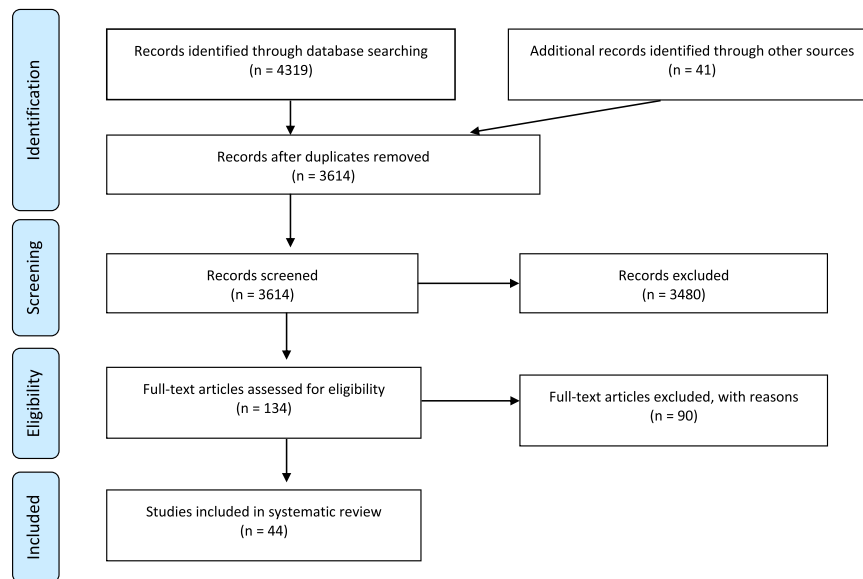


Fig. 1. Systematic review PRISMA flow diagram for study selection.

white matter connectivity in areas involved in emotion processing, such as in the uncinate fasciculus, amygdala-ventral PFC pathway and within the amygdala microstructure (Dennis et al., 2019; Posner et al., 2016; Rifkin-Graboi et al., 2013). Two studies reported alterations of subcortical grey matter volumes with FHR infants showing smaller midbrains and larger caudate, putamen, globus pallidus, and thalamus volumes (Rifkin-Graboi et al., 2013; Sethna et al., 2021).

3.1.2. Brain function

Two studies on resting state in FHR infants reported altered connectivity between key emotion processing regions, such as between the amygdala and PFC. However, contradicting results make the directionality unclear, with both hyperconnectivity and hypoconnectivity suggested (Posner, 2016; Qiu et al., 2015). The relatively small size of existing literature and heterogeneous methods may indicate that no association is present, with contradicting results possibly representing noise rather than true signal.

3.2. Childhood

This literature review identified 12 studies on the brain of 11,205 children aged 3–10 years (Table 1. B). This includes 7 studies assessing brain structure and 5 studies assessing brain function.

3.2.1. Brain structure

Three studies reported that increased maternal depressive symptoms during the second trimester, and 2 months postnatally, were associated with reduced cortical thickness in preschool and elementary school-aged children (El Marroun et al., 2016; Lebel et al., 2016; Sandman et al., 2015). Although reduced cortical thickness has been detected across studies, there is less agreement on which specific cortical regions are affected. The largest study (N = 654) in this age group reported reduced cortical thickness in the left superior frontal gyrus only (El Marroun et al., 2016), whilst others suggest different frontotemporal regions to be affected, including the right superior and medial orbital PFC, right inferior frontal region, and middle and superior temporal regions (Lebel et al., 2016; Sandman et al., 2015). One study also observed an increase in the surface area of the caudal middle frontal region in FHR youth (El Marroun et al., 2016).

A reduction of the putamen and right nucleus accumbens, both structures part of the basal nuclei that aid in movement coordination, have been detected in FHR children (Pagliaccio et al., 2014). FHR

children also show reduced hippocampal volume as well as a smaller CA-1 region (Hubachek et al., 2021). Changes in amygdala volume remain unclear. All three studies on this topic reported different directionality, including smaller right amygdala volume, increased bilateral amygdala volumes in FHR girls only, and no significant differences between FHR and FLR children (Acosta et al., 2020; Pagliaccio et al., 2020; Wen et al., 2017). When examining the microstructure of white matter fibers within the amygdala, postnatal depression in mothers was associated with increased FA of the right amygdala in offspring (Wen et al., 2017).

3.2.2. Brain function

FHR 5-year-old children have reduced resting state functional connectivity between the right amygdala and left OFC and temporal pole (Soe et al., 2018). In addition, the same study reported a sex-specific effect, with FHR girls showing reduced connectivity between the left amygdala and right insula, right putamen, bilateral ACC, and bilateral caudate. The three studies investigating reward-task functional connectivity in young offspring of depressed mothers focused on the neural response elicited by gaining a reward. Overall, two out of the three studies detected hypoactivation of the striatum, with another reported hypoactivation of the dorsolateral PFC and parahippocampal gyri (Luking et al., 2016; Morgan et al., 2019; Wiggins et al., 2017). Furthermore, one of those studies observed that hypoactivation of the striatum was associated with reduced reward-seeking behavior in FHR children (Morgan et al., 2019).

As a result of region analysis, hyperactivation of FHR youth's amygdala in response to negative emotional stimuli has been reported in one task-based fMRI study on emotion regulation (van der Knaap et al., 2018).

3.3. Adolescents

This literature review identified 23 studies on the brain of 7028 adolescents aged 11–18 (Table 1. C). This includes 6 studies assessing brain structure, 16 studies assessing brain function, and 1 study assessing both.

3.3.1. Brain structure

Two findings suggest that FHR daughters exhibit reduced cortical thickness, some of which is concordant with gray matter reductions seen in MDD. Adolescent females showed a significant reduction of cortical

Table 1
Systematic Review Article Summary Table.

A. Infants (> 2 years)							
Author	Year	N (Female)	Age years (SD)	Familial Risk Classification	Neuroimaging Measure	Region (s) of Interest	Main Finding
Sethna et al.	2021	FHR = 31 (11) FLR = 33 (27)	FHR = 0.4 (0.12) FLR = 0.4 (0.1)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical grey matter structure	Whole brain, midbrain.	↑ Caudate, putamen, globus pallidus and thalamus volume ↓ Midbrain volume
Dennis et al.	2019	Total = 24 (13)	Total = 0.55 (0.03)	Maternal depressive symptomatology: EPDS	White matter structure	Fronto-limbic regions, uncinate fasciculus	↓ FA of right uncinate fasciculus
Posner et al.	2016	FHR = 20 (14) FLR = 44 (23)	FHR = 0.1 (0.03) FLR = 0.1 (0.03)	Maternal depressive symptomatology: CES-D	Resting state fMRI; White matter structure	Amygdala, PFC	↓ Connectivity between amygdala and dorsal PFC ↓ Connectivity between R amygdala and R ventral PFC
Qiu et al.	2015	Total = 24 (12)	Total = 0.74 (0.02)	Maternal depressive symptomatology: EPDS	Resting state fMRI	Amygdala	↑ Connectivity between L amygdala and BL medial prefrontal cortex, ACC, insula, and temporal cortex
Rifkin-Graboi et al.	2013	FHR = 28 (13) FLR = 42 (19)	FHR = 0.77 (0.01) FLR = 0.77 (0.01)	Maternal depressive symptomatology: EPDS	White matter microstructure; Subcortical grey matter structure	Amygdala	↓ FA of amygdala = Amygdala volume
B. Childhood (2 – 10 years)							
El Marroun et al.	2016	Total = 654 (327)	Total = 7.9 (0.95)	Maternal depressive symptomatology: BDI	Cortical structure	Whole brain	↓ Thickness of L superior frontal gyrus ↑ Surface area of caudal middle frontal
Lebel et al.	2016	Total = 52 (20)	Total = 3.6 (0.5)	Maternal depressive symptomatology: EPDS	Cortical structure	Whole brain	↓ Thickness in R inferior frontal and medial and superior temporal areas
Sandman et al.	2015	Total = 82 (40)	N/A (6 – 9 range)	Maternal depressive symptomatology: CES-D	Cortical structure	Whole brain	↓ Thickness in R superior and medial orbital PFC
Hubachek et al.	2021	Total = 74 (31)	Total = 10.74 (0.84)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	↓ Hippocampal volume ↓ CA 1 region
Pagliaccio et al.	2020	FHR = 2938 (1407) FLR = 6780 (3217)	FHR = 9.8 (0.6) FLR = 9.9 (0.6)	Questionnaire battery of familial mental health history	Subcortical gray matter structure	Amygdala, hippocampus, striatum, pallidum, thalamus	↓ R putamen and nucleus accumbens volume
Acosta et al.	2020	Total = 28 (14)	Total = 4.2 (0.15)	Maternal depressive symptomatology: EPDS	Subcortical gray matter structure	Amygdala	↓ R amygdala volumes
Wen et al.	2017	Total = 235 (122)	Total = 4.58 (0.08)	Maternal depressive symptomatology: EPDS	White matter microstructure; Subcortical grey matter structure	Amygdala	↑ FA in R amygdala ↑ Amygdala volume in girls only
Soe et al.	2018	Total = 128 (71)	Total = 4.58 (0.08)	Maternal depressive symptomatology: EPDS, BDI	Resting State fMRI	Amygdala	↓ Connectivity between L amygdala and R insula, R putamen, BL ACC, BL caudate in girls only. ↓ Connectivity between R amygdala and L OFC, temporal pole.
Morgan et al.	2019	FHR = 25 (15) FLR = 31 (16)	FHR = 6.72 (N/A) FLR = 6.87 (N/A)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, OFC, PFC	↓ Activity of dorsal striatum to reward
Wiggins et al.	2017	FHR = 27 (14) FLR = 19 (14)	FHR = 7.44 (0.73) FLR = 7.64 (0.84)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, PFC, limbic regions	↓ Activation of R DLPFC and parahippocampalgyrus to reward ↑ Activation of R DLPFC and parahippocampal gyms to loss
Luking et al.	2016	FHR = 16 (8) FLR = 32 (17)	FHR = 9.05 (1.14) FLR = 9.28 (1)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, insula, ACC, amygdala	↓ Activation of striatum and anterior insula to reward ↓ Activation of striatum, anterior insula and parahippocampal regions to loss
van der Knaap et al.	2018	FHR = 47 (28) FLR = 37 (14)	FHR = 7.75 (0.76) FLR = 7.77 (0.95)	Maternal depressive symptomatology: BDI	Emotion regulation fMRI	Amygdala	↑ Activation of BL amygdala to negative emotional faces
C. Adolescents (11 – 18)							
Foland-Ross et al.	2016	FHR = 14 (14) FLR = 23 (23)	FHR = 14.11 (2.33) FLR = 13.29 (2.41)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Whole brain	↓ Thickness of fusiform, inferior, temporal, and lateral occipital gyri
Foland-Ross et al.	2015	FHR = 28 (28) FLR = 35 (35)	FHR = 13.2 (1.5) FLR = 13.9 (1.7)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Whole brain	↓ Thickness of R fusiform gyrus
Chai et al.	2015	FHR = 36 (18) FLR = 14 (6)	FHR = 11.1 (1.35) FLR = 11.6 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Emotion regulation fMRI; Subcortical gray matter structure	Amygdala	↑ Activation of amygdala to fearful faces ↓ Activation of ACC and supramarginal gyms to happy faces ↓ Amygdala volume

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Table 1 (continued)

A. Infants (> 2 years)							
Author	Year	N (Female)	Age years (SD)	Familial Risk Classification	Neuroimaging Measure	Region (s) of Interest	Main Finding
Mannie et al.	2014	FHR = 62 (39) FLR = 59 (35)	FHR = 18.8 (1) FLR = 19 (0.8)	Parental depression reported by participant	Subcortical gray matter structure	Hippocampus	= Hippocampal volume
Chen et al.	2010	FHR = 23 (23) FLR = 32 (32)	FHR = 12.76 (1.6) FLR = 12.9 (1.55)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	↓ Hippocampal volume
Hung et al.	2016	FHR = 20 (10) FLR = 20 (10)	FHR = 11.1 (1.57) FLR = 10.65 (2.12)	Parental depression: Structured clinical interview for DSM-IV	White matter structure	Whole brain	↓ FA in anterior cingulum, genu of corpus callosum.
Huang et al.	2011	FHR = 18 (10) FLR = 13 (7)	FHR = 15.7 (2.3) FLR = 15.5 (3)	Parental current and lifetime mood disorder diagnoses: FH-RDS	White matter structure	Whole brain	↓ FA in the L cingulum, splenium of corpus callosum, superior longitudinal fasciculi, uncinate fasciculi, inferior fronto-occipital fasciculi
Hirshfeld-Becker et al.	2019	FHR = 15 (N/A) FLR = 8 (N/A)	FHR = 10.9 (1.51) FLR = 11.3 (1.84)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	ACC	↑ Connectivity between subgenual ACC and inferior parietal lobule
Fischer et al.	2018	FHR = 20 (20) FLR = 25 (25)	FHR = 18.94 (2.62) FLR = 18.99 (2.61)	Maternal depression: Structured clinical interview for DSM-IV	Resting State fMRI	Limbic regions, ECN, SN	↑ Connectivity between amygdala and PFC ↑ Connectivity within SN ↑ Connectivity within CCN
Singh et al.	2018	FHR = 39 (21) FLR = 39 (24)	FHR = 13.93 (2.38) FLR = 13.85 (2.45)	Parental depression: Structured clinical interview for DSM-IV, FIGS	Resting State fMRI	Amygdala, ACC, PFC	↓ Connectivity between amygdala and R PFC ↓ Connectivity between amygdala and precuneus
Singh et al.	2018	FHR = 49 (22) FLR = 31 (26)	FHR = 12.98 (2.62) FLR = 12.55 (3.04)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	PCC	↓ Connectivity between PCC and BL amygdala, hippocampus
Chai et al.	2016	FHR = 27 (13) FLR = 16 (8)	FHR = 11.2 (1.67) FLR = 11.3 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	Limbic regions, DMN, CCN	↑ Connectivity between DMN and subgenual ACC ↑ Connectivity between amygdala and R inferior frontal gyrus ↓ Connectivity between L DLPFC and subgenual ACC ↓ Connectivity within CCN
Frost Bellgowan et al.	2015	FHR = 16 (8) FLR = 18 (9)	FHR = 13.2 (0.7) FLR = 12.6 (0.7)	Maternal depression: Structured clinical interview for DSM-IV	Resting State fMRI	DMN, SN	↓ Connectivity between DMN and R ventral striatum, BL postcentral gyri, and R posterior insular cortex
Clasen et al.	2014	FHR = 11 (11) FLR = 13 (13)	FHR = 13.82 (0.75) FLR = 13.54 (0.88)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	CCN	↓ Connectivity between R inferior frontal gyrus and R dorsolateral PFC, BL medial PFC
Fischer et al.	2019	FHR = 17 (17) FLR = 18 (18)	FHR = 18.74 (2.47) FLR = 19.09 (2.93)	Maternal depression: Unspecified	Reward processing fMRI	Striatum	↓ Activation of striatum during reward anticipation ↑ Activation of middle frontal gyrus during reward anticipation ↓ Activation of superior frontal gyrus and cuneus during reward
Colich et al.	2017	FHR = 15 (15) FLR = 23 (23)	FHR = 12.83 (1.57) FLR = 13.07 (1.36)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain	↓ Activation of putamen to loss
Olino et al.	2015	Total = 33 (19)	Total = 12.98 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain, striatum	↓ Activation of ventral striatum and ACC to reward
Olino et al.	2014	FHR = 14 (11) FLR = 12 (8)	FHR = 15.85 (3.09) FLR = 15.58 (2.59)	Parental depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain	↓ Activation of striatum during reward anticipation
Sharp et al.	2014	FHR = 19 (19) FLR = 19 (19)	FHR = 13 (1.92) FLR = 13.71 (1.85)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum	↓ Activation of R ventral striatum to reward
Gotlib et al.	2010	FHR = 13 (13) FLR = 13 (13)	FHR = 12.2 (1.7) FLR = 12.7 (1.4)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, insula, ACC	↓ Activation of putamen and L insula during reward anticipation ↑ Activation of R insula during reward anticipation
Pilhatsch et al.	2014		FHR = 14.54 (0.33) FLR	Parental depression: Unspecified	Emotion regulation fMRI	Amygdala	↑ Activation of dorsal ACC to loss ↑ Activation of amygdala to negative stimuli

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Table 1 (continued)

A. Infants (> 2 years)							
Author	Year	N (Female)	Age years (SD)	Familial Risk Classification	Neuroimaging Measure	Region (s) of Interest	Main Finding
Joormann et al.	2012	FHR = 28 (15) FLR = 136 (68)	= 14.56 (0.33)	Maternal depression: Structured clinical interview for DSM-IV	Emotion regulation fMRI	Limbic regions, PFC, ACC	↑ Activation of L ventrolateral PFC during sad mood induction ↓ Activation of dorsolateral PFC and ACC during mood regulation
		FHR = 20 (N/A) FLR = 27 (N/A)	FHR = 11.9 (1.21) FLR = 11.74 (1.29)				
Mannie et al.	2011	FHR = 28 (16) FLR = 28 (13)	FHR = 18.79 (1.4) FLR = 19.68 (1.44)	Parental depression: Reported by participant	Emotion regulation fMRI	Whole brain	↓ Activation in L dorsolateral PFC to fearful faces
D. Young Adulthood (19 – 25)							
Ozalay et al.	2016	FHR = 24 (24) FLR = 24 (24)	FHR = 22.3 (2.1) FLR = 22.1 (2.1)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Fronto-limbic regions	↓ Volume and thickness of temporoparietal and dorsomedial PFC
Durmusoglu et al.	2018	FHR = 27 (27) FLR = 26 (26)	FHR = 22.3 (2.1) FLR = 22.1 (2.1)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	= Hippocampal volume ↓ CA 1 region
Simsek et al.	2017	FHR = 16 (16) FLR = 15 (15)	FHR = 21.94 (2.32) FLR = 22.53 (1.8)	Maternal depression: Unspecified	Emotion regulation fMRI	Amygdala, PFC	= No significant differences
Mannie et al.	2008	FHR = 18 (9) FLR = 16 (10)	FHR = 19.8 (0.9) FLR = 19.9 (0.7)	Parental depression: Reported by participant	Emotion regulation fMRI	ACC	= Activation in ACC to negative, neutral, and positive stimuli

Note: ↑ Represents an increase. ↓ Represents a decrease. = Represents no significant difference.

thickness in the fusiform gyri, which was also found in their depressed mothers (Foland-Ross et al., 2015, 2016). These reports of reduced cortical thickness in FHR youth support the findings in younger age groups. However, there is a lack of agreement across these studies on which exact regions demonstrate reduced cortical thickness.

The two studies reporting on hippocampal volume in FHR adolescents did not agree on the directionality, with one suggesting a volume reduction, whereas another detecting no significant differences (Chen et al., 2010; Mannie et al., 2014). Amygdala volumes appear to be reduced in the only study that investigated amygdala structure (Chai et al., 2015). These results show a lack of agreement and/or repeated findings across studies on the directionality of subcortical gray matter volumes, an issue that persists from reports of younger age groups.

A reduction of white matter integrity has been detected in FHR adolescents in two studies. This includes the cingulum, corpus callosum, superior longitudinal fasciculus, inferior frontotemporal fasciculus, and uncinate fasciculus (Huang et al., 2011; Hung et al., 2016). Furthermore, lower FA of the cingulum, particularly within the ACC region, was associated with elevated depression scores in FHR youth (Hung et al., 2016). Concordant with findings in infants, FHR adolescents appear to have regional reductions of white matter integrity.

3.3.2. Brain function

Seven studies reported abnormalities in resting-state connectivity networks in FHR adolescents and young adults. In FHR compared to FLR adolescents, the DMN appears to be less strongly connected with the ACC, posterior insular cortex, and postcentral gyrus (Chai et al., 2016). Another study identified diminished connectivity between the DMN and the ventral striatum (Frost Bellgowan et al., 2015). Hypoconnectivity was also observed in the CCN by two studies, particularly between the dorsolateral PFC, ACC, and inferior frontal gyri (Chai et al., 2016; Clasen et al., 2014). Three out of the seven studies reported aberrant resting state connectivity between regions implicated in mood processing and emotional regulation have also been reported by. FHR adolescents had stronger connections between the ACC and inferior parietal lobule and weaker connections between the amygdala, orbitofrontal PFC, and precuneus (Hirshfeld-Becker et al., 2019; Singh et al., 2018b). Furthermore, they also demonstrated hyperconnectivity at rest between the

posterior cingulate cortex and subcortical structures such as the amygdala and hippocampus (Singh et al., 2018a; 2018b). Hyperconnectivity between the amygdala and dorsolateral PFC has been detected in FHR adolescents (Fischer et al., 2018). Overall, the large heterogeneity between studies and the small number of reproduced findings makes it difficult to conclude the directionality of activity and exact regions affected within these resting state networks.

Six studies detected altered activation patterns during reward processing in FHR offspring. Four out of six studies reported a blunted activity in the striatum was reported during reward anticipation and reward receiving (Fischer et al., 2019; Olinio et al., 2014, 2015; Sharp et al., 2014). Additionally, two studies reported FHR offspring showing increased activation within the putamen and insula during reward anticipation and hypoactivation in the striatum, insula, and parahippocampal region during reward loss (Colich et al., 2017; Luking et al., 2016). Similarly, during reward anticipation, the middle frontal gyrus was more active in older FHR adolescents compared to healthy controls and those with a depression diagnosis (Fischer et al., 2019). This finding on older FHR adolescents who were past the age of typical MDD onset suggests the possibility of a neurobiological marker of resilience.

Four studies showed that high-risk adolescents demonstrate altered neural activation in the amygdala and PFC areas during emotional response. When viewing negatively valenced emotional stimuli, FHR adolescents showed more activity in ACC and dorsolateral PFC, and less activity in the amygdala than FLR youth (Chai et al., 2015; Mannie et al., 2011; Pilhatsch et al., 2014). Blunted activation in the dorsolateral PFC was also observed during mood regulation (Joormann et al., 2012). These results suggest altered emotion processing in FHR adolescents.

3.4. Young adults

This literature review identified 4 studies on the brain of 166 young adults aged 19–25 (Table 1. D). This included 2 papers on brain structure and 2 papers on brain function.

3.4.1. Brain structure

Reduced cortical thickness of the temporal-parietal region and

dorsomedial PFC has been detected in a sample of FHR young adult daughters (Ozalay et al., 2016). No change in hippocampal volume had been observed (Durmusoglu et al., 2018). However, similar to the results of FHR adolescents and adults with depression, a smaller CA-1 region of the hippocampus was found in FHR young adults (Durmusoglu et al., 2018).

3.4.2. Brain function

Two fMRI studies assessing emotion processing found no differences in the amygdala, ACC, and PFC activity during the presentation of negative, positive, or neutral stimuli (Mannie et al., 2008; Simsek et al., 2017). The contrast in findings between altered emotion processing detected in FHR adolescents and no change in FHR young adults suggests a possible marker of resilience in brain activation when dealing with emotional stimuli. However, further research is required to confirm whether such a neurobiological protective factor exists.

4. Discussion

In this review, we examined neural markers of familial risk for depression. We focused on a wide age range, infancy to early adulthood, to encompass the time during which brain development is most rapid and the risk of depression onset increases (Herrman et al., 2022; Levman et al., 2017). Although large heterogeneity between studies creates difficulty in making conclusions, we have found some consistencies across brain structure and function between FHR youth and adults with depression. This presents the possibility of the existence of familial neural risk factors for depression and underlies the importance of additional research.

4.1. Brain structure

The most consistent finding across age groups is the presence of reduced cortical thickness in FHR youth (Fig. 2). Reduced cortical thickness has been detected in FHR offspring as young as age 4 and as old as 25 (Lebel et al., 2016; Ozalay et al., 2016). Studies on adults with MDD also report smaller cortical volume that is most likely attributed to reduced cortical thickness (Bora et al., 2012; Lai, 2013; Schmaal et al., 2020). This similarity between FHR offspring and adults with MDD suggests that reduced cortical thickness may be a familial neural risk factor for depression.

Reduced cortical thickness in FHR offspring is most frequently reported in frontal and temporal regions (El Marroun et al., 2016; Foland-Ross et al., 2015; Ozalay et al., 2016). These regions are typically implicated in emotion regulation and goal-directed behavior, faculties of which are often impaired in depression (Zhang et al., 2018). However, there is less agreement between studies about the specific location(s) that are most affected, making functional claims uncertain. What is apparent is that reduced cortical thickness, not cortical thickening, occurs in FHR youth. Cortical grey matter reduction is a normal process of brain maturation, occurring as the child ages (Levman et al., 2017). This is done by increased pruning, the removal of inefficient dendrites and synapses, as well as by increased myelination, the addition of myelin sheaths, improving the efficiency of neural signals (Natu et al., 2019; Parker et al., 2020). Future studies need to assess cortical thickness longitudinally, to understand whether FHR youth have a thinner cortex to begin with or whether they experience atypical brain development that may result in a thinner cortex with age.

Loss of white matter tract integrity in FHR offspring is the second relatively consistent finding. Studies report lower FA values in FHR infants and adolescents, but there is little agreement over the specific tracts affected (Dennis et al., 2019; Huang et al., 2011; Hung et al., 2016). Reduced integrity of white matter tracts is found in depressed adults, particularly within the genu of the corpus callosum, corona radiata, and cingulum (Schmaal et al., 2020). The axonal disruption that is associated with lower FA values in adults with MDD has been linked to

executive, cognitive and behavioral deficits that are seen in depression (Coloigner et al., 2019). Therefore, it is possible that reduced white matter integrity found in FHR offspring may be a familial risk factor for depression. However, gaps in the literature persist, with no studies examining white matter content in FHR young children and young adults. Longitudinal studies may provide further insight into developmental differences of white matter in familial risk youth compared to those of lower risk.

The association between high familial risk and subcortical gray matter structures is more unclear. Comparable to findings in adults with MDD, there is little consensus among studies on volumetric differences of the amygdala in FHR offspring (Acosta et al., 2020; Chai et al., 2015; Ho et al., 2022; Pagliaccio et al., 2014; Wen et al., 2017). Reports on subcortical structures such as the thalamus, caudate, pallidum, and midbrain are too few to make any conclusions. Although decreased hippocampal volumes are associated with depression, results are inconsistent in FHR offspring (Geerlings and Gerritsen, 2017; Schmaal et al., 2016). Therefore, it is still unclear whether hippocampal abnormalities precede or are a consequence of MDD.

Recent studies have detected subcortical shape alterations in adults with depression, such as of the basolateral amygdala and CA-1 region of the hippocampus (Ho et al., 2020). A smaller CA-1 region has similarly been reported in a couple of studies of FHR children and young adults, appearing as one of the more consistent findings in this review (Durmusoglu et al., 2018; Hubachek et al., 2021). Caution due to the small number of studies on this topic prevents us from making any definite conclusions. However, it does raise questions on whether studying subcortical gray matter shape, in addition to volume, may be beneficial in providing additional information on gray matter structures in FHR youth.

4.2. Brain function

Assessing similarities across functional brain findings has proven to be more challenging than brain structure. The field of fMRI is newer than that of structural neuroimaging, with greater heterogeneity in analysis methods, templates, and choice of brain regions to investigate (Schmaal et al., 2020). Particularly, the choice between region-focused and whole-brain analysis creates difficulty in comparing resting state data. We found 10 studies that investigated the resting state in FHR offspring. Although a few similarities across findings did emerge, such as amygdala – PFC connectivity, the DMN, and CNN, the directionality of these findings were less consistent (Fig. 3). The lack of consistent findings is not exclusive to FHR youth, as functional literature on adults with MDD similarly shows great heterogeneity in findings (Kaiser et al., 2015; Yan et al., 2019). This stresses the importance of establishing harmonized processing methods, standard seed networks, and templates to allow greater comparability of functional data between research groups.

Task-based fMRI, such as reward and emotion processing, have even greater heterogeneity due to task selection. Although task paradigms attempt to illicit similar responses (i.e. perceptual discrimination task for emotion processing) slight differences and/or adaptations across studies add to the heterogeneity of findings (Bishop et al., 2004; Hariri et al., 2005). This is particularly evident across studies on emotion processing, with most studies using different tasks which may contribute to the patchwork of results. However, there is some agreement across studies on functional reward processing. Consistent reports of reduced striatal activation during reward anticipation appear in FHR children and adolescents (Gotlib et al., 2010; Morgan et al., 2019; Olinio et al., 2015; Sharp et al., 2014; Wiggins et al., 2017). This is concordant with the reduced striatal activation associated with increased depression severity and the altered activation that is common in adults with depression (Arrondo et al., 2015; Segarra et al., 2016; Zhang et al., 2018). This suggests that altered reward processing may be a neural risk factor for depression. However, additional research is warranted particularly on younger FHR offspring to elaborate on when this marker

Brain Structure	Familial High Risk				Depression
	Infancy	Childhood	Adolescence	Early Adulthood	Adults
Cortical Thickness	No data	Reduced	Reduced	Reduced	Reduced
Cortical Surface Area	No data	Increased	No data	No change	No change
Amygdala Volume	No change	Inconsistent	Increased	No data	Inconsistent
Hippocampal Volume	No data	Reduced	Reduced	No change	Reduced
CA-1 of Hippocampus	No data	Reduced	No data	Reduced	Reduced
Thalamic Volume	Increased	No data	No change	No data	Reduced
White Matter FA	Reduced	No data	Reduced	No data	Reduced

Fig. 2. Structural brain changes in high familial risk offspring across age compared to adults with MDD. Note: 'No data' indicates that no studies have been performed on this brain structure for the given age group. 'Reduced' indicates that all studies found a reduction or decrease in the investigated brain structure. 'Increased' indicates that all studies on a given topic found an increase in the brain structure measured. 'No change' indicates that all studies on the given topic found no statistically significant result between FHR and FLR. 'Inconsistent' indicates that at least one of two or more studies on a given topic found a result that is opposite to the findings of others.

	Familial High Risk				Depression
Brain Function	Infancy	Childhood	Adolescence	Early Adulthood	Adults
Resting State					
Amygdala - PFC	Inconsistent 	Reduced 	Inconsistent 	No data 	Inconsistent
DMN	No data 	No data 	Inconsistent 	No data 	Inconsistent
CCN	No data 	No data 	Reduced 	No data 	Reduced
Reward Processing					
Striatum - Reward Anticipation	No data 	No data 	Reduced 	No data 	Reduced
Striatum - Reward	No data 	Inconsistent 	Reduced 	No data 	Reduced
Emotion Processing					
Amygdala - Negative Stimuli	No data 	Increased 	Inconsistent 	No change 	Inconsistent

Fig. 3. Functional brain changes in high familial risk offspring across age compared to adults with MDD.

may first emerge.

4.3. Future directions

We have identified several similarities as well as discrepancies in brain alterations between FHR offspring and adults with MDD. In doing so, we have noted a few shortcomings of the current literature on neural markers in FHR youth. The first is the small number of reproduced findings due to only a few studies examining a given modality or region of interest in FHR offspring. Even across studies that investigate the same topic and make similar conclusions (i.e. reduced cortical thickness), only a handful of studies with relatively small sample sizes exist. An addition of rigorous studies with larger sample sizes would enrich our understanding of neural markers of familial risk to depression and provide more certainty on the emerging findings. We have also described the shortcoming of fMRI result heterogeneity. The development of streamlined analysis techniques would allow for improved comparison across studies, allowing further insight into the functional alterations that may exist in FHR offspring (Schmaal et al., 2020).

Throughout this review, several additional gaps in the literature have become apparent. Figs. 2 and 3 show the various structural and functional brain alterations present in FHR youth. One of the striking visual findings is the lack of data investigating neural measures across different age groups. Filling these gaps could provide us with a better developmental perspective on when brain alterations may first emerge and how they progress with age. Furthermore, many topics have not yet been investigated. Altered gyrification and reduced intracortical myelin have been observed in depression but not yet explored in FHR offspring (Lake et al., 2017; Long et al., 2020; Sacchet and Gotlib, 2017). Research on these topics could further enrich our perspective on brain alterations present in FHR offspring as well as provide neurobiological explanations for their occurrence.

Another shortcoming in current literature is some overlap of age between studies, particularly between adolescents and young adults. The average age of MDD onset is between 14 and 16 (Herrman et al., 2022). Therefore, it is possible that asymptomatic FHR offspring older than 16 may be a phenotypically distinct group compared to those who are younger. This argument is supported by a few studies, which suggest that the brain alterations present in older asymptomatic FHR offspring differ from those observed in FHR offspring who became depressed (FHR-MDD) as well as low risk controls (Fischer et al., 2021; Nimarko et al., 2019; Toenders et al., 2019). For example, older FHR adolescents showed greater activation in the middle frontal gyrus during reward anticipation, a trend not seen in FHR-MDD and FLR groups, despite having blunted striatal activation during reward tasks (Fischer et al., 2016). This suggests a possible compensatory mechanism that might allow for the adaptive cognitive reappraisal of stimuli and may be a marker of resilience (Berpohl et al., 2009; Erk et al., 2010). Future studies should make more direct comparisons between brain alterations found in asymptomatic versus symptomatic older youth offspring to improve our understanding of such mechanisms. Multiple studies presented in this review have a large overlap in age range, particularly in the adolescent and young adult categories. This makes it difficult to discern whether a result is representative of FHR offspring before the typical age of onset versus those who are older and may have forms of compensatory brain alterations. Stricter separation of youth prior to the age of onset and those past the age of onset would not only increase our understanding of whether certain brain alterations are adaptive in FHR youth and potentially remove some inconsistency of results found in these age groups.

Depression is more common in females compared to males (Herrman et al., 2022). Multiple studies have focused on the effect of maternal depression on the offspring's brain, with 29 out of 44 studies included in this review categorizing youths' familial risk status based solely on maternal depression. However, there are reports of paternal depression being associated with varying psychological and behavioral outcomes in

male and female offspring (Gutierrez-Galve et al., 2019; Lewis et al., 2017; Thiel et al., 2020). Future studies need to compare the effects of maternal and paternal depression on offspring brain development and whether any sex-specific associations are present. Furthermore, 13 out of 27 studies on adolescents and young adults included in this review have exclusively female samples. Sex differences in structural brain alterations have been reported in younger samples of FHR youth (Acosta et al., 2020; Soe et al., 2018; Wen et al., 2017). Additional research on brain alterations detected in older male and female FHR youth could provide insight into the presence of possible sex-specific neural markers, which could elaborate on the varying phenotypic presentation of depression in males and females.

4.4. Limitations

We started this review by asking a broad question about brain differences across a broad age range. The strength of this approach is that we can report on patterns found across these age groups from a variety of brain measurement methods. However, the downside is that the included literature is heterogeneous. Most eligible articles did not report information on the recruitment of participants and effect sizes of findings that would allow state-of-the-art risk bias assessment or a quantitative meta-analysis. Consequently, this review is limited to qualitative assessment of the results from eligible studies. The lack of quantitative results and bias risk assessment means that our conclusions are limited to patterns of reported findings across a variety of eligible studies, and we are unable to weigh the relative importance of each study when drawing conclusions. Furthermore, it is important to note that neural markers in youth discussed here may not only be representative of an increased risk of depression but also possibly of other disorders with overlapping risks, such as anxiety and bipolar disorder (Rasic et al., 2014). Examination of age effects in brain correlates of familial risk was limited by the cross-sectional design used by most published studies. Future longitudinal studies would be a valuable contribution to understanding neural differences in FHR and FLR youth across brain development. A final limitation is that we did not pre-register this review before conducting the literature search.

5. Conclusion

Structural and functional brain alterations that are associated with depression appear in youth at high familial risk for depression. This points to neural markers of depression vulnerability existing prior to disorder onset. However, streamlined fMRI analyses and an increased number of studies whose findings reproduce current results would increase our confidence in the emerging conclusions presented in this review. Furthermore, future studies are necessary to gain further perspective on when various neural markers first emerge and whether there are any sex-specific trends present. Improved detection and understanding of the course of neural markers that precede MDD may allow earlier implementation of interventions to reduce the burden of depression.

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Data statement

The extracted data are available as supplementary material

accompanying this article. This includes a table summarizing key points from all articles that were synthesized in the review, such as author, publishing year, sample size, age, familial risk classification, neuroimaging measure, region(s) of interest and main finding(s). This data table has been included as part of the manuscript submission.

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.

Data Availability

Data will be made available on request.

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Anna Nazarova performed the literature search, synthesized articles, and drafted the manuscript. Rudolf Uher conceived the study and provided input at all stages of work on the review. Matthias Schmidt and Jacob Cooley contributed to key decisions and revised the manuscript for important content.

Note

Fig. 2 and Fig. 3 should be in color in print.

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